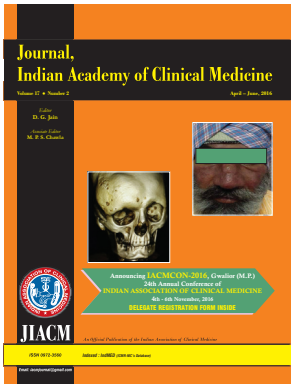

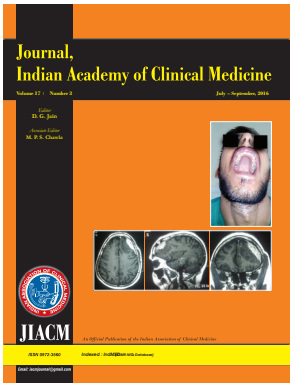

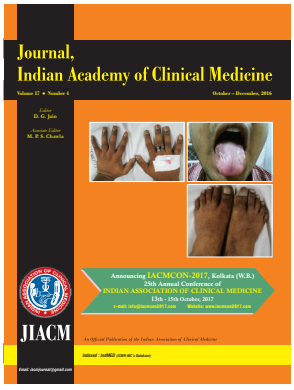

From the Editor

It has been a privilege and an honour editing this nationally read medical journal – the *Journal, Indian Academy of Clinical Medicine (JIACM)* – six years as its Associate Editor and then another six as Editor. Even before that, for many years I had been actively involved in the editing process backstage. As I bid *adieu*, I must admit that I have enjoyed every minute of the eventful seventeen years of deep involvement with the *JIACM*. Looking back, it has indeed been a unique and challenging experience, but more than that it has been a very fulfilling one academically as it honed my scientific temper further, nourished my reading habit, improved my analytical skills, and sharpened my clinical acumen. All this in turn has had a positive effect in my day-to-day clinical work. Here, I am reminded of what my father – the late internist Dr. G.B. Jain – always said and believed: "Academic success and medical qualifications make only half the doctor. The other half is made by bedside manners, compassion for the sick, and a keen desire plus selfless effort to sincerely guide the patient through his ailment, his lonely battle…"

At the *JIACM*, I had instituted successfully a unique approach insofar as acceptance of articles was concerned. I solicited the help/guidance of peer reviewers/referees only where I felt there was a genuine need to do so. I had adopted the practice of personally reading each and every article at least three times before its publication. Apart from all this, I made sure that papers from internists/hospitals/institutions from even the remotest, far flung areas of the country get to see the light of day in the *JIACM*. Any manuscript which was found to have interesting and worthy clinical material but was unsuitably worded and/or structured, was never rejected. I made sure that it was re-done, refined, polished, and then published. Most of the journals are known to reject shoddily written articles even if they contain rich clinical material. They do not have a policy of working upon and improving the presentation of such articles.

Donning the hat of a medical journalist has its fair share of bouquets and brickbats. And I have been no exception. Anyway, I have tried my best to be an easily accessible editor at all times, to all authors and readers. I could always gauge the anguish of authors awaiting acceptance of articles and their subsequent publication, but was helpless due to the fact that ours is a quarterly *journal*, hence a rather long waiting period for publication of accepted articles. However, the constant pressure for acceptance/publication of particular article(s) has not affected the *JIACM*'s selection process. Merit has always been the sole criteria – as it should be in the sciences – for acceptance of articles. The proof has always been there for readers to savour in each and every issue, including this one. I must also disclose here that editing the *JIACM* on a shoestring – budget, manpower, resources – has not been a cakewalk. But with a dedicated and committed team, the *JIACM* has sailed smoothly, weathered many storms.

As I conclude my tenure as Editor and Publisher of the *JIACM*, I wish to sincerely thank my mentor Padma Bhushan Professor B.M. Hegde, and especially all my family – wife Seema, sons Dr. Dhruv, Dr. Vikram, and daughter-in-law Sanya – for their patience, support, and assistance at all hours during all these challenging and hectic years.

My heartiest congratulations go to Dr. M.P.S. Chawla and Dr. Sumeet Singla to whom I hand over the reins as the Editor and Associate Editor respectively from the next issue onwards. I wish them good luck and success, and hope that they too will enjoy editing the *JIACM* as much as I did! My special thanks go out to the technical team of the *JIACM* – Mr. Yash Pal Satmukhi (circulation & advertising), Mr. Vijay Shanker Vashisht (typesetting), and Mr. Avinash Kumar (production) for their untiring efforts.

Finally, dear readers and contributors, I thank you all for your immense support, encouragement, constructive criticism and cooperation. And for me, now it is time to take a break and move on.

Goodbye and take care. Jai Hind!

– Dr. D. G. JAIN
drdgjain@yahoo.co.in

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VIEWPOINT

JIACM 2016; 17(4): 263-64

Can your own immune system kill cancers? Ultimately, truth prevails

*BM Hegde**

"The ultimate measure of a man is not where he stands in moments of comfort and convenience, but where he stands at a time of challenge and controversy".

– Dr. Martin Luther King Jr.

My firm conviction is that nature has provided us with a very robust immune system which I call as the inner healer which is geared to heal most, if not all, of the ailments that man is heir to under most circumstances. It is only in the unlikely event of that failing does man become critically ill with his health falling outside the healthy chaos attractor limits to go close to the death attractor trajectory. Rarely does one come back from there in spite of the much hyped area of the ICUs intensive interventions which incidentally give the corporate hospitals' 90% of their profit by keeping such dying patients in the last ten days of their sojourn in this world. Ever since I joined the medical school in 1956, I suffered from this dilemma of my childhood environment encouraging self-healing and my new medical school environment encouraging a pill for every ill or a surgical quick-fix. Not even the best of my teachers ever emphasised the possibility of self-cure – not even to mention it as a remote possibility.

When I started to study cancer as a medical student my feeling was that cancer was NEVER cured by our three-pronged attack of chemotherapy, radiation and mutilative surgery. This was further strengthened by that lovely book, *The Science of Medicine and its Quiet Art,* written by a great brain in England, the then Regius Professor of Medicine in the Oxford University and a respected haemato-oncologist, David Weatherall. He strongly felt that our future generation will never forgive us for these methods of treatment and the consequent sins committed by us which are worse than the red hot iron branding for all diseases in the olden times by our forefathers! Does history repeat itself? This happens because we fail to learn from our history. In that beautiful book, *Bad Medicine*, (Doctors harming patients since Hippocrates), the author David Wootton, so graphically documents our crime on mankind since the dawn of western, so called, modern medicine. If we do not learn from history, warned the great Roman thinker Cicero, we will be forced to relive history! Are we not doing just that in this *Kaliyuga*?

I have developed a self-curing regimen for cancer and have been trying it on patients who come to me with desperation after having suffered the consequences of their harrowing experience of the triple whammy prohibitively expensive conventional cancer cures? Naturally, their immune systems were at their worst at that time. Despite that, most of them had a comfortable life for the rest of their life enjoying life with their kith and kin after starting the alternate regime. One patient came to me wanting NOT to go for his treatment at the age of 69 years. I got his glands biopsied and they showed metastatic anaplastic adenocarcinoma but the pathologist could not say where it originated! He had just Ayurvedic immune boosters and nothing else. He is now 81 and very healthy. Had no discomfort at any time up until now. Interestingly, his glands have also disappeared.

With the advent of quantum physics, science has understood that now *we can comprehend much more than what we can grasp*. The human body being an illusion of human consciousness (mind), there is nothing by way of body disease. Almost all illnesses originate in the mind and end in the mind, if ever they do. Matter is not made out of matter; it is made out of energy. Thus disease becomes an altered energy pattern of the body; the latter can now be assessed accurately by Fritz Albert Popp's bio-photon camera.

I have been trying quantum healing of illnesses by our own immune system. I felt I should try it on myself before trying it on patients as I did not want to be a heroic doctor with the hapless patient in the hero's role. My personal impression is that quantum healing works wonders sans medicines. There are stray reports of quantum healing in cancer also. In the olden days these reports were called anecdotal and dismissed by the western medical "scientists", but the good news is that in a recent article in the "prestigious" journal *Nature* (the King of science journals), there was an article extolling the virtues of *N for 1 studies* (single patient studies) as far superior to our conventional RCTs (randomised controlled studies) sold as a gold standard of evidence based medicine.

The good news is that the mainline cancer researchers are now slowly realising the futility of their three-pronged war

Padma Bhushan; Former Vice-Chancellor, Manipal University; Editor-in-Chief, The Journal of the Science of Healing Outcomes (JSHO); Chairman, State Health Society's Expert Committee, Govt. of Bihar, Patna; Visiting Professor of Cardiology, The Middlesex Hospital Medical School, University of London, U.K.; Affiliate Professor of Human Health, Northern Colorado University, U.S.A.

on cancer. They have realised that the immune system is a better bet to fight cancer, the backbone of Ayurveda! However, their obsession with reductionist chemicals to stimulate the immune system is bound to fail as all reductionist chemicals are rejected as soon as they enter the body as alien and outside poison to be sent to the liver for destruction and the consequent rise in non-alcoholic cirrhosis of liver in the world! Look at their foolishness? CNN (Cable News Network) in one of its important broadcasts recently had this to say: "Immunotherapy is quickly emerging as the future of cancer treatment, scientists say. The therapy works by harnessing the immune system to fight cancer from within. There was another big win in the advancement of immunotherapy treatments for cancer this week. The US Food and Drug Administration (FDA) approved an immunotherapy drug called Keytruda, which stimulates the body's immune system, for the first-line treatment of patients with metastatic non-small-cell lung cancer. In other words, the drug could be the very first treatment a patient receives for the disease, instead of chemotherapy. Keytruda is the only immunotherapy drug approved for first-line treatment for these patients. So it seems, the future of cancer care may be in our own immune systems, but how exactly does it work, and what are its pros and cons?"

"It's certainly going to become an independent way of treating cancers," said Dr. Philip Greenberg, head of immunology at the Fred Hutchinson Cancer Research Centre in Seattle, during the International Cancer Immunotherapy Conference in New York in September. "Immunotherapy has essentially undergone a sort of revolution in the last decade in the sense that something that was experimental – and there were still questions about what role it would have in the way cancer is treated – is completely turned around, and now it's clear it's effective," Greenberg said.

German physician Dr. Paul Ehrlich, who won the Nobel Prize in physiology in 1908, proposed using the immune system to suppress tumour formation in the "immune surveillance" hypothesis. "Cancer immunotherapy really refers to treatments that use your own immune system to recognise, control, and hopefully ultimately cure cancers," said Jill O'Donnell-Tormey, CEO of the Cancer Research Institute, during the conference in New York last month. "Many people for many years didn't think the immune system was really going to have a role in any treatment for cancer," she said, "but I think the entire medical community (and) oncologists now agree that immunotherapy's here to stay." That much for their ignorance so far. History is replete with such gross injustices killing millions.

The subtle efforts of the sugar lobby in the 1950s to show fat in bad light vis-a-vis sugar in the killer disease of vessels blocks eventually was discovered and the world was relieved of the false fat myth by the American Diet Guidelines. It is now known that fat and cholesterol are not the demons that they were made out to be and they are vital parts of human nutrition as every cell in the human body must have a strong cell membrane for good health. The 1950s book by a thinker professor of nutrition in the London University, John Yudkin, about the dangers of sugar – Pure, White, and Deadly – which was banned then along with its author who was stripped of his professorship (and the poor man eventually died) has now been resurrected! Thank God for that. Interestingly, the recent statin recommendation committee of the American Cardiology group still recommends statins for some sub-groups.

We have come a full circle from ignoring the all-powerful immune system as the basis of all disease management and making our patients suffer for our ignorance for decades to realise that the immune system is our inner healer. Hope the west will now learn from Ayurveda that only holistic treatment helps and not treatment with reductionist chemicals. May God save mankind from our ignorance and the consequent scientific hubris?

"Attitude is a little thing that makes a big difference".

– Sir Winston Churchill.

"There is no way that negative actions or unwholesome deeds can result in joy and happiness. Joy and happiness, by definition, are the results of fruits of wholesome actions. The basic sources of happiness are a good heart, compassion and love."

– The XIV Dalai Lama.

ORIGINAL ARTICLE

JIACM 2016; 17(4): 265-69

Prevalence of peripheral neuropathy in Indian prediabetes subjects and its correlation with metabolic risk markers

Vishwas Gulati, BMS Lamba**, Pulin Kumar Gupta***, MPS Chawla**, Debopriya Ghosh****, Mahesh Kakanale****, RS Taneja***

Introduction

Diabetes mellitus is becoming one of the most important health problems not only in developed countries but also in developing countries. The transition from the early metabolic abnormalities that precede, i.e., impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), to diabetes may take many years; however, current estimates indicate that most individuals (perhaps up to 70%) with these pre-diabetic states eventually develop diabetes[1].

It is estimated that some 344 million people worldwide or 7.9% in the age group 20 - 79 years had IGT in 2010, the vast majority of whom live in low and middle income countries. By 2030, the number of people with IGT is projected to increase to 472 million, or 8.4% of the adult population[2].

Diabetic neuropathy is the most common and troublesome complication of diabetes having significant morbidity and resulting in a huge economic burden for diabetes care. Diabetic patients have a 12 times higher risk of amputations when compared with non-diabetic subjects, due to diabetic neuropathy[3]. The incidence of neuropathy increases with the duration of diabetes; ultimately up to 50% of patients are affected. Improved glycaemic control has been shown to prevent and delay progression of diabetic neuropathy, emphasising the importance of early diagnosis and aggressive management in these patients. There is increasing evidence that patients with milder degrees of abnormal glucose metabolism, including impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are also at risk for developing symptomatic polyneuropathy. In most populations, IGT is more prevalent than IFG and there is some degree of overlap, but IFG and IGT identify substantially different segments of the population with impaired glucose regulation[2]. It is well known that neuropathy has a metabolic component in its pathophysiology. Hence early metabolic aberrations seen in impaired glucose tolerance (IGT) may also lead to changes in nerve conduction. Hence the present study is being undertaken to know the prevalence of neuropathy in prediabetic subjects and its association with various metabolic risk factors.

Materials and methods

The study was conducted in 50 individuals who were prediabetics as per criteria of American Diabetic Association (ADA), presenting to the department of medicine, PGIMER, Dr. Ram Manohar Lohia Hospital, New Delhi with age and sex matched healthy controls (non diabetics and normal fasting glucose and normal glucose tolerance). Prediabetes is defined as impaired fasting glucose (IFG): fasting plasma glucose 100 - 125 mg/dl after 8 hrs of no calorie intake; and/or impaired glucose tolerance (IGT): 2 hrs plasma glucose 140 - 199 mg/dl after 75 gm of glucose challenge during an oral glucose tolerance test (OGTT)[4] for this study, informed consent was taken along with ethical committee approval.

Patients of age 35 - 65 years were included in the study. Patients presenting with other causes of neuropathy like inherited neuropathy, alcoholic neuropathy, drug-induced neuropathy, toxin-induced neuropathy, neuropathies associated with macrocytic anaemia, renal insufficiency, thyroid disorder, malignancy, or any other systemic illness were excluded by a detailed history and clinical examination.

Both the cases and the control population were evaluated by a detailed history regarding age, sex, presence of hypertension, and family history of diabetes or CAD. History of smoking habits and alcohol intake was also taken. A complete general physical examination and systemic examination was carried out and any abnormality recorded. Thorough neurologic examination of upper and lower limbs was carried out which included symptoms like numbness or no feeling in the feet, pricking sensation in the feet, deep aching or burning pain, unusual difficulty in climbing stairs, decreased ability to feel hot or cold and signs on skin like atrophy of subcutaneous tissues, dryness, cracking or shiny skin, loss of hair, ulcerations were also noted. During the neurologic history, peripheral, somatic, central, and autonomic neuropathic symptoms were recorded. Peripheral sensory examination included testing for pain, touch, temperature (small fibre sensation), and vibration and joint position senses (for large fibre sensation). Sensation was tested by using 10 gram

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monofilament, and vibration sense was tested by using 126 Hz tuning fork. Motor system examination included tone of muscles, power of the muscle and deep tendon reflexes. In the absence of other known causes of neuropathy, abnormal findings in neuropathic signs, neuropathic symptoms and quantitative testing or combination of these was taken as clinical neuropathy. Nerve conduction study was performed with standard stimulation and recording technique using the software CADWELL SIERRA WAVE. Sensory nerve conduction was measured in median nerve and sural nerve. Standard statistical tests were applied for analysis of the data.

Observations and results

The total number of patients in our study were 50 (31 males and 19 females) and total number of control cases were 30 (19 males and 11 females). The mean age of cases in our study was 52.04 ± 7.69 years. Maximum numbers of cases were in the age group of 46 - 55 years.

History of hypertension was obtained in a total of 15 (30%) cases and 4 (13.3%) controls. History of smoking was present in 13 (26%) cases and 5 (16.6%) controls. Family history of diabetes was present in 19 (38%) cases and 2 (6.6%) controls.

Table I: Biochemical features of the study group.

Parameters	Mean value ± S.D (in cases)	Mean value ± S.D (in controls)
FPG (mg/dl)	96.56 ± 16.23	75.00 ± 12.54
OGTT (mg/dl)	151.9 ± 24.98	112.5 ± 10.66
HbA1c (%)	4.48 ± 0.76	3.57 ± 0.51
LDL (mg/dl)	99.94 ± 29.93	85.67 ± 20.93
HDL (mg/dl)	46.94 ± 9.06	42.60 ± 6.70
Triglycerides (mg/dl)	138.74 ± 47.34	119.50 ± 37.42

Table II:Anthropometric measurements.

Parameters	Mean value ± S.D (in cases)	Mean value ± S.D (in controls)
Weight (kg)	67.71 ± 10.6	63.87 ± 6.79
BMI (kg/m²)	25.64 ± 3.45	23..30 ± 2.45
Waist circumference (cm)	85.62 ± 10.95	82.8 ± 4.89
Waisthip ratio	0.91 ± 0.11	0.85 ± 0.04

Based only on clinical examination, neuropathy was present in 4 out of 50 cases (8%), whereas abnormality on nerve conduction study (either sensory or motor or both) was found in 10 out of 50 cases (20%) and 1 out of 30 controls. Abnormality in sensory nerve conduction study was found in 6 cases whereas abnormality in both sensory and motor nerve conduction study was found in 4 cases. No patient was found to have abnormality in pure motor nerve conduction study alone. Out of 10 cases with nerve conduction abnormality, 60% were males and 40% were females. 15 cases were hypertensive, and nerve conduction abnormality was found in 5 (33.33%) of them. BMI > 25 kg/m² is present in 24 (48%) cases out of which 8 (33.33%) had nerve conduction abnormalities. Association between BMI and nerve conduction abnormalities was statistically significant ($p = 0.034$). 7 patients with nerve conduction abnormalities had increased waist circumference and the association was statistically significant ($p = 0.05$). Increased waist-hip ratio was present in 58% of cases and the association was statistically significant ($p = 0.04$). Family history of diabetes mellitus was present in 19 (38%) cases out of which 7 (14%) had abnormalities of nerve conduction whereas 12 (24%) had normal nerve conduction study. The mean total cholesterol levels in cases was 186 ± 24 mg% and peripheral neuropathy was present in 3 patients with total cholesterol > 200 mg% and 7 patients in those with levels < 200 mg% ($p < 0.5$). The mean LDL levels were 90 ± 22 mg%. LDL > 100 mg/dl was found in 19 (38%) cases and nerve conduction abnormalities were found in 4 of them. The mean HDL levels were 46 ± 15 mg%. Low HDL was seen in 26% prediabetic subjects. Raised triglycerides levels were seen in 38% of cases out of which 14% had nerve conduction abnormality ($p < 0.05$). Prevalence of dyslipidaemia (presence of one or more abnormal lipid parameters) in cases was 76%. Raised LDL level, low HDL levels, and high triglycerides levels were present in 19 (38%), 13 (26%) and 19 (38%) cases respectively.

25 (50%) prediabetic subjects had Impaired fasting glucose (IFG) of which 6 (24.16%) had nerve conduction abnormalities ($p = 0.046$). 30 (60%) prediabetic subjects had IGT. 9 (33.3%) IGT patients had nerve conduction abnormalities ($p < 0.036$). Mean HbA1c among prediabetics was 4.48 ± 0.76%. It was seen in 7 cases (14%) out of which 4 had nerve conduction abnormalities ($p < 0.002$). 6 patients with HbA1c < 5.7% had NCV abnormality. Microalbuminuria was seen in 7 (14%) prediabetics, 4 (8%) of which had nerve conduction abnormalities ($p < 0.023$). Only 2 prediabetic subjects had evidence of retinopathy, both of which had abnormal nerve conduction. So presence of peripheral neuropathy in prediabetes has significant association with the level of glycaemic control as well as atherogenic dyslipidaemia (high TG or Low HDL), WHR, family history of diabetes and presence of other microvascular complication (i.e., nephropathy and retinopathy).

Discussion

Although in our study prevalence of clinical neuropathy is 8%, but using nerve conduction abnormalities as a measure of neuropathy it is found that the prevalence of neuropathy in cases compared to controls is 20% and is statistically significant ($p = 0.046$).That implies that not only in diabetes, but also in prediabetics, NCV should be relied upon as a test to early diagnosis of neuropathy because < 50% of cases are picked up by clinical examination.

6 out of 25 IFG subjects have nerve conduction abnormalities and 9 out of 30 IGT subjects have nerve conduction abnormalities ($p < 0.05$). In the MONICA/KORA Augsburg (Germany) study by Zeigler *et al* prevalence of polyneuropathy was 11.3% for those with IFG and 13.0% for those with IGT[5]. Viswanathan *et al* reported that IGT group of subjects exhibited a significantly lower mean Motor Conduction Velocity (MCV) level when compared with the Normal Glucose Tolerance (NGT) subjects[6]. Franklin *et al* in San Luis Valley Diabetic Study found the prevalence of neuropathy to be 11.2% in IGT subjects[7]. Cohen *et al* reported that nerve conduction studies demonstrate that neuropathy is already present in 10 - 18% of patients at the time of diabetes diagnosis, suggesting that peripheral nerve injury occurs at early stages of disease and even with milder glycaemic dysregulation[8]. This higher prevalence of polyneuropathy in our cases (IFG and IGT both) as compared to western literature can be explained by the fact that since metabolic syndrome and insulin resistance is more in people of the Asian subcontinent (which are known to increase the chances of neuropathy) along with other microvascular and macrovascular complications which are seen much more common in Indians than in western population. Also, one other contributory factor may be the rampant use of insecticides/drugs/toxins in ground water.

In our study among prediabetic cases with neuropathy, sensory neuropathy was present in 6 out of 10 cases and sensori-motor neuropathy was present in 4 out of 10 cases that is in accordance with studies by Singleton *et al* who reported that most patients with IGT and associated neuropathy have a symmetric, distal sensory polyneuropathy with prominent neuropathic pain[9]. Sumner *et al* also found out that 81% of neuropathy patients with IGT had exclusively sensory complaints, and 92% recognised neuropathic pain as a dominant symptom of their neuropathy[10]. This fact can be explained by small unmyelinated fibre loss and altered morphology in patients with neuropathy associated with IGT and early diabetes as shown by Smith *et al*[11].

Mean age for IFG subjects was 52.04 ± 7.36 years and mean age for IGT subjects was 51.63 ± 7.64 years. In a MONICA/KORA Augsburg (Germany) study by Zeigler *et al* mean age for IFG was 66.6 ± 8.1 years and for IGT was 69.3 ± 7.8 years[5]. In a study by Green *et al* (UK) on peripheral neuropathy in impaired glucose tolerance individuals, average age in IGT subjects was 50 ± 5 years[12]. So there is a wide variation in the mean age of subjects in different study groups.Younger age of IGT subjects in our study may be attributed to younger age of onset of diabetes in the Indian population as compared to other ethnic groups. As mentioned earlier, metabolic syndrome in our population is much more common and occurs at least 10 years earlier than in the west, so prediabetes in India may be even much earlier than what we got in our results and the same logic applies to earlier occurrence of micro- as well as macro-vascular complications in Indians.

Lipid abnormalities were widely present in our study.There was a significant ($p < 0.05$) difference between mean LDL and HDL values the between prediabetic group and the control group. Prevalence of dyslipidaemia (presence of one or more abnormal lipid parameters) in prediabetics in our study was 76%. Raised LDL levels, low HDL levels, and high triglycerides levels were present in 38%, 26%, and 38% cases respectively. Raised triglycerides were present in 7 out of 10 cases with neuropathy and its association with nerve conduction abnormalities was statistically significant ($p = 0.030$). Snehalata *et al* in their study have reported the presence of dyslipidaemia in 56.9% of the IFG subjects and 80.9% of IGT subjects[13]. The EURODIAB study established a significant association between cholesterol and fasting triglycerides and the development of diabetic neuropathy[14]. Dyslipidaemia in Indian subjects (and so our cases) does not need any more explanation. But our results showed that as compared to LDL,TG levels were more correlated to NCS and here lies the importance of non-HDL which is also proven in many Indian studies. In fact, in the Indian context, non-HDL cholesterol is probably a better marker of dyslipidaemia than LDL in Indians. PPAR-α agonists like fenofibrate and PPAR-α agonists like pioglitazone are known to decrease hsCRP and MAU apart from TG and HbA1C which itself may be a reason for these drugs to retard or decrease neuropathy in diabetes (and maybe prediabetes also). In our study, the prevalence of BMI ≥ 25 kg/m^2 was 48% among prediabetics with a mean BMI of 25.64 ± 3.45 kg/m^2. Among 10 patients with neuropathy, BMI ≥ 25 kg/m^2 was present in 8 cases ($p = 0.034$). Various studies have consistently reported an increased BMI in prediabetic subjects compared to non diabetic subjects. Mohan *et al* have reported that 54.1% of IGT subjects have BMI ≥ 25 kg/m^2 in their study (CUPS 14)[15]. Mean BMI for IGT subjects in their study was 24.9 ± 4.0 kg/m^2. The result of our study is thus consistent with that study.

Similar results were obtained for waist circumference and

waist-hip ratio which was present in 44% and 58% of prediabetics and the association with neuropathy was statistically significant. In the MONICA/KORA Augsburg study, waist circumference was significantly associated with neuropathy and may contribute to a higher prevalence of neuropathy in IGT subjects compared to NGT subjects[5]. In a study by Gordon *et al* on lifestyle intervention for pre-diabetic neuropathy diet and exercise counselling resulted in a significant improvement in weight which was associated with improvement in measures of small fibre function[16]. This highly significant association in our study may be because of more number of male patients as well as the concomitant impact of lipids and HbA1C on polyneuropathy.

A study by Costa *et al* in 548 patients with type 2 diabetes showed that those with the metabolic syndrome were twice as likely to have neuropathy as those without[17]. Tesfaye *et al* stated that in diabetics without neuropathy at baseline, markers like hypertension, hyperlipidaemia, and increased body mass index were each independently associated with a higher risk of developing neuropathy[14]. Insulin resistance with prediabetes and diabetes is a part of the metabolic syndrome, which also consists of hypertension, hyperlipidaemia, and obesity. The individual components of the metabolic syndrome have been implicated as risk factors for small fibre neuropathy. Obesity (and so high BMI and WHR) is a major marker for microvascular complications of diabetes. Peripheral neuropathy is in fact one of the earliest microvascular complication. This correlate even extends to prediabetes where the main pathology is insulin resistance. Western people have more muscle mass as compared to Indians, and because of high WHR and obesity, the figure and significance is much higher in our Indian subjects.

In our study, 14% of prediabetic subjects had HbA1c ≥ 5.7. Neuropathy is present in 4 out of 7 cases with HbA1c ≥ 5.7 ($p = 0.023$). Silverman *et al* used HbA1c as a screen for previously undiagnosed prediabetes and found that for diagnosing prediabetes, HbA1c has a sensitivity of 54.8% and specificity of 71.3%[18]. 86% of our patients had HbA1c <5.7% and that stresses the fact that IFG and IGT are probably better clinical criterion for future prognostic and diagnostic implications. In the Indian subcontinent we should not wait for HbA1c > 5.7%, rather lifestyle and diet modification should start much before that as we have seen that many patients with HbA1c < 5.7% had polyneuropathy. As we know that the pathology of 72 diabetics dates back 5 years or more before diagnosis. IGT/IFG is the time where lifestyle modification and even treatment with metformin should commence.

In our study, prevalence of microalbuminuria was 14% among prediabetics, and none of the controls have microalbuminuria. Neuropathy is present in 4 out of 7 subjects with microalbuminuria. Sumner *et al* observed that among > 5,000 Maoria and European subjects, microalbuminuria was found in 21% of those with diabetes and 16% of those with IGT, but only 4% of normoglycaemic individuals[19].

In our study, retinopathy was found in 2 cases both of which have evidence of neuropathy ($p = 0.032$). Independent studies have noted an approximate four-fold increase in the prevalence of retinopathy among Pima Indians with IGT compared with age-matched control subjects. In the Western Samoa survey, 10% of IGT subjects had retinopathy as compared with 17% of those with newly diagnosed diabetes and 45% of known diabetic subjects[20]. In AusDiab study by Elizabeth *et al*, those individuals with IFG or IGT who were classified as abnormal on the overall neuropathy score, 20.4% were classified as having retinopathy. Compared with those without neuropathy, individuals with neuropathy were nearly four times more likely to have albuminuria[21]. This association is self-explanatory as retinopathy and nephropathy are the other two dreaded microvascular complications along with neuropathy. Since the basic pathology behind them is the same, so the co-occurrence is self explainable. So prediabetes needs to be diagnosed early not only to prevent cardiovascular morbidity but also neuropathy which is probably a non-reversible microvascular complication having negative impact on quality of life and also is almost similar in incidence in prediabetics as well as diabetics.

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"Your fame or your person, which is dearer?
Your person or your goods, which is worth more?
Gain or loss, which is the greater bane?
...Know contentment, and you will suffer no disgrace;
Know when to stop, and you will meet with no danger."

– TAO TE CHING 44.

ORIGINAL ARTICLE

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Serum high-sensitivity C-reactive protein after acute ischaemic stroke is associated with stroke severity and functional disability

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Abstract

***Background:** C-reactive protein is the most reliable marker of inflammation. This is one of the most sensitive acute phase reactants after tissue damage or inflammation. CRP levels in serum can rise dramatically after myocardial infarction, stroke, stress, trauma, infection, inflammation, surgery, or neoplastic infiltration. There is growing evidence of the prognostic importance of C-reactive protein in ischaemic stroke. However, the independent value of CRP after stroke has not been established.*

***Objectives:** To measure the high-sensitivity C-reactive protein level in patients with acute ischaemic stroke, to correlate the hs-CRP level with clinical severity of stroke at onset and to study its prognostic significance in acute ischaemic stroke.*

***Methods:** 50 patients with ischaemic stroke, admitted within 24 hours after the onset of symptoms were included for this prospective case-control study . Fifty healthy controls were also taken for valid comparisons. Hs-CRP and NIH stroke scale (NIHSS) were measured at the time of admission. Short-term functional outcome was measured by modified rank in scale (mRS) 7 days after admission and at 3 months after the event.*

***Results:** Most of the patients were in > 60 year age group (48%). Stroke was more common in males (70%) than females (30%). Most common risk factors for stroke were hypertension (46%), and diabetes mellitus (26%). The mean value for hs-CRP at admission was 4.185 (± 2.2400) mg/dl in patients and 0.980 (± 0.337) mg/dl in control group. The difference in hs-CRP levels between cases and controls was significant (p = < 0.001). Serum hs-CRP was significantly correlated with stroke severity at onset (p value < 0.001) and long-term outcome (p value < 0.001).*

***Conclusion:** Admission levels of hs-CRP have significant positive correlation with the initial severity of stroke (assessed by NIHSS score) with high levels seen in patients with higher severity of stroke. Serum hs-CRP was an independent predictor of the long-term outcomes after stroke.*

***Keywords:** National Institute of Health Stroke Severity Scale (NIHSS), modified Rankin Scale (mRS), cerebrovascular accident.*

Introduction

Stroke is one of the leading causes of mortality and morbidity worldwide. Ischaemic stroke is second only to coronary artery disease as the major cause of mortality. It is now widely accepted that inflammation plays a major role in the development and progression of atherosclerosis[1]. Inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP) are an important predictor of atherosclerotic disease, coronary risk, and stroke[2]. Hs-CRP – an acute phase reactant, is significantly increased in inflammatory disorders and it has been shown to enhance immune reactivity[3, 4]. High-sensitivity C-reactive protein (hs-CRP) levels have attracted clinical attention as a predictive marker of atherosclerosis because it plays an integral part in the inflammatory process of atherosclerosis[1]. It has recently been shown that elevated hs-CRP levels independently predict the risk of future stroke and TIA in the elderly[5,6].

Large population-based studies show that high CRP is a risk factor for future cardiovascular events[7,8,9]. The recent JUPITER trial shows that the use of rosuvastatin in patients with high CRP has a significant impact both in reducing the CRP level and in lowering future vascular events[10]. This indicates the role of inflammation in atherogenesis and suggests that CRP can be used as a marker of future events. The role of CRP as a marker during and after ischaemic stroke is less extensively studied in comparison to coronary artery disease. The Rotterdam study shows that although high CRP is associated with stroke risk, their use in the assessment of individual stroke risk is limited[11]. On the other hand, the Framingham study shows that high CRP is associated with a greater risk for ischaemic stroke or TIA[12]. Studies in patients who already had a stroke show an association between high CRP and stroke presentation, outcomes and future vascular events. Moreover, the results from some studies were negative. In their pivotal review, Di Napoli *et al* concluded that there is insufficient evidence to justify the routine use of CRP for either primary or secondary risk stratification for cerebrovascular disease alone[13]. In addition, only a few studies have analysed the relationship between elevated admission CRP levels and stroke severity or stroke aetiology.

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The aim of this study was to help clarify the role of early CRP in ischaemic stroke by determining its association with stroke severity and functional outcome after stroke.

Material and methods

Study population

The present study was a case control study which included 50 patients of acute ischaemic stroke admitted in the medicine wards of Safdarjung hospital. Fifty age and sex matched controls not having any evidence of stroke/TIA, or CAD were also studied for comparison. Patients presented within 24 hours of development of signs and symptoms of stroke were included in the study. Non contrast CT/MRI was done to confirm the presence of ischaemia/infarction, or absence of haemorrhage. All cases of haemorrhagic stroke, cardioembolic stroke, transient ischaemic attack, recurrent stroke, subarachnoid haemorrhage, myocardial infarction, or acute coronary syndromes, brain tumour, major systemic disorders, and malignancy were excluded. Patients having history of recent infection, surgery, and trauma were also excluded. Informed written consents were obtained from all the patients and controls. A detailed clinical examination was done on admission, then on the seventh day of admission, and 3 months after stroke onset. Also, history of diabetes, hypertension, alcohol intake, and smoking was taken to ascertain the presence of any risk factors.

Stroke severity was assessed for each patient at admission and on the seventh day after stroke onset using the NIHSS (National Institute of Health Stroke Severity Scale) score. Stroke severity was categorised as no stroke (NIH = 0), minor stroke (NIH = 1 - 4), moderate stroke (NIH = 5 - 15), moderate/severe stroke (NIH = 15 - 20), severe stroke (NIH = 21 - 42)[14].

Functional disability was evaluated using the mRS (modified Rankin Scale) at day 7 and 3 months of admission[15].

Laboratory investigations

Laboratory investigations were performed within 24 hours of admission. The tests included complete blood count, renal functions (blood urea and serum creatinine) serum electrolytes , serum bilirubin (total, direct, indirect), ESR, lipid profile, blood sugar (random, fasting, and post-prandial) – if required, coagulation profile, high sensitivity C-reactive protein levels, urine (routine and microscopy). CT scan, chest X-ray, ECG were done within 24 hours of presentation. For Hs-CRP estimation, the samples were processed within 60 minutes. The serum was kept in ice (-20° C) till estimation of Hs-CRP solid phase enzyme immunoassay (ELISA method).

Statistical analysis

The correlations between hs-CRP on admission or on seventh day and the prognostic scale for functional disability at seventh day and 3 month after stroke onset was analysed with Spearman's rank order correlation. The correlation between hs-CRP and stroke severity at onset (assessed by NIHSS score) was analysed with Spearman's rank order correlation. A paired 't' test was performed to analyse differences in hs-CRP values on admission and on seventh day after admission. Independent 't' test was used to evaluate differences between hs-CRP levels and each risk factor for ischaemic stroke and to compare the levels of hs-CRP in stroke patients with those of healthy controls.

Results

The study sample comprised 50 patients (n = 50) admitted to the medicine ward who were enrolled in the study after taking informed consent from the patient or family members over a period, i.e., from January 2012 to December 2012. 50 controls from healthy population were also taken during the same period. The majority of our study population (48%) was in the > 60 year age group at presentation (Table I).

There were significant differences between the Hs-CRP levels of the patients (4.185 ± 2.240 mg/dl) and those of healthy controls (0.980 ± 0.337 mg/dl). No significant difference was found between the hs-CRP levels at admission and seventh admission day (p = 0.5252) Table I.

Table I: Baseline characteristics of the study groups.

	Patients with acute stroke	Normal controls
Age d		
≤ 40	12%	12%
41 - 60	40%	44%
> 60	48%	44%
Sex (M/F)	35/15	35/15
Hypertension	46%	None
Diabetes mellitus	26%	None
Smoking	14%	None
Alcohol	10%	None
Hypercholesterolaemia	22%	None
Hs-CRP levels (mean ± SD) at admission*	4.185 ± 2.2400	0.980 ± 0.337
Hs-CRP levels (mean ± SD) at 7th admission day**	4.48 ± 2.357	

**p< 0.001: between patients with stroke and controls;*

***P = 0.5252 between Hs-CRP at admission and 7th admission day.*

Hs-CRP levels at admission were compared between the patients with stroke risk factors and those without risk

factors. hs-CRP levels were not significantly affected by presence of risk factors like age, sex, diabetes mellitus, hypertension, smoking, and alcohol intake and hypercholesterolaemia (Table II).

Table: II: Comparison of hs-CRP (mg/dl) between the patients with stroke risk factors and those without.

	hs-CRP on admission	P value
Age		
≤ 40	3.58 ± 2.52	
41 - 60	4.23 ± 2.07	0.783
> 60	4.29 ± 2.37	
Hypertension (yes/no)	4.538 ± 2.4845/3.885 ± 2.0073	0.309
Diabetes mellitus (yes/no)	5.215 ± 2.5235/3.823 ± 2.0467	0.053
Smoking (yes/no)	5.170 ± 3.2201/4.025 ± 2.0456	0.213
Alcohol (yes/no)	3.262 ± 2.0107/4.288 ± 2.2611	0.336
Hypercholesterolaemia (yes/no)	5.28 ±1.68/3.87 ±2.29	0.064

There was a significant difference in the mean value of the serum hs-CRP in the patients categorised as having minor, moderate, moderate/severe, or severe disease according to the NIHSS (Table III).

Table III: Mean serum hs-CRP values on admission in patients as per NIHSS category on admission.

NIHSS category on admission	Hs-CRP (Mean ± SD)
Minor stroke (1 - 4)	1.92 ± 0.56
Moderate stroke (5 - 15)	3.62 ± 1.61
Moderate/severe stroke (15 - 20)	6.85 ± 1.07
Severe stroke (13 - 42)	9.75 ± 0.35
Total	4.18 ± 2.24
P value (ANOVA)	< 0.001

We also found a significant difference in the mean values of serum hs-CRP and the functional outcome at day 7 and 3 months after the onset of stroke. Patients who obtained high score on mRS at day 7 (poor outcome) showed significantly higher values of mean serum hs-CRP at admission 6.13 ± 1.80 mg/dl when compared with patients with low mRS score (non poor outcome) with mean value 2.65 ± 1.01 mg/dl. Further, on assessing the correlation (ρ) between the values of serum hs-CRP with the functional outcome at day 7, it was found that a strong positive correlation exists between the levels of serum hs-CRP and the mRS score (Table IV).

Similar results were also obtained at a follow-up of 3 months where patients with mRS score > 3 (poor outcome group) had significantly higher serum hs-CRP levels (7.00 ± 1.56 mg/dl at admission) as compared to patients with mRS scores < 4 (3.08 ± 1.31 mg/dl). Spearman's correlation co-efficient (ρ) was found to be positive indicating a direct correlation between serum hs-CRPlevels at admission and mRS score at 3 months of follow-up (Table V).

Table IV: Correlation of hs-CRP at admission and hs-CRP at 7th day of stroke with mRS score (at day 7)

Mean ± standard deviation	Poor outcome (n = 22)	Non poor outcome (n = 28)	Correlation co-efficient (ρ)	P value
hs-CRP at admission	6.13 ± 1.80	2.65 ± 1.01	0.739	< 0.001
hs-CRP at 7th day	7.61 ± 1.45	3.26 ± 1.24	0.790	< 0.001

Table V: Correlation of hs-CRP at admission and hs-CRP at 7th day of stroke with mRS score (at 3month)

Mean ± standard deviation	Poor outcome (n = 14)	Non poor outcome (n = 36)	Correlation co-efficient (ρ)	P value
hs-CRP at admission	7.00 ± 1.56	3.08 ± 1.31	0.746	< 0.001
hs-CRP at 7th day	7.60 ± 1.45	3.26 ± 1.24	0.762	< 0.001

Discussion

Patients with ischaemic stroke were found to have significantly higher levels of hs-CRP than in controls. The mean value for hs-CRP at admission was 4.185 (± 2.2400) mg/dl in patients and 0.980 (± 0.337) mg/dl in control group. The difference in the mean values of serum hs-CRP between the groups was significant (p < 0.001). Patients with stroke had higher mean hs-CRP level at seventh admission day 4.48 (± 2.357) mg/dl than hs-CRP at admission 4.185 (± 2.240) mg/dl.The difference was not statistically significant.

No significant correlation was found between hs-CRP levels and other ischaemic stroke risk factors, including age, sex, hypertension, diabetes mellitus, smoking, alcohol intake, and hypercholesterolaemia in the present study.

Various studies in the literature show results that support our observations. In the Bergen stroke study, Idicula *et al*. reported that higher hs-CRP levels were independently associated with greater admission stroke severity and mortality among patients with ischaemic stroke[16]. In a prospective cohort study comprising 1,462 health examinees, Rost *et al*, reported that 196 patients developed stroke and TIAs. Using Cox proportional hazard models, it was found that participants with a higher level of hs-CRP showed higher relative risk ratios[12]. The data from these studies support the results of our study.

A direct correlation was also found between serum hs-CRP and mRS scores indicating that patients with high levels at admission have higher mRS scores and therefore, poorer outcomes.

Previous studies also reported that in stroke patients the measurement of hs-CRP within 24 hour of stroke symptoms

can be an independent predictor of prognosis. Eikelboom *et al* concluded that hs-CRP levels were most markedly elevated in patients with stroke caused by large-artery disease, which tends to cause larger infarcts and greater disability and they were significantly lower in patients with stroke caused by small-artery disease which cause small infarcts[17]. Winbeck *et al* observed that an increase in CRP level between 12 and 24 hours after the onset of symptoms predicts an unfavourable outcome and is associated with an increase in the incidence of cerebrovascular and cardiovascular events[18].

These findings clearly indicate that levels of serum hs-CRP can be used as markers to predict the long-term prognosis of patients with acute ischaemic stroke. Lower admission levels of serum hs-CRP seem to confer a protective advantage on the long-term outcomes being associated with lower mRS scores indicating a better outcome in these patients. Similarly, patients with higher serum hs-CRP are expected to have higher mRS scores indicating poor long-term outcomes.

Patients with elevated hs-CRP associated with high risk of further vascular events might benefit from an aggressive secondary prevention. There are several non drug interventions to lower CRP. These include weight loss, diet, exercise, and smoking cessation[19,20]. Moreover, some drugs – particularly aspirin[21,22], statin[23,24], and angiotensin-converting enzyme inhibitors – have shown to decrease CRP level[25]. However, there are not enough evidences to support their role in clinical practice. Further trials are needed to determine whether medications can decrease the incidence of stroke in patients with high hs-CRP levels.

Conclusion

High CRP level is associated with stroke severity at admission and is an independent predictor of adverse outcome after ischaemic stroke.

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ORIGINAL ARTICLE

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Usage of platelet transfusions in the medical care setting in a tertiary care hospital

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Abstract

***Background:** Platelet utilisation, during the last two decades, has increased all over the world more than the use of any other blood component. The present study was conducted to study the pattern of usage of platelet transfusion and its appropriateness in the medical care setting of a tertiary care hospital.*

***Methods:** It was a prospective study, conducted at Rajindra Hospital/Govt. Medical College, Patiala between January 2012 and June 2013. One hundred patients receiving platelet concentrate transfusion in the medicine indoor department were evaluated. British Committee for Standards in Haematology guidelines (2003) were used to study the appropriateness of platelet transfusions. Indication of platelet transfusion was recorded for every patient. Pre- and post-transfusion platelet count and Corrected Count Increment (CCI) was calculated for every patient.*

***Results:** Out of 100 patients, 55 (55%) were males and 45 (45%) were females and the median age was 40.48 ± 14.20 years. Out of 100 platelet concentrate transfusion, 39 (39%) transfusions were prophylactic and 61 (61%) were therapeutic. Most common indication for prophylactic transfusion was in patients on chemotherapy (30.76%) and in patients of dengue (30.76%). Out of 39 prophylactic transfusions, 17 (43.58%) were inappropriate. The most common indication of therapeutic transfusion was bleeding in patients of dengue. Single Donor Platelets (SDP) were given to 11 patients only. Platelet refractoriness was not observed in any patient.*

***Conclusion:** There is a need to promote the optimum use of platelet concentrates. The use of SDP platelets also needs to be increased.*

***Keywords:** Appropriate platelet transfusion, therapeutic platelet transfusion, prophylactic platelet transfusion.*

Introduction

Platelets together with the coagulation system, constitutes a major defence against blood loss. Platelets are among the most valuable commodities in transfusion medicine. Platelet use during the last years has increased with the advent of more aggressive chemotherapeutic regimens and bone marrow and haematopoetic progenitor cell transplantation. On one hand, the ready availability of platelet concentrates has undoubtedly made a major contribution to modern clinical practice, but various studies have shown a wide variation in clinical practice in the transfusion of platelets.They showed a significant amount of platelet transfusions outside of recommended guidelines. Therefore this study was conducted to study the pattern of usage of platelet transfusion and their appropriateness in a tertiary care hospital[1].

Material and methods

This study was conducted at the department of Medicine, Rajindra Hospital/Govt. Medical College, Patiala in Punjab between January 2012 and June 2013. The study was conducted on 100 patients in the medicine indoor department. Age, sex and indication of platelet transfusion (haematological vs. non haematological, and prophylactic vs therapeutic) were recorded for every patient. Pre- and post-transfusion platelet count was measured in every patient. Corrected count increment (CCI) was calculated for every patient to assess the presence of platelet refractoriness.

$$CCI = \frac{\text{post-transfusion count} - \text{pre-transfusion count}}{\text{Platelets given} \times 10^{11}} \times \text{body surface area (in } m^2)$$

(platelet count taken as n x 10^9/L).

Platelet refractoriness is defined as CCI < 5 x 10^9 m^2/l at 1 hour and < 2.5 x 10^9 m^2/l at 24 hours post-transfusion.

British Committee for standards in haematology (BCSH) guidelines 2003 were used to assess the appropriateness of platelet transfusion.

BCSH guidelines are as follows[2]:

Indications

Prophylactic

1. Platelet count < 10 x10^9/l without additional risk factors.

   A threshold of 5 x 10^9/l may be appropriate if there are

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concerns that alloimmunisation could lead to platelet refractoriness.

2. Platelet count < 20 x 10^9/l with additional risk factors such as fever, sepsis, concurrent use of antibiotics, on chemo/radiotherapy, other abnormalities of haemostasis.
3. Platelet count < 50 x 10^9/l if patient is undergoing minor invasive procedures , epidural anaesthesia, gastroscopy and biopsy, insertion of indwelling lines, transbronchial biopsy, liver biopsy, etc. It is recommended that bone marrow aspiration and biopsy may be performed in patients with severe thrombocytopenia without platelet support provided that adequate surface pressure is applied.
4. Platelet count < 100 x 10^9/l if patient is undergoing major surgical procedures (especially on critical sites such as brain or eyes).
5. Platelet count < 100 x10^9/l in patients with massive transfusion.

Therapeutic

In any patient who is bleeding and in whom thrombocytopenia is considered a major contributory factor.

In immune thrombocytopenia, platelet transfusion should be reserved for patients with life-threatening bleeding from gastrointestinal or genitourinary tracts, into central nervous system or other sites associated with severe thrombocytopenia[2].

Results

Out of 100 patients, 55 (55%) were males and 45 (45%) were females. The maximum number of patients were in the age group of 41 - 50 years. The mean age was 40.48 ± 14.20 years. Out of 100 patients, 39 received prophylactic transfusion and 61 received therapeutic transfusion. In prophylactic transfusion, the most common indication was thrombocytopenia in patients on chemotherapy and thrombocytopenia in patients of dengue. Out of 39 prophylactic transfusions, 9 (23.09%) were for haematological indications. Out of 9 haematological indications, 2 patients were with pancytopenia, 6 were of CML and 1 was of AML. Pre-transfusion platelet count was recorded for every patient. In patients with prophylactic transfusion, most common platelet count recorded was between 5 x 10^9/l - 10 x 10^9/l. Overall, 22 (56.4%) prophylactic transfusions were appropriate and 17 (43.58%) were inappropriate. 17 inappropriate transfusions are significant (p = 0.02) (Table I).

Out of 61 therapeutic transfusions, the most common indication was bleeding in patients of dengue. The next most common indication was in patients with sepsis with thrombocytopenia and in patients with alcoholic liver disease with cirrhosis. Single donor platelets (SDPs) were used in only 11 transfusions and Random Donor Platelets (RDPs) were used in 89 transfusions. In every patient, CCI calculated was more than 7.5 x 10^9 m^2/l at 1 hour and 2.5 x 10^9 m^2/l at 24 hours. No patient was found to be refractory to platelet transfusion (Table II).

Table I: Pre-transfusion platelet count in appropriate/ inappropriate platelet transfusions.

S. No.	Pre-transfusion platelet count	Number of appropriate transfusions	Number of inappropriate transfusions	p value
1.	1 x 10^9/l - 5 x 10^9/l	5	0	0.02
2.	5 x 10^9/l - 10 x 10^9/l	27	0	(< 0.05)
3.	10 x 10^9/l - 15 x 10^9/l	14	3	Significant
4.	15 x 10^9/l - 20 x 10^9/l	18	6	
5.	20 x 10^9/l - 25 x 10^9/l	7	4	
6.	25 x 10^9/l - 30 x 10^9/l	7	1	
7.	30 x 10^9/l - 35 x 10^9/l	2	1	
8.	35 x 10^9/l - 40 x 10^9/l	2	0	

Table II: Post-transfusion mean CCI in different medical conditions.

Indication	CCI at 1 hour (n x 10^9 m^2/l)	CCI at 24 hours (n x 10^9 m^2/l)
ALD cirrhosis	15.67	13.50
AML	17.33	14.67
CML	17.50	14.62
Pancytopenia	16.14	14.00
Chemotherapy	15.50	12.93
Sepsis	18.00	16.60
Dengue	17.22	14.62
ITP	18.50	16.25
Malaria	16.33	14.00
Cirrhosis	17.00	15.00

Discussion

The use of blood products to support patients undergoing the large variety of medical and surgical interventions has continued to increase very significantly over time. Relevantly, significant practice variation in the use of blood products exists among practitioners and institutions, largely due to lack of robust clinical trial data which are important

for providing practitioners evidence based guidelines for appropriate blood product utilisation[3]. Regular audit of platelet use in hospitals is usually not done according to the standard guidelines.

Over past few decades, use of platelets is continuously increasing. Demand for platelet components continues to increase, raising concern about future shortage in supply of platelets. The use for platelet transfusion is particularly increasing in patients of oncology and haematological indications. In our study, a significant proportion of platelets were administered to patients on chemotherapy and patients with haematological indications. This is similar to the results observed in the study by Saluja *et al*[4] in which the most common indication for prophylactic transfusion was in haemato-oncology.

Overall, 22 (56.41%) prophylactic platelet transfusions were appropriate. In these 22 patients, prophylactic platelet transfusion was given to patients with platelet count < 10 x 10^9/l without any additional risk factor and to patients with platelet count < 20 x 10^9/l, prophylactic transfusion was given in presence of additional risk factors such as fever, sepsis, etc. In our study, 17 (43.58%) prophylactic transfusions were inappropriate . Schofield *et al*[5] reported 29% inappropriate transfusions. In these 17 transfusions, prophylactic platelet transfusions were given at higher platelet count. In comparison to other studies, the percentage of inappropriate transfusion is significantly high. This indicates that the hospital needs to regularly check the transfusion practices so as to reduce the inappropriate use of platelets.

Single donor platelets were used in 11 patients only. In a study by Vipra *et al*[6], all transfusions were with SDPs. The major advantage with apheresis platelets is that enough platelets can be collected from a single donor to constitute the transfusion dose. The reduction in donor exposures by using apheresis platelets has potential advantage of reducing transfusion transmitted infections and the incidence of platelet alloimmunisation. So the use of SDPs need to be increased. CCI should be calculated for every patient receiving platelet transfusion to document platelet refractoriness.

Conclusion

Platelet transfusions are an important therapy and their use will probably continue to increase. Knowledge regarding platelet transfusion guidelines is a must which will go a long way to increase the appropriateness of platelet transfusion.

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"There's no knowledge without right faith,
No conduct is possible without knowledge,
Without conduct, there's no liberation,
And without liberation, no deliverance."

– Mahavira.

ORIGINAL ARTICLE

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Clinical profile of *Plasmodium vivax* malaria

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Abstract

Long considered a benign infection, Plasmodium vivax is now recognised as a cause of severe and fatal malaria despite its low parasitic biomass, the increased deformability of vivax-infected red blood cells, and an apparent paucity of parasite sequestration. Severe malaria due to P. vivax infection is increasingly observed now-a-days with multiple organ failures. In this study we have presented P. vivax clinical profile and compared the risk factors and morality in vivax with falciparum infection.

Material and methods: All acute febrile patients were screened for malaria parasites by peripheral blood smear and rapid diagnosis test (RDT). Patients with co-existent P. vivax and P. falciparum infection were excluded from this study, and detailed history and examination findings were recorded. All of them were subjected to routine haematological, urine, and biochemical investigations with parasite count. All of them were followed till the last, i.e., up to full recovery or death.

Results: 418 cases of malaria from Haldwani, Bareilly, and Gorakhpur were included in this study, of whom 187 of P. vivax and 231 of P. falciparum malaria, 124 cases of P. vivax malaria cases were from Gorakhpur (East UP). Maximum number of cases were seen during wet season, i.e., July to September (54%). During this period they were severe with increased parasitaemia. Amongst 187 cases of P. vivax there were 124 males and 63 females with mean ± SD of 36.2 ± 9.8 years. Typical paroxysm of intermittent fever was seen in 90.9%, continuous fever in 5.3 %, jaundice in 33.1%, hypotension in 14.9% cases. Thrombocytopenia (platelets < 10,000/cu mm) was commonly seen in 58.2% cases of whom 13.9% had platelets < 40,000/cu mm with bleeding manifestation in 9.1 % cases. Other complications seen were hepatic 11.7%, renal 14.4%, cerebral (convulsions 4.8%, coma 2.1%) 6.9% and pulmonary involvement in 3.2% cases. Mortality (8.5%) increased with advancing age (above 50 years 75%) in vivax malaria whereas in falciparum it was 12.5%.

Conclusion: Vivax malaria is now-a-days common with increased mortality which increases with advancing age. Thrombocytopenia is very common in vivax malaria. The renal, hepatic, cerebral involvement occurs with increasing frequency. Advancing age metabolic acidosis parasitaemia and multiorgan failure are the risk factors with fatal outcome.

Key words: Vivax malaria, parasite count, thrombocytopenia, organ failure.

Introduction

Plasmodium vivax malaria, the second major human malaria species constitute about 41% of malaria cases worldwide[1-3]. In India, 60 to 65 % of infections are due to *P. vivax* and 35 % due to *P. falciparum*. Long considered a benign infection, *P. vivax* is now recognised as a cause of severe and fatal malaria despite its low parasite biomass, the increased deformability of vivax-infected red blood cells, and an apparent paucity of parasite sequestration[4]. *P. vivax* malaria transmission is low, but where both *P. falciparum* and *P. vivax* malaria prevail, the incidence rate of *P. vivax* tends to peak – in people of all ages especially the younger age group – than of *P. falciparum*[5].

Among the four species of Plasmodium that affects humans, only *P. vivax* and *P. ovale* have the ability to form trophozoites[6] – parasite stages in the liver that causes relapses. *P. vivax* preferentially invades reticulocytes and this may lead to anaemia. The residual malaria burden of *P. vivax* is underestimated and is increasing in some regions of the world[2]. Various studies have shown a strong association between *P. vivax* infection and severe disease and death. Taking this background, the present study is planned to study the clinical profile of *P. vivax* malaria and compare the risk factors and fatal outcomes with *P. falciparum* cases.

Material and methods

Four hundred eighteen (418) cases of proven *P. vivax* and *P. falciparum* malaria from Haldwani (Uttarakhand), Bareilly (West UP), and Gorakhpur (East UP) were included in this study. All patients of malaria have been screened for species diagnosis and patients with coexistent *P. vivax* and *P. falciparum* infection were excluded from the study. All the cases of acute onset of febrile fever were diagnosed by clinical features supported by peripheral blood film positive for *P. vivax* and *P. falciparum* and/or rapid diagnostic test (RDT) showing evidences of *P. vivax* and *P. falciparum*. All patients underwent optimal malarial antigen test to rule-

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out mixed infection. The parasite count has been made from the peripheral blood smear and expressed as numbers of sexual parasite and gametocyte per microlitre of blood and calculated from the number of parasitised cells per 200 leukocytes in a thick film stained with Giemsa stain, i.e., numbers of parasite x total leucocyte count/200[7,8].

A detailed history was taken and clinical examination was done. Routine haematological tools and screening and/or X-ray chest was also done. Urine was examined in detail with special attention to albuminuria and microscopic examination. Twenty-four hours urine output was noted. Liver and renal function tests were performed. Severe malaria score (MSS) for identifying the prognostic variables and severity of the disease[9].

All patients were managed with antimalarials and supportive measures as per WHO guidelines. Radical treatment was given with primaquine for 14 days. Renal replacement (haemodialysis) therapy was given to clinically and biochemically indicated patients. Patients were followed-up for one month for their outcome.

Observations

Four-hundred eighteen cases of malaria were studied at Haldwani (184 cases), Bareilly (31 cases) and Gorakhpur (203). The onset of malaria cases concentrated in the later part of the summer and rainy season, i.e., July – September (54%) even though sporadic cases were seen throughout the year. Patients coming during the wet season are comparatively severe and serious. Main age group affected was the 3rd (19.6%), 4th (23.2%), and 5th (22.7%) decades of life (mean + SD = 36.9 ± 11.8%) with male: female ratio of 2.1:1 (Table I). *P. falciparum* malaria cases were more from Haldwani (135 or 73.4%) and Bareilly (17 or 54.8%) whereas *P. vivax* were more from Gorakhpur (124 or 61.1%), Fever (96.2%) with headache, bodyache, and prostration (88.2%) was the most common clinical manifestation. Intermittent fever with typical paroxysm of tertian fever was seen in 170 or 90.9% of cases whereas continuous fever was seen in 10 or 5.3% of cases (Table II). Fifteen patients (8.1%) had 2 peaks of typical paroxysm within 24 hrs. In addition to fever and bodyache, patients had nausea and/or vomiting (49.2%), diarrhoea (25.6%), and pain abdomen (19.8%). Thirty-two patients (17.2%) developed dehydration (hypovolaemia) due to nausea, vomiting, and diarrhoea. Amongst the organ specific manifestation were jaundice (62.1 or 33.1%), hepatosplenomegaly (31.5%), and anaemia (58 or 31.1%) followed by renal manifestations in the form of oliguria (31.1%) and anuria (5.3%). Altered consciousness (16.1%) of whom four were in comatose state, convulsions (4.8%) and petechial haemorrhage with bleeding (9.1%) were the serious manifestation. Two patients out of six patients who were in respiratory distress

Table I: Age and sex distribution.

Age group in years	Haldwani (n = 184)						Bareilly (n = 31)						Gorakhpur (n = 203)						Total (n = 418)	
	P. falciparum			*P. vivax*			*P. falciparum*			*P. vivax*			*P. falciparum*			*P. vivax*			No. of cases	%
	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total	M	F	Total		
< 20	7	2	9	3	5	8	-	-	-	1	1	2	4	1	5	9	2	11	35	8.3
21 - 30	26	14	40	4	2	6	2	2	4	2	2	4	8	5	13	9	6	15	82	19.6
31 - 40	20	10	30	6	2	8	3	-	3	2	1	3	12	11	23	16	14	30	97	23.2
41 - 50	24	10	34	11	4	15	3	1	4	1	1	2	12	2	14	17	9	26	95	22.7
51 - 60	10	5	15	4	3	7	3	2	5	-	-	-	8	5	13	16	8	24	64	15.3
61 - 70	3	2	5	3	-	3	1	-	1	2	-	2	6	1	7	13	1	14	32	7.6
> 70	2	-	2	1	1	2	-	-	-	1	-	-	2	2	4	3	1	4	13	3.3
Total	92	43	135	32	17	49	12	5	17	9	5	14	52	27	79	83	41	124	418	100%
%	50.0	24	73.4	17.4	9.2	6.6	38.5	16.1	54.8	29	16.1	45.2	25.6	13.0	38.9	40.7	20.2	61.1	-	-
Age range	14 -71 yrs			18 - 69 yrs			23 - 66 yrs			16 - 68 yrs			12 - 74 yrs			8 - 73 yrs			8 - 74 yrs	
Mean ± SD yrs	34 ± 10.6			43.6 ± 9.8			36.9 ± 8.2			28.6 ± 7.9			38.6 ± 10.6			36.6 ± 11.8			36.9 ± 11.8	
Sex ratio M:F	2.1:1			1.8:1			2.4:1			1.8:1			1.9:1			2.0:1			2.1:1	

revealed bilateral basal pulmonary infiltration in the X-ray chest PA view, and one of them expired (Table III).

Table II: Presenting clinical features.

	Symptoms and signs	*Plasmodium vivax* (n = 187)	
		No. of cases	%
	A. General features		
1. Fever	Intermittent	170	90.9
	Continuous	10	5.3
2. Hypothermia < 36.5° C		2	1.1
3. Headache, bodyache, and prostration		160	88.2
4. Nausea and/or vomiting		92	49.2
5. Pain in abdomen		37	19.8
6. Fainting attacks, vertigo, giddiness		10	5.3
7. Sleep disturbances		6	3.2
8. Dehydration (hypovolaemia)		32	17.2
	B. Systemic features		
1. CNS	Altered consciousness (coma)	30 (4)	16.1
Convulsion		9	4.8
Ataxia		1	0.54
2. Renal	Oliguria < 500 ml/day	58	31.1
	Anuria < 50 ml/day	10	5.3
	Black coloured urine	-	0
3. Gastrointestinal	Diarrhoea	48	25.6
	Jaundice	62	33.1
	Hepatomegaly	30	16.1
	Splenomegaly	15	8.1
	Hepato-splenomegaly	59	31.5
4. Miscellaneous	Petechial spots, mucosal bleeding	17	9.1
	Anaemia	58	31.1
	Oedema over feet and puffiness of face	10	5.3
	Hypotension (BP < 90 mmHg systolic)	28	14.9
	Respiratory distress	6	3.2

Routine laboratory finding revealed (Table III) anaemia (< 10 gm%) in 42 or 21.7% of cases of whom 7 cases had severe anaemia (Hb < 8.0 gm%) (Table III), leukopenia (TLC <4,000/cumm) in 39 or 20.8% cases, and thrombocytopenia (platelets <1,00,000/cumm) in 108 or 60.8% cases, while 26 (13.9%) cases had platelets count less than 40,000/cumm of whom 17 cases or 9.1% manifested bleeding disorder; life-threatening major haemorrhage was not seen. Parasite count of >5,000/cumm was present in 25 (18.4%) cases with mean ± SD 3,820.5 ± 125.52/cumm. Gametocytes were detected in 10 (5.3%) cases with mean ± SD 45.8 ± 128/cu mm. 68 cases (36.4%) showed evidence of renal manifestation in the form of oliguria urine < 500 ml/day in 58 cases (31.1%), and anuria urine <50 ml/day in 10 cases (5.3%). The blood urea was raised (>80 mg%) in 23 cases (14.4%) and serum creatinine (> 3.8 mg %) in 15 cases (8.3%). Proteinuria (>500 mg/day) in 48 cases (24.9%), pus cells (>25/hpf) in 62 cases (33.1%), and RBC (>10/hpf) in 22 cases (11.7%). Acute renal failure (S. creatinine >3.87 mg%) was seen in 15 cases (8.3 mg%). Ten cases were put on haemodialysis and three of them expired.

Table III: Rountine laboratory findings.

	Laboratory findings	*P. vivax* (n = 187)	
1. Haematological		No .of cases	%
Haemoglobin	< 8.0 gm%	7	3.0
	8 - 10 gm%	35	18.7
	10 - 12 gm%	26	13.9
TLC	< 4,000/cumm	39	20.8
	> 10,000/cumm	6	2.6
Platelets	< 40,000/cumm	26	13.9
	40,000 - 50,000/cumm	51	30.4
	50,000 - 1,00,000/cumm	31	16.5
2. Urinary findings			
Sp. gravity	> 1.020	45	24.1
Proteinuria	< 500 mg/day	139	75.1
	> 500 mg/day	48	24.9
Haemoglobinurea		-	-
Haematuria	> 10/hpf	22	11.7
Pus cells	< 25/hpf	62	33.1
	> 25/hpf	115	66.9
Granular cast		2	1.1
Cylindruria		10	5.3
3. Chest X-ray:- Alveolar infiltrates with scattered opacification, no cardiomegaly		2	1.07
4. Parasite count (asexual)		N = 136	
	< 1000/cumm	15	11.0
	1000 - 5000/cumm	96	70.6
	> 5000/cumm	25	18.4
Range/cumm		805 - 9600	
Mean ± SD		3820.5 + 125.5	

Hypoglycaemia with blood sugar < 60 mg% (Table IV) was present in 8 cases (4.2%). The serum transaminases levels (> 2-fold of normal) and serum bilirubin (> 3.0 mg%) were elevated in 25 (13.3 %) and 19 (10.1%) of cases respectively.

Hyponatraemia (≤ 130 meq/l) and hyperkalaemia (> 5.5 meq/l) was observed in 32 (17.1%) and 36 (19.2%) was respectively.

Table IV: Biochemical findings.

Biochemical findings	*P. vivax* (n = 187)	
	No. of cases	%
1. Blood sugar < 60 mg%	8	4.2%
Range	38 - 116 mg%	
Mean ± SD	82.6 ± 9.8	
2. Blood urea > 80 mg%	23	14.4%
Range (mg%)	48.2 - 138.6	
Mean ± SD (mg%)	102.6 ± 10.9	
3. S. creatinine > 3.8 mg%	15	8.3%
Range (mg%)	3.6 - 7.8	
Mean ± SD (mg%)	3.2 ± 2.9	
4. S. bilirubin > 3.0 mg%	19	10.1%
Range (IU)	1.92 - 6.8	
Mean ± SD (IU)	3.62 ± 2.92	
5. SGPT or ALT > 80 (IU)	22	11.7%
Range (IU)	48 - 132	
Mean ± SD (IU)	79.8 ± 35.2	
6. SGOT or AST > 80 (IU)	25	13.5%
Range (IU)	36 - 126.2	
Mean ± SD (IU)	76.2 ± 34.9	
7. S. sodium < 130 mg/l	32	17.1%
Range (mg/l)	102.6 - 146.1	
Mean ISD (mg/l)	119.2 ± 6.8	
8. S. potassium > 5.5 mg/l	36	19.2%
Range (mg/l)	3.2- 7.2	
Mean ± SD (mg/l)	4.9 ± 3.2	

Table V reveals comparative features of severity and risk factors of disease between *P. vivax* and *P. falciparum*. Mortality was more in *P. falciparum* (12.5%) in comparison to *P. vivax* (8.5%), but in both cases it was in the advanced age (> 50 years mean ± SD 59.3 ± 6.82 years). *P. vivax* cases have various complications and even though mortality was high in *Plasmodium falciparum*, certain complications were more in *P. vivax* cases and proved to be fatal, e.g., thrombocytopenia (< 40,000/cumm), serum transaminases (> 2-fold rise), hyperbilirubinaemia, and pulmonary distress. Mortality is supposed to be multifactorial.

Discussion

Vivax malaria is mostly described as a benign disease but there were significantly more cases of vivax malaria reported from Gorakhpur (124 cases or 61.1%). Similarly Kochar *et al*[14] observed 60 - 65% of infection in India due to the *P. vivax,* and 35 - 40% due to *P. falciparum*. Only few cases of *P. malariae* have been reported from Orissa and Karnataka with sufficient deaths and complications. Hence, the present study was undertaken to find out various complications of vivax malaria and to compare them with those of falciparum malaria (Table V). The exact causes of changes in the clinical profile of vivax malaria are uncertain. It may include genetic alteration of the parasite or change in vector and its biting habits, or chloroquine resistance, or increasing use of ACTs[2,11,4].

Table V: Mortality and risk factors in malaria.

Risk factors	Total n = 45		*P. vivax* n = 16		*P. falciparum* n = 29	
	No. of cases	(%)	No. of cases	(%)	No. of cases	(%)
1. Deaths out of 418	45	17.7	16	8.5	29	12.5
2. Age						
> 50 yrs	33	73.3	12	75	21	72.5
Mean ± SD (yrs)	59.3 ± 682		65.8 ± 8.82		60.8 ± 9.24	
< 50 yrs	12	26.7	4	25	8	27.5
Mean ± SD (yrs)	36.6 ± 7.92		35.8 ± 9.2		39.2 ± 7.92	
3. Haemoglobin						
< 8 gm%	20	44.4	5	31.25	15	51.7
> 8 gm%	25	55.6	11	68.75	14	48.3
4. Parasite count						
>5,000/cumm	30	66.6	11	68.75	19	65.5
< 5,000/cumm	15	33.3	5	31.25	7	34.4
5. Platelet count						
< 40,000/cumm	26	57.8	12	75	14	48.3
> 40,000/cumm	19	42.2	4	25	15	51.7
6. SGPT/ALT > 80 IU	32	71.1	13	81.25	19	62.4
7 S. bilirubin > 3 mg%	31	68.8	13	81.25	18	62.06
8. S. creatinine > 3 mg%	30	66.6	10	62.5	20	68.23
9. Cerebral involvement	14	31.1	3	18.75	11	37.9
10. Pulmonary (ARDS)	4	8.8	2	12.5	2	6.9

Mohapatra *et al*[8] reported the geographical heterogenicity and seasonal variation influencing the prevalence of malaria and mixed malaria most commonly seen the in wet season (July-October) than dry season. We have observed the same, even though sporadic cases were seen throughout the year. This variation may be due to relative abundance of the species in the geographical area. This could result from

variation in the presence of mosquito species, which may have species-specific transmission.

Myoung-Don *et al*[12] have observed and described two different patterns of clinical features, depending on the geographical origin of the parasite. As we observed in tropical areas, the clinical attacks occur throughout the year with increased incidence during wet season, i.e., July to October as observed by Mohapatra *et al* too[8]. This could also result from variations in the presence of mosquito species which may have species-specific transmission. Seasonal variation of *P. falciparum*, *P. ovale,* and *P. vivax* had been reported from Malawi and Papua New Guinea[13]. It has been observed that malaria patients attending during the wet season were more likely to develop severe malaria than during other parts of the year[8].

Clinical features revealed the fever to be of intermittent nature with typical paroxysm as described in literature. As we observed this pyrexia was associated with worsening headache (88.2%), malaise, and loss of appetite, nausea and/or vomiting (49.2), diarrhoea (25.6) which leads to dehydration hypovolaemia (17.2%). As infection continues, it will lead to splenomegaly, hepatomegaly and both with anaemia[14/12]. The organ-specific complaints (Table II) are more because of severe malaria with parasite count of more than 5,000/cumm was present in 18.4% (range 805 - 6,800/ cu mm; mean ± SD = 3,820.5 ± 125.5/cumm) and 11% of cases had a parasite count of less than 1,000/cumm. A recent study showed that the optimal test – a dipstick test for the rapid diagnosis of malaria – did not identify blood samples containing parasites at a concentration of <100/ cumm of blood[15].

Anaemia was said to be less common in vivax malaria in comparison to falciparum malaria[11]. Limaye[11] reported anaemia in 3% cases while Tjiha[4] reported anaemia in South-East Asia in 19%. In the present study we have observed haemoglobin less than 10 gm% in 21.3% cases and severe anaemia (Hb < 8.0 gm%) in 3.0% of cases. Anaemia in vivax malaria is said to be due to recurrent bouts of haemolysis of predominantly uninfected erythrocytes with increased fragility[16].

The incidence of leucopenia (TLC <4,000/cumm) in the present series of cases (20.8%) was similar as reported in other studies[11,18,19]. This leucopenia is due to the localisation of leukocytes away from peripheral blood to spleen and other marginal pools rather than actual depletion or stasis. This is said to be a transient finding.

Thrombocytopenia (platelets < 1,00,000/cu mm) was a frequent finding as much as it was present in 85.1% cases[11,12]. We have observed thrombocytopenia in 60.8%, and 13.9% of cases revealed a platelet count less than 40,000/cumm. It resulted in bleeding presenting as petechial spots and mucosal bleeding in 9.1% of cases. Life-threatening major haemorrhage was not seen. The mechanism of thrombocytopenia is poorly understood but recent studies have suggested that elevated levels of platelet-associated immunoglobulin G and macrophage colony-stimulating factor may be responsible for it[12].

The mechanism of organ involvement in vivax malaria is debatable. Enhanced inflammatory responses as well as the sequestration of parasitised red cells in microcirculation were thought to be the possible mechanisms[10,11]. A strong linear trend exists between increased levels of C-reactive protein, TNF-alpha, IFN-gamma, IFN-gamma/IL-10 and severity of vivax malaria. TNF-alpha are found to be higher in vivax malaria as compared to falciparum malaria with a similar degree of parasitaemia[11,20,21]. Respiratory distress (ARDS) was seen in 6 cases (2.1%) and two of them revealed alveolar infiltrates with scattered tiny opacities. This is said to be due to possibility of pulmonary inflammatory response to parasite killing[21]. Thus the inflammatory and immunological response plays a significant role in the pathophysiology of severe vivax malaria. The symptoms developed after the commencement of antimalarial therapy. Lung injury is associated with the inflammatory increase in alveolar capillary membrane permeability[21].

Jaundice as seen in 33.1% of cases is the way of presentation of hepatic dysfunction which is associated with conjugated or unconjugated hyperbilirubinaemia and elevated serum transaminases (Table IV). Mild jaundice (22.9%) may be due to haemolysis with serum bilirubin up to 5 mg% but high levels (S. bilirubin >5 mg%) can only be due to associated hepatocyte dysfunction. As per the WHO (2000), the signs of hepatic dysfunction are unusual, but a study from North-west India reported the evidence of hepatic encephalopathy in 15 cases. Kocher *et al*[14,22] in histopathological examination of 20 cases, revealed swollen hepatocytes (100%), malarial pigment deposition (75%), inflammatory infiltrates (60%), congestion of hepatocyte (50%), along with centrizonal necrosis in 25% of cases. Usually this hepatic dysfunction returns to normal baseline with appropriate treatment within 2 - 3 weeks, whereas the same phenomenon in viral hepatitis takes 6 - 8 weeks.

We have observed the CNS involvement in 21.4% or 40 cases in the form of altered consciousness in 16.1% of cases with comatose stage in 4 cases, convulsions in 9 (4.8%) cases and ataxia in one patient. *P. vivax* malaria is said to be more common in India (60 - 70%) and is an important cause of morbidity. The same pathogenesis of both sequestration related and non-sequestration related complications[23,22,14]. This leads to cerebral malaria and presents as acute febrile encephalopathy, convulsions, and coma. It may even cause status epilepticus.

Malaria is a parasitic disease of great epidemiological importance in the tropics, and malarial acute renal failure (ARF) is emerging as a big nephrological issue. ARF occurs commonly in *P. falciparum* malaria[24,11,4] but now-a-days it is also seen in *P. vivax* malaria. Most cases are oliguric, hypercatabolic, and associated with other complications, probably depending on the relative impact of different pathogenic mechanism. Jaundice, haemolysis, thrombocytopenia, and hypotension are commonly associated with malarial ARF[24,25]. Jaundice was seen in 33.1% with serum bilirubin > 3.0 mg% in 10.1% cases and hypotension BP < 90 mmHg (systolic) in 14.9% of cases. Mehta *et al*[26] has reported ARF in 16, 3, and 5 patients of *P. falciparum*, *P. vivax* and mixed infections respectively from Mumbai, and malaria causing ARF continues to be one of the leading cause of ARF in South-East Asia, Vietnam, India, and Africa[24,25]. Possible mechanism will be stickiness of parasitised cells which tend to adhere to adjacent RBCs, platelets, and capillary endothelium. This results in the formation of intravascular rosettes and clumps that can impede the microcirculation of internal organs. The endothelial cytoadherance, sequestration, increases whole blood viscosity and capillary lumen obstruction by sticky cell aggregates which together contribute to renal ischaemia and acute renal failure[25,24,14,11]. Acute tubular necrosis due to renal ischaemia is the predominant mechanism. Table V gives the comparative figures of mortality and risk factors in *P. vivax* and *P. falciparum* malaria. Mortality of vivax malaria (8.5%) was less than falciparum malaria (12.5%). Mortality in vivax malaria increased with age in both vivax and falciparum malaria. In both cases, 75% of deaths were above 50 years of age. The same has been reported by Nadkar *et al*[5] and Limaye *et al*[11,8]. A large multicentric treatment trial conducted in Asia concluded that the presenting syndrome in severe malaria depends on age, and age is an independent risk factor for a fatal outcome of the disease[4,26]. The severity of the disease and mortality is due to multiorgan failure. Higher risk factors in vivax malaria in comparison to falciparum malaria was parasitaemia , thrombocytopenia, hepatic, renal, and pulmonary involvement which has been cited in Indian studies[4,11,14, 24-26].

Conclusion

The essential feature of severe malaria is sequestration of erythrocytes that contain mature forms of the parasites in the deep vascular beds of the vital organs thus producing various complications. However, severe anaemia and thrombocytopenia that causes bleeding diasthesis is produced by haemolysis, reduced red blood cell deformity of parasitised and non parasitised RBCs, increased splenic clearance, reduction in platelets survival, decreased platelets production, and increased splenic uptake of platelets can be produced by *P. vivax* and *P. falciparum* infection. Severe vivax malaria is very common with increasing mortality. Patients of vivax malaria should be monitored more consciously for occurrence of different complications as their early detection and treatment or referral to a higher centre can be life-saving. The mortality in *Plasmodium vivax* malaria increases with increasing age. Thrombocytopenia and anaemia are common in severe vivax infection. Renal, hepatic, lung, and cerebral involvement also occur with increasing frequency.

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ORIGINAL ARTICLE

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Study of the left ventricular systolic and diastolic functions in cases of non alcoholic fatty liver disease by echocardiography

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Abstract

***Background:** NAFLD is the hepatic manifestation of metabolic syndrome and is usually associated with obesity, diabetes, dyslipidaemia, and insulin resistance. Studies show that metabolic syndrome is associated with increased cardiovascular morbidity and mortality.*

***Objective:** This study was performed to evaluate the left ventricular systolic and diastolic functions in normotensive and non diabetic patients with NAFLD by various echocardiographic parameters and to find out the correlation between different grades of fatty liver and insulin sensitivity.*

***Methods:** In this cross-sectional prospective study, carried out at VMMC and Safdarjung Hospital, New Delhi, 35 non diabetic, normotensive NAFLD patients and 35 controls in the age group of 25 - 60 years were studied and they underwent 2D echocardiography to study myocardial performance index, tissue Doppler imaging (E/E') and left atrial volume index. The grades of NAFLD were correlated with echocardiographic parameters of systolic and diastolic functions. The association of insulin sensitivity (as estimated by QUICK index) with these echocardiographic parameters was also studied.*

***Results:** The percentage of NAFLD cases with abnormal left atrial volume index was significantly higher, 11.4% compared to control group 0% (p value = 0.039).*

The percentage of subjects with abnormal E/E' in cases group was 37.1% and in the control group was 22.9%. 48.6% of cases had abnormal value of myocardial performance index while only 40% of controls had abnormal value of myocardial performance index. 28.6% of cases had an abnormal ejection fraction while only 11.4% of controls had an abnormal ejection fraction. 14.3% of cases had abnormal value of left ventricular mass index while only 5.7% of control group had abnormal values. None of the control subjects had abnormal value of insulin sensitivity index while 37.1% of NAFLD cases had abnormal value of insulin sensitivity index suggesting evidence of insulin resistance among the NAFLD cases, P < 0.001. These parameters also correlated with grades of fatty liver, though these results were not statistically significant. These parameters also showed a significant negative correlation with insulin sensitivity index, (P < 0.001).

***Conclusion:** NAFLD causes subtle changes in left ventricular systolic and diastolic functions and tissue Doppler imaging, myocardial performance index, and left atrial volume index are very sensitive methods to pick up these subtle changes and are superior to conventional echcocardiography.*

***Key words:** NAFLD, metabolic syndrome, myocardial performance index, tissue Doppler imaging (E/E'), left atrial volume index, left ventricular mass index, insulin sensitivity (QUICK index).*

Introduction

Non Alcoholic Fatty Liver Disease (NAFLD) is defined as fat accumulation exceeding 5% to 10% by the weight of liver[1]. NAFLD is the commonest cause of chronic liver disease and is associated with significant liver related morbidity and mortality in population-based studies. NAFLD is the hepatic manifestation of metabolic syndrome. Metabolic syndrome is associated with increased cardiovascular morbidity and mortality[2,3]. Insulin resistance is the key factor of Metabolic Syndrome implicated in development of non alcoholic fatty liver disease. Pathological picture of non alcoholic fatty liver disease, ranging from simple steatosis to steatohepatitis, advanced fibrosis and cirrhosis. NAFLD is associated with obesity, type 2 diabetes mellitus, dyslipidaemia, and hypertension. Each of these abnormalities carries a cardiovascular risk and together they are often characterised as the Insulin resistance syndrome[4].

Given that glucose intolerance and insulin resistance precede the development of overt diabetes, these factors could be associated with abnormal myocardial performance. Recent studies have demonstrated high prevalence of left ventricular remodelling and diastolic dysfunction in patients with metabolic syndrome. However, most of these studies included patients with obesity and/or hypertension which are independent risk factors for diastolic dysfunction. Currently there is scarce data on alteration in LV structure and function in non diabetic, normotensive patients with metabolic syndrome. Fotbolcu *et al*[1] had shown impaired

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LV systolic and diastolic functions in cases with NAFLD subjects from Turkey. In this study, we planned to investigate the LV systolic and diastolic functions with echocardiography in normotensive, non diabetic patients with NAFLD in Indian subjects.

Material and methods

A cross-sectional prospective study was conducted at VMMC and Safdarjung Hospital medicine and cardiology department. 35 non diabetic, normotensive NAFLD patients and 35 controls in the age group of 25 - 60 years were studied. NAFLD was defined as a patient with or without otherwise unexplained AST and ALT elevation at least 1.5 times above upper border of normal and in whom hepatic imaging results were compatible with fatty liver and when other likely causes of liver disease and particularly significant alcohol intake (> 140 g weekly in men and > 70 g weekly in women) had been rigorously excluded. Fatty liver was diagnosed on basis of USG and was given graded I, II, or III. Patients with alcoholic liver disease, hepatitis B, hepatitis C, acute fatty liver of pregnancy, intake of drugs such as amiodarone, methotrexate, diltiazem, expired tetracycline, HAART, tamoxifen, glucocorticoids, inflammatory bowel disease, environmental poisons like phosphorous, mushroom poisoning, HIV, total parenteral nutrition, and patients having gastric bypass, jejuno-ileal bypass surgeries, known cardiac disease and other known metabolic and endocrine disorders known to cause NAFLD were excluded from the study. Detailed physical examination was carried out and lab investigations like liver function tests, fasting and 2-hour post-prandial blood sugar, HBsAg and anti-HCV antibody, HbA_1C, insulin sensitivity index (QUICK index) were done. Echocardiographic and Doppler assessments were performed by 2.5 MHz phased array transducer. Myocardial performance index was calculated as the sum of isovolumetric contraction time (IVCT) and relaxation (IVRT) divided by ejection time (ET)[5], ejection fraction was calculated as (LV end diastolic volume-LV end systolic volume)/LV end diastolic volume, left atrial volume index was calculated as left atrial volume = 0.85 x left atrial area length1x left atria area length 2/shortest left atrial length, left atrial volume index = left atrial volume/BSA[6], left ventricular mass index was calculated as left ventricular mass index (g/m^2) = {1.04 x [(IVST + LVID + PWT)^3 – LVID] - 14 g}/BSA(IVST-interventricular septum thickness, LVID-left ventricular internal diameter, PWT-posterior wall thickness, all measured during diastole) (formula of TROY)[7]. The quantitative insulin sensitivity check index (QUICK index) was calculated by estimating inverse of the sum of the logarithms of the fasting insulin and fasting glucose by using this formula 1/(log {fasting insulin μU/mL} + log {fasting glucose mg/dl})[8]. Statistical significance of the quantitative variables for comparing the NAFLD (cases) and the control group (healthy), the unpaired student t test was used. Statistical significance of the qualitative variable was assessed by chi square test. $P < 0.05$ was taken as a level of significance. Pearson co-efficient was applied to calculate the correlation of echocardiography parameters with insulin sensitivity index and with grades of fatty liver. The data was analysed by using SPSS statistical software version 16.1.

Results

Out of the 70 subjects, 35 (50%) were NAFLD cases and 35 (50%) were controls. Out of the 35 NAFLD cases, 12 (34.3%) were in grade I, 12 (34.3%) were in grade II and 11 (31.4%) were in grade III. Mean age among controls was 42.08 ± 10.19 years. Among the various grades of fatty liver, the mean age was 41.92 ± 13.13 years, 37.08 ± 12.49 years and 46.09 ± 12.14 years among grade I, grade II and grade III respectively. Among the subjects 43 (61.4%) were males and 27 (38.6%) were females. Among the different grades of fatty liver grade I consisted of 10 males and 2 females, grade II consisted of 7 males and 5 females and grade III consisted of 5 males and 6 females.

The minimum value of QUICK index among NAFLD cases was 0.299 and maximum value was 0.472. The minimum value among controls was 0.339 and maximum value was 0.411. The mean value of QUICK index among NAFLD cases was 0.37640 while it was 0.37440 among controls.

The percentage of subjects with abnormal QUICK index in NAFLD cases was 37.1% and in the control group was 0% and this difference was statistically significant, p value < 0.001 (Table I).

Table I: Distribution of insulin sensitivity index among cases and controls.

	Insulin sensitivity index (QUICK Index)	
	Normal QUICK index	**Abnormal QUICK index**
NAFLD cases	22 (62.9%)	13 (37.1%)
Control	35 (100%)	0 (0%)

The percentage of subjects with abnormal left atrial volume index in NAFLD cases was 11.4% and in the control group was 0%, and this difference was statistically significant, p value = 0.039 (Table II).

The percentage of subjects with abnormal E/E′ in NAFLD cases was 37.1% and in the control group was 22.9% but this difference was not statistically significant, p value = 0.192 (Table III).

In this study, the Pearson correlation between QUICK index and ejection fraction was positive that means: as insulin sensitivity decreases ejection fraction also declines. The

value of Pearson correlation came out to be 0.750 and it was statistically significant as denoted by a p value of < 0.001. When we compared this correlation of QUICK index with different grades of fatty liver we found that in grade I fatty liver cases the Pearson correlation was 0.534 but was not statistically significant as denoted by p value of 0.073 but in grade II cases, Pearson correlation was 0.872 and was statistically significant as denoted by p value of < 0.001. This correlation showed the same trend in grade III cases where Pearson correlation was 0.778 and was again statistically significant with p value of 0.005 (Table IV).

Table II: Distribution of left atrial volume index among cases and controls.

	Left atrial volume index	
	Normal LAVI	**Abnormal LAVI**
NAFLD cases	31 (88.6%)	4 (11.4%)
Control	35 (100%)	0 (0%)

Table III: Distribution of E/E' among cases and controls.

	Tisssue Doppler imaging E/E'	
	Normal E/E'	**Abnormal E/E'**
NAFLD cases	22 (62.9%)	13 (37.1%)
Control	27 (77.9%)	8 (22.9%)

In this study, the Pearson correlation between QUICK index and myocardial performance index was negative that means as insulin sensitivity decreases myocardial performance index increases. The value of Pearson correlation came out to be -0.925 and it was statistically significant as denoted by a p value of < 0.001. When we compared this correlation of QUICK index with different grades of fatty liver we found that in grade I fatty liver cases the Pearson correlation was -0.919 and it was statistically significant as denoted by p value of < 0.001. Similarly, in grade II cases, Pearson correlation was -0.938 and was statistically significant as denoted by p value of < 0.001. This correlation showed the same trend in grade III cases where Pearson correlation was -0.906 and was again statistically significant with p value of < 0.001 (Table IV).

In this study, the Pearson correlation between QUICK index and left atrial volume index was -0.782 and it was statistically significant as denoted by a p value of < 0.001. When we compared this correlation of QUICK index with different grades of fatty liver we found that in grade I fatty liver cases the Pearson correlation was -0.743 and it was statistically significant as denoted by p value of 0.006. Similarly, in grade II cases Pearson correlation was -0.840 and was statistically significant as denoted by p value of < 0.001. This correlation showed the same trend in grade III cases where Pearson correlation was -0.749 and was again statistically significant with p value of 0.008 (Table IV).

In this study, the Pearson correlation between QUICK index and left ventricular mass index was -0.671 and it was statistically significant as denoted by a p value of < 0.001. When we compared this correlation of QUICK index with different grades of fatty liver, we found that in grade I fatty liver cases the Pearson correlation was -0.566 and it was statistically significant as denoted by a borderline significant p value of 0.055. Similarly, in grade II cases, Pearson correlation was -0.581 and was statistically significant as denoted by p value of 0.048. This correlation showed the same trend in grade III cases where Pearson correlation was -0.792 and was again statistically significant with p value of 0.004 (Table IV).

In this study, the Pearson correlation between QUICK index and E/E' was -0.846 and it was statistically significant as denoted by a p value of < 0.001. When we compared this correlation of QUICK index with different grades of fatty liver, we found that in grade I fatty liver cases the Pearson correlation was -0.923 and it was statistically significant as denoted by p value of < 0.001. similarly, in grade II cases Pearson correlation was -0.778 and was statistically significant as denoted by p value of 0.003. This correlation showed the same trend in grade III cases where Pearson correlation was -0.860 and was again statistically significant with p value of 0.001 (Table IV).

Discussion

The initial reports of the association between NAFLD and

Table IV: Correlation between insulin sensitivity index and various echocardiographic parameters among all cases and also among various grades of fatty liver disease.

	EF		MPI		LAVI		LVMI		E/E'	
	Pearson	**p**	**Pearson**	**P**	**Pearson**	**p**	**Pearson**	**p**	**Pearson**	**p**
All cases	.750	<.001	-.925	<.001	-.782	<.001	-.671	<.001	-.846	<.001
Grade I	.534	.073	-.919	<.001	-.743	.006	-.566	.055	-.923	<.001
Grade II	.872	<.001	-.938	<.001	-.840	.001	-.581	.048	-778	.003
Grade III	.778	.005	-.906	<.001	-.749	.008	-.792	.004	-.860	.001

various surrogate markers for cardiovascular disease suggest that NAFLD may be a marker of cardiovascular disease. Recent studies have demonstrated high prevalence of left ventricular remodelling and diastolic dysfunction in patients with metabolic syndrome.

Ejection fraction was decreased among NAFLD patients as compared to healthy controls. Ejection fraction was lower among the NAFLD patients though it was not statistically significant as denoted by p value of 0.073. As we move from grade I to grade III, more and more patients have abnormally decreased ejection fraction, though this result was not statistically significant. As the insulin sensitivity decreases, ejection fraction also declines, $P < 0.001$.

Ejection fraction is an indicator of systolic function of left ventricle but it is not a sensitive indicator of early systolic dysfunction and cannot detect smaller differences among the groups.

Myocardial performance index was increased among NAFLD patients suggesting decreased systolic function, though it was not statistically significant as denoted by p value of 0.470. Myocardial performance index correlated with grades of fatty liver. As the grade of fatty liver increases, more and more patients have abnormally high value of myocardial performance index, though this result was not statistically significant. Myocardial performance index shows a significant negative correlation with insulin sensitivity index, $P < 0.001$. MPI is considered to be the sum of an index reflecting systolic function and an index reflecting diastolic function. MPI has previously been shown to be a sensitive indicator for symptomatic heart failure.

Left atrial volume index was higher among the NAFLD patients, and this difference was statistically significant as denoted by a p value of 0.039. Left atrial volume index has been suggested as a marker of the severity and duration of diastolic dysfunction. It is a sensitive indicator for elevation of filling pressures, and atrial remodelling from chronic pressure overload. LA dilatation provides prognostic information even in subjects with normal LVEF.

Left ventricular mass index was higher among the NAFLD group but this difference was statistically insignificant as denoted by a p value of 0.373. In patients with hepatic steatosis, abnormalities in myocardium may precede functional and structural cardiac remodelling, leading to increased LV mass and diastolic dysfunction. In addition, fasting plasma insulin has been found to be the strongest independent predictor of LV Mass.

E/E′ was higher among the NAFLD group but this difference was not statistically significant as denoted by a p value of 0.192. E/E2 ratio is used as the initial measurement for estimation of LV filling pressures, particularly in those patients with preserved systolic function. TDI has been applied to several subsets of patients to show a correlation with systolic and diastolic cardiac function. (E/E2) has been proposed as a tool for assessing LV filling pressures and myocardial relaxation. TDI parameter shows better linear correlation with diastolic parameters and provides a simple means of diagnosing diastolic dysfunction.

Left atrial volume index, left ventricular mass index and E/E′ were increased among NAFLD patients suggesting diminished diastolic function. Left atrial volume index, left ventricular mass index and E/E′ correlated with grades of fatty liver, though these results were not statistically significant. Left atrial volume index, left ventricular mass index and E/E′ showed a significant negative correlation with insulin sensitivity index, $P < 0.001$. E/E′ showed a trend towards higher values in NAFLD although it was not significant in other studies done previously. E/E′ is higher in NAFLD although it was still in the normal to borderline range.

None of the control subjects had abnormal value of insulin sensitivity index, while 37.1% of NAFLD cases had abnormal value of insulin sensitivity index suggesting evidence of insulin resistance among the NAFLD cases, $P < 0.001$. The mean value of insulin sensitivity index decreases as we move up in the grade of fatty liver suggesting increasing insulin resistance as grade of fatty liver increases.

Conclusion

Our findings not only confirm the findings of prior research that NAFLD subjects have reduced left ventricular systolic and diastolic functions, but also suggest that the underlying mechanism for this dysfunction could be insulin resistance as shown by abnormal value of insulin sensitivity index in our NAFLD patients. We have also established in our study that these echocardiographic parameters of systolic and diastolic function correlate with the grade of fatty liver but this finding needs to be confirmed by longitudinal studies as currently there is no data available which correlates the echocardiographic parameters with grades of fatty liver. Thus, we can conclude that NAFLD causes subtle changes in left ventricular systolic and diastolic functions and that tissue Doppler imaging, myocardial performance index, and left atrial volume index are very sensitive methods to pick up these subtle changes, and are superior to conventional echcocardiography.

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"There are no nations, there is only humanity.
And if we don't come to understand that right soon,
there will be no nations,
because there will be no humanity."

– ISAAC ASIMOV.

ORIGINAL ARTICLE

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A prospective observational study of the disease profile of the Muslim patients attending the out-patient department of internal medicine during the Ramadan fasting season

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Abstract

***Background:** Ramadan is the fasting month of the muslim calendar. There is a paucity of data on the prevalence of morbidity among those who visit the out-patient department of the hospital while observing the Ramadan fasting.*

***Materials and methods:** The clinical profile of the 61 muslim patients who visited the out-patient department of internal medicine of the speciality hospital during the holy Ramadan fasting season at Moodabidri, Karnataka, South India was collected. The diagnosis of all the medical conditions was classified according to the International Classification of Diseases (ICD-10) coding system, and the demographic profile and clinical data were analysed.*

***Results:** It was observed that the majority of the patients were females, n = 38 (61.7%), and most of them, n = 24, (63.15%) belonged to the age group of 50 years and above. The diseases of the respiratory system (J00-J99) were found to be the most common (n = 25, 40.32%) and the diseases of the digestive system (K00-K93) (n = 11, 17.74) were the second. Three most prevalent specific diseases for the entire study population as per the age and gender were Lower Respiratory Tract Infection ([LRTI] [J22]) (n = 15, 24.19%) as the most common medical condition, followed dyspepsia (K30) (n = 10, 16.12%), and Bronchial Asthma (J45) (n = 5, 8.06%).*

***Conclusions:** This study emphasises the need for a large global multi-centre prospective study of the patients while observing Ramadan fasting, with a hope of getting the right insight into the various modern problems faced by the human race, especially diabetes, metabolic syndrome, dyslipidaemia, obesity, and systemic hypertension.*

***Key words:** Ramadan fasting, out-patient department, prevalence of disease, muslim patients.*

Introduction

Ramadan is the fasting month of the muslim calendar. Ramadan takes place once a year and lasts for one month. Fasting during the month of ramadan is one of the five holy pillars in the Islamic faith and is an obligation for all its followers. During this holy month, healthy adult muslims are required to abstain from eating, drinking, and from any sexual activity between dawn and sunset, in an effort to achieve better self control. The feeding and water intakes take place from sunset to dawn. There are drastic changes in the type, timing of food intake, and great disruption in the sleep pattern and so on. Studies have shown that the disruption in feeding and sleep schedules can adversely affect the health by changes in the stress system, immunological system, and the circadian rhythm[1,2]. During these fasting days, few diseases can flare up and few others can go into remission[2]. There is very little data on the prevalence of morbidity among those who visit the out-patient department of the hospital while observing the Ramadan fasting. People generally try to avoid seeking medical advice and try to postpone their hospital visit during the fasting season with fear of disruption of their religious rituals while following the medical advice. Over here, we have made an effort to study the disease pattern among the muslim patients visiting the out-patient department of internal medicine of our hospital during the Ramadan fasting season.

Materials and methods

Aims and objectives

To study the clinical profile of the muslim patients visiting the out-patient department of the internal medicine of a speciality hospital during the holy Ramadan fasting season at Moodabidri, Karnataka, South India.

Inclusion criteria

1. All age groups
2. Both sexes
3. Muslim patients who are observing the Ramadan fasting

Exclusion criteria

1. Muslim patients who are not observing the Ramadan fasting

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2. Muslim patients who are reporting to the emergency department of the hospital

Study design

All the patients reporting to the out-patient of the department of internal medicine of Alva's health centre, Moodabidri, South India, who met the inclusion and exclusion criteria were included in the study. The study period was from 10th July 2013 to 7th August 2013 (Ramadan fasting days followed at Moodabidri, South India).

A total of 61 patients were included in the study. Demographic data like age, sex of the patients were noted. A detailed medical history was taken followed by detailed clinical examination which included the general physical and systemic examination. This was followed by relevant investigations like haematological parameters, metabolic work-up, chest X-ray, ECG, etc., as required for the diagnosis of the clinical problem. The diagnosis of all the medical conditions was made by the physician and these were classified according to International Classification of Diseases (ICD-10) coding system. The patients who presented with more than one medical condition were included in the tabulation of each of the diseases with which they presented.

Results

A total of 61 patients were enrolled in the study after following the inclusion and exclusion criteria. One patient was found to be having two disease conditions and was included under both disease categories in the study. The demographic profile of the patients studied is presented in Table I and Fig.1 as per age and gender. It was observed that the majority of the patients were females, n = 38 (61.7%) and most of them, n = 24, (63.15%) belonged to the age group of 50 years and above. Similar observation was found among the male patients, [n = 24 (38.7%)] and majority of them, [n = 11, (45.83%)] belonged to the age group of 50 years and above. Thus, a total of 35 patients (56.45%) were found, belonging to the age group of 50 years and above. However, this data was found statistically not significant.

Table I: Demographic profile of the patients studied.

Age group	Frequency (n = 62)	Males (n = 24,38.7%)	Females (n = 38,61.7%)	P value
10 - 29 years	14 (22.58%)	05 (20.83%)	09 (23.68%)	(X2 = 3.69
30 - 49 years	13 (20.96%)	08 (33.33%)	05 (13.15%)	p = 0.158)
50+	35 (56.45%)	11 (45.83%)	24 (63.15%)	NS

The prevalence of the major disease categories among the study population as per the International classification of diseases (ICD-10) categories is presented overall and for

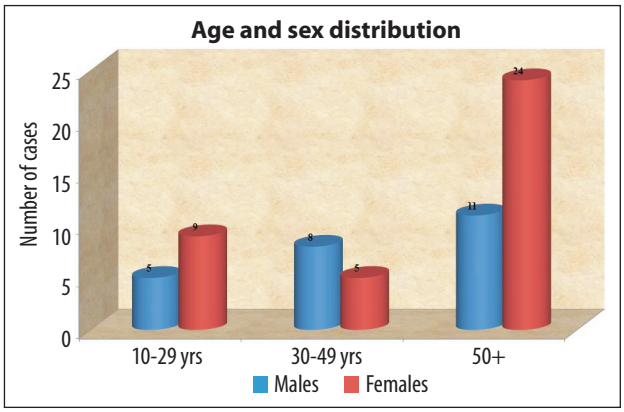

Fig. 1: *Showing demographic profile of the patients studied.*

males and females separately in the Table II and Fig. 4. The diseases of the respiratory system (J00-J99) were found to be the most common (n = 25, 40.32%) when compared to any other disease among the patients studied. Diseases of the digestive system (K00-K93) were the second most common disease group (n = 11, 17.74%). Diseases of the respiratory system were also the most common disease category (n = 19, 50%) among the female patients. Whereas, it was the diseases of the digestive system, which were found to be the most common (n = 8, 33.33%) among the male patients. All these data were found to be statistically significant (p = 0.05, p = 0.0187).

Table II along with Fig. 2 and Fig. 3 presents three most prevalent specific diseases for the entire study population as per the age and gender. Lower respiratory tract infection (LRTI) (J22) was found to be the most common medical condition (n = 15, 24.19%) in the Ramadan study population. Dyspepsia (K30) ranked second (n = 10, 16.12%) and bronchial asthma (J45) was the third (n = 5, 8.06%) most common condition. Dyspepsia was found to be the most prevalent medical condition (n = 08, 33.33%) among

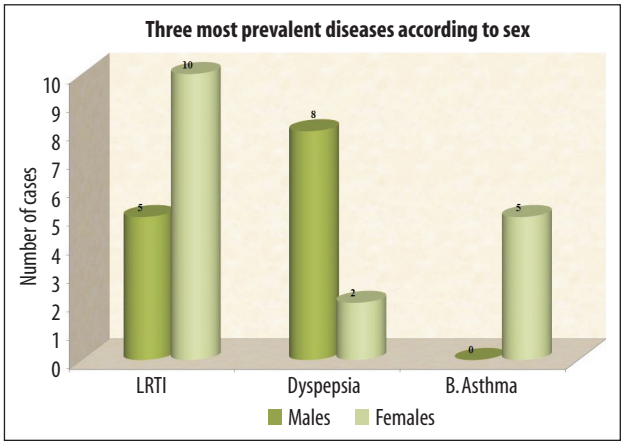

Fig. 2: *Showing the three most prevalent diseases according to sex,*

Table II: Prevalence of the disease categories among the patients.

S. No.	Disease category	ICD no	Total frequeny (n = 62)		Males (n = 24)		Female (n = 38)		p value
			Frequency	Prevalence (%)	Frequency	Prevalence (%)	Frequency	Prevalence (%)	
1.	Diseases of the respiratory system	J00-J99	25	(40.32%)	6	25	19	50	00.05 sig
2.	Diseases of the digestive system	K00-K93	11	(17.74%)	8	33.33	3	7.89	0.0187sig
3.	Endocrine, metabolic, nutritional diseases	E00-E90	8	(12.90%)	3	12.5	5	13.15	0.994 ns
4.	Diseases of the musculoskeletal system and connective tissues	M00-M99	3	(4.83%)	2	8.33	1	2.63	0.3080 ns
5.	Diseases of the circulatory system	I00-I99	3	(4.83%)	1	4.16	2	5.26	0.8446 ns
6.	Diseases of the genitourinary system	N00-N99	3	(4.83%)	2	8.33	1	2.63	0.308 ns
7.	Infective and parasitic disease	A00-B99	1	(1.61%)	1	4.16	0	0	
8.	Mental disorders	F00-F99	2	(3.22%)	0	0	2	5.26	
9.	Diseases of the nervous system and sense organs	G00-G99	2	(3.22%)	1	4.16	1	2.63	
10.	Diseases of the skin and subcutaneous tissues	L00-L99	1	(1.61%)	0	0	1	2.63	
11.	Others		3	(4.83%)	0	0	3	7.89	1.1542 ns

Table III: Three most prevalent diseases according to age and sex.

S. No.	Disease	ICD no	Total frequency	Male	Female	10 - 29 years		30 - 49 years		50+	
				(n = 24)	(n = 38)	M	F	M	F	M	F
1.	LRTI	J22	15 (24.19%)	05 (20.83%)	10 (26.31%)	01	00	02	01	02	09
2.	Dyspepsia	K30	10 (16.12%)	08 (33.33%)	02 (5.26%)	01	01	03	00	04	01
3.	Bronchial asthma	J45	05 (8.06%)	00 (00)	05	00	00	00	02	00	03

P value $x^2 = 9.907$ $p = 0.007$ *hs*

the males, and the lower respiratory tract infection was found to be the most common medical problem (n = 10, 26.3%) among the females. The third most common disease condition was bronchial asthma (J45) and it was observed only among the female patients in our study.

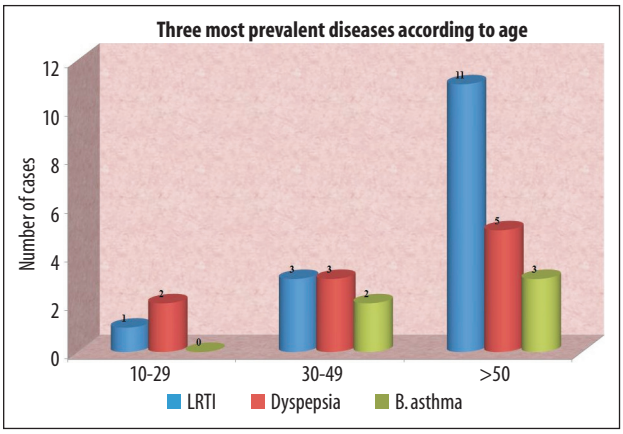

Fig. 3: *Showing three most prevalent diseases according to age.*

Further, all the three most prevalent disease conditions were found to be more common among the elderly patients belonging to the age group 50 years and above. Once again, all these data were found to be statistically highly significant (p = 0.007).

Discussion

During the Ramadan fasting, there is a radical change in the lifestyle of a patient. These changes in the lifestyle can adversely affect the health. To the best of our knowledge, this is the first study describing the patterns of disease prevalence among the muslim patients visiting the internal medicine out-patient department of a hospital while observing the Ramadan fasting. However, the study population is somewhat small, but this limitation is purely due to the fact that muslims are a minority religious community at Moodabidri, where the study was undertaken. A total of 61 patients were studied and there were more females (n = 38, 61.7%) in the study as compared to the

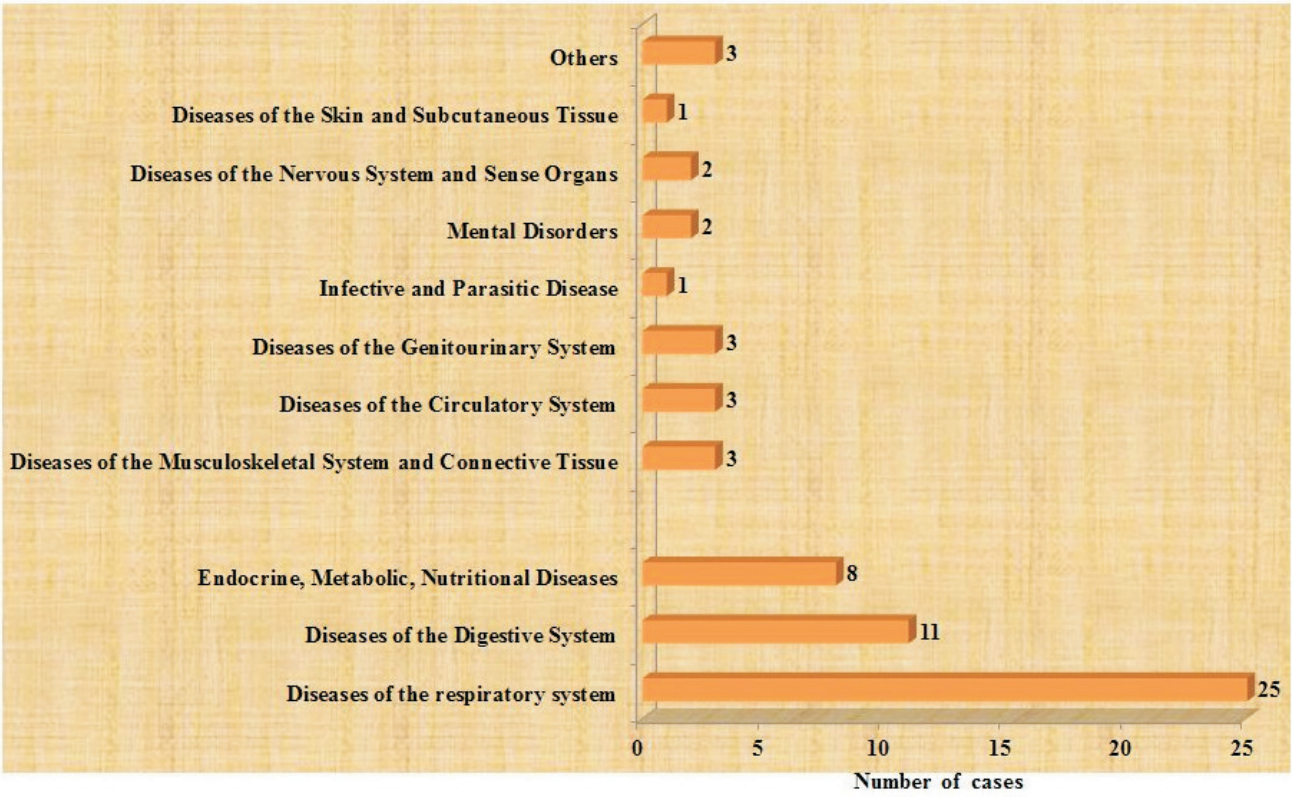

Fig. 4: *Showing prevalence of the major disease categories among the patients.*

males (n = 24, 38.7%). The patients belonging to the older age group (50 years and above) were found to be visiting the hospital (n = 35, 56.45%) more often than other age groups. This demographic profile of the patients has been shown in the Fig. 1 and Table I. However, this observation was found statistically not significant. In Table II and Fig. 4, we have presented the prevalence of the major disease categories studied. In our study, the diseases of the respiratory system (J00-J99) were found to be the most common (n = 25, 40.32%) when compared to any other disease among the patients studied. Diseases of the digestive system (K00-K93) were the second most common disease group (n = 11, 17.74%). Extensive search of the available medical literature did not show any studies on the prevalence of diseases among the muslim patients attending the out-patient department of internal medicine during the Ramadan fasting season, so as to compare our study observations. However, a study done at Turkey to determine impact of Ramadan on demographics and frequencies of disease-related visits in the emergency department found that visit frequencies for hypertension and uncomplicated headache in Ramadan were significantly higher than in non-Ramadan months. They also found that the patients with diabetes presenting in Ramadan were found to be younger than their peers in the rest of the year. They did not find any increase in the prevalence of other diseases during the Ramadan fasting in the study[3]. We have presented the most prevalent diseases according to age and sex in the Fig. 2, Fig. 3, and Table III. The three most prevalent disease conditions were, lower respiratory tract infections [(LRTI) (J22) (n = 15, 24.19%)] which ranked first, followed by dyspepsia (K30) which ranked second (n = 10, 16.12%), and bronchial asthma (J45) was the third (n = 5, 8.06%) most common condition.

Among the diseases of the respiratory system (J00-J99), the lower respiratory tract infections (LRTI) (J22) were the most common medical condition (n = 15, 24.19%) in the Ramadan study population. Bronchial asthma (J45) was the third (n = 5, 8.06%) most common condition. But, bronchial asthma (J45) was seen only among the female patients. This increased incidence of bronchial asthma in our study could be due to the reluctance of the patients to use bronchodilators during the fasting hours. Several reports and studies have shown the increased incidence of acute exacerbation of bronchial asthma especially due to stopping of the medications[2,4]. On the contrary, Bener *et al*[5] in their population based study found no significant differences in hospital admissions and mean spirometric values for asthma

in the month of Ramadan when compared to the non-fasting season.

In our study, we found diseases of the digestive system (K00-K93) as the second most common disease group (n = 11, 17.74%) and dyspepsia (K30) the second most (n = 10, 16.12%) prevalent medical condition. Dyspepsia was also, found to be the most prevalent medical condition (n = 08, 33.33%) among the males in the diseases of the digestive system (K00-K93). Kucuk *et al*[6] in their study observed an increased incidence of duodenal ulcer perforation during Ramadan fasting, and cautioned the patients with dyspepsia to take special care while observing the Ramadan fasting. Similarly, Amine *et al*[7] found peptic ulcer as the most frequent cause of acute upper GI bleed during the Ramadan fasting. In another study, Gokakin *et al*[8] also found an increased incidence of duodenal ulcers and duodenitis during the Ramadan month. Ramadan fasting increases of the gastric acidity over 24 hours, and it is more in the daytime. Gastric acidity peaks at the end of the fasting period. Hence, the patients with pre-existing duodenal ulcer run a higher risk of complications during the month of Ramadan than the rest of the year[9].

Salim *et al*[10] in their systematic review of literature about the impact of religious Ramadan fasting on cardiovascular diseases found no change in the incidence of acute cardiac illness in the cardiac patients while observing fasting. A similar result was observed by other investigators in their respective studies[11,12]. We had three patients (4.83%) presenting with diseases of the circulatory system (I 00 - I99) in our study and the incidence was found to be statistically not significant.

The target blood sugar levels in diabetes are achieved through adjusting the diet, exercise, and medication. A change in any one of these three things can alter the blood sugar levels and result in complications due to either hyperglycaemia or hypoglycaemia. In addition, there are risks of developing diabetic ketoacidosis and dehydration as well. Since, ramadan fasting involves abstinence from food and water for twelve hours or more during the day from dawn to dusk, it is obvious that the advice regarding exercise and medication will have to be modified during this period[13]. Salti *et al*[14] observed an increased incidence of severe hypoglycaemia in their diabetic patients while observing Ramadan fasting. Similarly, a study done at Algeria showed that severe hypoglycaemia was the main reason for hospitalisation during the holy month. Diabetic ketoacidosis, dehydration, and orthostatic hypotension were the other diabetes related complications seen during fasting in their study[15]. There were eight patients with diabetes mellitus included in our study. However, most of them (n = 7) turned up for routine follow-up and one presented with osmotic symptoms due to hyperglycaemia. No one presented with features of hypoglycaemia.

Conclusion

Ramadan fasting is a fascinating and unique opportunity available to the clinicians worldwide to study the patients under the fasting physiological situation year after year. A largest ever global multi-centre prospective study should be contemplated to study the patients in relation to the prevalence of various diseases, impact on cardiovascular risk factors, physiological and biochemical changes in the subjects comparing fasters and nonfasters before, during, and after Ramadan. Who knows, the study may give us a breakthrough, with a right insight into the various modern problems faced by the human race, especially the diabetes, metabolic syndrome, dyslipidaemia, obesity, and systemic hypertension.

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"If you derive pleasure from the good which you have performed and you be grieved for the evil which you have committed, you art a true believer ... ... when action pricks your conscience, forsake it."

– PROPHET MUHAMMAD.

REVIEW ARTICLE

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Non-bacterial pneumonias

Balachandra S Bhat, M Vadivelan***

Abstract

The spectrum of non-bacterial pneumonias includes viral, fungal, parasitic and lipoid pneumonias. Non-bacterial infection of the lungs is caused by viruses, fungi and parasites. The common non-bacterial pneumonias, their clinical presentation and management in day-to-day practice are being discussed here.

Key words: Viral pneumonia, fungal pneumonia, parasitic pneumonia, lipoid pneumonia.

Introduction:

Pneumonia is a syndrome caused by acute infection that is characterised by clinical and/or radiographic signs of consolidation of the lung. The use of the term has been extended to include non-bacterial infection of the lungs caused by a wide variety of micro-organisms.

Classification of non-bacterial pneumonias:-

1. Viral pneumonias
2. Fungal pneumonias
3. Parasitic pneumonias
4. Lipoid pneumonia

1. VIRAL PNEUMONIAS

a) Influenza virus pneumonia

It is the most common among the viral pneumonias. Influenza virus is an RNA virus and belongs to the *orthomyxoviridae* family. 3 serotypes of influenza virus exist – A, B, and C. Influenza A virus is the most virulent pathogen. The virus maintains its infectivity by undergoing antigenic drift (small number of amino acid substitutions) and antigenic shift (large number of amino acid substitutions) due to changes in the haemagglutinin protein. Epidemics occur with viral drift and pandemics occur with viral shift[1].

Influenza B virus is responsible for outbreaks in populations staying together in closed spaces like schools and military camps .The least common serotype among the influenza virus is Influenza C.

Incubation period of influenza is 1 - 2 days.The virus is spread by respiratory secretions of infected patients. Transmission of virus occurs by aerosols that are generated by coughing, sneezing, personal contact, and by contact with fomites.There is involvement of ciliated columnar epithelial cells of the respiratory tract. The virus replicates in the infected cells and spreads to the adjacent healthy cells. Infected cells show degenerative changes, necrosis, and desquamation.

There are three clinical types of influenza pneumonia[2]:-

1. Primary influenza viral pneumonia
2. Influenza with secondary bacterial pneumonia
3. Mixed viral and bacterial pneumonia

Clinical manifestations of primary viral pneumonia are dry cough, throat pain, headache, and myalgia. Increase in dyspnoea and cyanosis are commonly seen in these patients. Influenza with secondary bacterial pneumonia is manifested as high grade fever and cough with purulent sputum. The organisms that are commonly isolated in respiratory specimens include *Streptococcus pneumoniae, Staphylococcus aureus* and *Haemophilus influenzae*. Mixed viral and bacterial pneumonia is the most common pneumonic complication of illness caused by the influenza virus. It leads to a gradually progressive illness.

Radiologic features of influenza are non-specific and are seen as bilateral diffuse, patchy infiltrates.The virus can be isolated from throat or nasopharyngeal swabs and sputum by culture method. Real-time polymerase chain reaction (RT-PCR) is a useful method that detects viral nucleic acid and is a highly sensitive and specific test.

High-risk populations

1. Young children and elderly (> 65 years)
2. Bronchial asthma and chronic obstructive pulmonary disease (COPD) patients
3. Chronic hepatic and renal disease
4. Pregnant females[3]
5. Cancer patients
6. HIV-infected patients

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Management

1. Antiviral therapy: Oseltamivir is a neuraminidase inhibitor that has been approved for treatment in patients within 48 hours of onset of symptoms.
2. Supportive measures: Anti-pyretic like paracetamol is used for fever; analgesic like ibuprofen can be given for bodyache and myalgia. Cough suppressant for dry cough can provide symptomatic relief.

b) Respiratory syncytial virus pneumonia

Respiratory syncytial virus (RSV) is the second most common viral cause of pneumonia in adults. It is an important cause of pneumonia in the elderly population. The virus is highly infectious and spreads by contact with respiratory droplets and fomites. High risk factors for RSV infection include infants, patients with congenital heart disease, and those on immunosuppressive drugs[4].

Patients with RSV pneumonia typically present with fever, non-productive cough, otalgia, anorexia, and dyspnoea. Wheezes, rales, and rhonchi are common physical findings.

X-ray findings in RSV infection are non-specific. They include bilateral alveolar opacities and interstitial shadows[5]. Methods of isolating the virus are cultures of nasopharyngeal swab and tracheal aspirate. RT-PCR is also helpful in the diagnosis of RSV infection.

Severe cases of RSV pneumonia can be treated with the antiviral drug, ribavirin. The drug is also indicated in patients at high risk of developing complications due to the infection.

C) Chickenpox pneumonia (Varicella pneumonia)

Chickenpox is caused by *Varicella zoster* virus (VZV). It is generally a mild infection of early childhood. Pneumonia may occur in one-third of adult cases affected by chickenpox. Pneumonia occurs within the first 4 - 5 days after onset of the rash. Complications include secondary bacterial infections, encephalitis, and hepatitis. Reye's syndrome can occur in patients if aspirin is given for treating fever. The pneumonia tends to be more severe in chronic smokers.

Clinical features of the disease include dry cough and pleuritic chest pain. Haemoptysis may occur in some cases.

The chest X-ray shows patchy or diffuse bilateral alveolar shadows that can progress rapidly. Nodular calcific shadows scattered in both lung fields can be seen in the later stages of the disease.

Acyclovir 10 mg/kg IV 8 hourly for 7 days is indicated in varicella pneumonia.

Prevention: VZV immunoglobulin if given to susceptible patients within 4 days of exposure is effective in reducing the severity of illness. The Centers for Disease Control and Prevention (CDC) recommend two doses of chickenpox vaccine for healthy children, adolescents, and adults who do not have evidence of immunity to the virus. Isolation of patients is required to protect immunocompromised subjects from exposure to the virus.

d) Measles pneumonia

Measles is caused by a paramyxovirus. The virus produces a highly contagious infection that commonly affects young children. Spread of the virus occurs by respiratory droplets. Bronchitis and pneumonia are the common lower respiratory tract manifestations of measles[6].

Clinical manifestations of measles are fever, dry cough, and rhinitis, in the initial stage. Later, there is appearance of a maculopapular rash on the face and neck that progresses to involve the trunk and extremities.

The chest X-ray shows pulmonary infiltrates and hilar lymphadenopathy in a patient with pneumonia that occurs secondary to measles infection.

No specific treatment exists for primary measles pneumonia. Management is supportive. Antibiotics are indicated if secondary bacterial infection occurs.

e) Adenovirus pneumonia

Adenovirus is a DNA virus isolated from human adenoid tissue. It can cause severe illness in immunocompromised patients. Commonly, it causes acute tracheo-bronchitis in adults, conjunctivitis, febrile upper respiratory disease, pneumonia, gastrointestinal illness, haemorrhagic cystitis, rash, and neurologic disease[7].

Clinical features are fever, sore throat, rhinorrhoeam and dry cough.

The chest X-ray shows focal infiltrates with no specific findings. Viral culture from naso-pharyngeal aspirate or swab is the gold standard for identifying adenovirus infection.

Treatment is supportive with analgesic, and cough suppressants. Anti-viral drugs like a combination of cidofovir and ribavirin can be used in patients on immunosuppressive therapy (bone marrow transplant recipient patients).

f) Cytomegalovirus (CMV) pneumonia

CMV is the commonest cause of viral pneumonia in immunocompromised patients[8].

Patients at high risk of developing CMV pneumonia are those with HIV infection, organ transplant recipients and non-Hodgkin's lymphoma.

Clinical features of CMV pneumonia are non-specific and include fever, dry cough, and dyspnoea.

Chest X-ray in patients with CMV pneumonia shows bilateral asymmetric ground-glass opacities and small centri-lobular nodules.

Diagnosis of CMV infection is achieved by demonstration of typical intra-nuclear inclusion bodies in broncho-alveolar lavage (BAL) fluid and trans-bronchial biopsy specimens.

Ganciclovir or foscarnet is indicated in the treatment of CMV pneumonia. Valacyclovir provides prophylaxis against CMV infection in immunosuppressed patients[9].

2. FUNGAL PNEUMONIAS

Fungal pneumonia occurs following spore inhalation or by reactivation of a latent infection.

I) Endemic fungal infections

Endemic fungal infections are seen in immunocompetent hosts and immunocompromised patients in a defined geographic location. Examples of endemic fungal infections are histoplasmosis, blastomycosis, and coccidioidomycosis.

II) Opportunistic fungal infections

Opportunistic fungal infections are seen in patients with congenital or acquired defects in their host defences. Examples of opportunistic fungal infections are aspergillosis, cryptococcosis, mucormycosis and pneumocystis jirovecii pneumonia.

High-risk groups

1. Haematologic malignancies (on chemotherapy)
2. Haematopoietic stem cell transplant recipients
3. Solid organ transplant recipients
4. Patients on chronic steroid therapy
5. Patients with HIV infection
6. Post-splenectomy patients

I) Endemic fungal infections

The organisms are present in the soil of a particular geographic region. Most infections caused by them are sub-clinical. Symptomatic infection is usually associated with a high burden of organisms.

a) Histoplasmosis

Histoplasma capsulatum is isolated from soil contaminated by bird or bat faeces. Inhaled spores are 2 - 5 μm in diameter. Multiplication converts spores into yeasts in the body and they get ingested by macrophages. They proliferate and get disseminated to the liver and spleen. Granuloma formation occurs in the affected organ and leads to caseation, necrosis, and calcification[10].

Clinical features

a) Mild acute pneumonitis: This manifests as a flu-like illness. Chest X-ray can be normal in this condition. Spontaneous resolution of illness commonly occurs over a period of time.

b) Pneumonia: Patients present with fever and chills, productive cough and pleuritic chest pain. Chest X-ray shows the presence of pulmonary infiltrates with hilar lymphadenopathy.

c) Progressive primary infection: This is a severe form of infection that occurs in immunocompromised patients[11]. Patients present with cough, fever, and weight loss. Chest X-ray shows the presence of multiple nodules with hilar lymphadenopathy.

The organism can be cultured from sputum or broncho-alveolar lavage (BAL) fluid. Since histoplasma is slow-growing, cultures become positive only after many weeks. Tissue samples can demonstrate the organism by Periodic acid-Schiff (PAS) staining. Enzyme immuno-assay (EIA) can detect histoplasma antigen in the urine. This is helpful in the diagnosis of disseminated histoplasmosis in immunocompetent patients[12].

Treatment

Liposomal amphotericin B is the drug of choice in HIV infected patients with disseminated histoplasmosis[13]. Patients with mild-to-moderate pulmonary histoplasmosis can be treated with itraconazole. If the patient is unable to tolerate itraconazole therapy, then second-line drugs like voriconazole, posaconazole and fluconazole can be considered in the management.

b) Blastomycosis

Blastomyces dermatitidis grows in the soil and the spores get converted to yeast forms in the lungs after inhalation. The yeast form undergoes multiplication in

the lungs and may spread to other organs. Haematogenous spread of the fungal infection can occur at this point of time. The infection can occur sporadically or in epidemics.

Clinical features

Mild disease: This presents with low grade fever, cough, anorexia and weight loss.

Epidemic disease: This usually presents with fever, chills, bodyache, productive cough, and pleuritic chest pain.

Chest X-ray findings are non-specific. It can show pulmonary infiltrates, consolidation, or a miliary pattern. Severe infection can cause acute respiratory distress syndrome (ARDS).

Extra-pulmonary blastomycosis can cause cutaneous lesions. Skin lesions are usually multiple, circumscribed ulcers.

Culture of the organism from BAL fluid or lung biopsy specimen is the diagnostic test for blastomycosis. Culture results can be obtained after 2 - 4 weeks, as the organism is slow growing. The organism can be visualised on histopathologic examination of tissue samples after PAS staining.

Antigen detection by enzyme immunoassay (EIA) in urine or serum samples of patients is a rapid test that is useful in the diagnosis of blastomycosis[14].

Treatment

Liposomal amphotericin B is used in the management of severe infection and in immunocompromised patients. The dose of amphotericin B is 3 - 5 mg/kg body weight that is given intravenously until the patient becomes stable. This is followed by a course of itraconazole that is given orally as 200 mg tablets twice daily for 6 - 12 months. Itraconazole is used in the same dose for patients with mild-to-moderate blastomycosis for a period of 6 - 12 months.

Patients with cutaneous lesions should be treated as those having severe infection.

c) Coccidioidomycosis

This infection occurs from a fungus in the soil, *Coccidioides immitis*. It is usually a mild and self-limiting infection. The organism is present as moulds in the environment and reaches the alveoli by dispersion and inhalation. Spherule formation occurs in the lungs, that contains endospores. Endospores are released when the spherule ruptures on reaching maturation. Endospores are responsible for spreading the infection to other organs.

Clinical features

Patients present with fever, headache, cough, chest pain, and dyspnoea.

Chest X-ray may show consolidation in one or more areas of the lung that can undergo cavitation. Disseminated coccidioidomycosis can occur after the primary pulmonary infection, especially in immunocompromised patients. It is associated with a high risk of meningitis and carries a bad prognosis.

Diagnosis is made by demonstrating the organism in tissue samples by histopathologic examination after silver staining. Serology is also helpful in diagnosing coccidioidomycosis. Screening can be done with an enzyme immunoassay (EIA). Complement fixation and immunodiffusion tests have better sensitivity and specificity in the diagnosis of this fungal infection[15].

Treatment

Liposomal amphotericin B is the drug of choice for treatment of severe coccidioidomycosis and in immunocompromised patients. The drug is administered intravenously at 3 - 5 mg/kg body weight daily. Once clinical improvement occurs, fluconazole is given in the dose of 400 mg orally for a period of 12 months[16].

Voriconazole and posaconazole can be used in the treatment of meningitis caused by *Coccidioides immitis*.

II) Opportunistic fungal infections

a) Aspergillosis

Aspergillus fumigatus is the most common cause of human disease among the different aspergillus species. The spectrum of disease can be classified according to the immune status of the patient, which is as given below:-

1. Hypersensitivity: Manifests as allergic broncho-pulmonary aspergillosis (ABPA).
2. Normal immunity: Manifests as saprophytic aspergillosis.
3. Immunosuppressed: Manifests as invasive pulmonary aspergillosis.

1. *Allergic broncho-pulmonary aspergillosis (ABPA):-*

It occurs as a hypersensitive immune response to aspergillus conidial or mycelial antigens. 2% of patients with bronchial asthma and 2 - 15% patients with cystic fibrosis can develop ABPA.

2. *Saprophytic aspergillosis (Mycetoma):-*

Mycetomas are seen in immunocompetent patients with structurally abnormal lungs due to cavitary diseases like tuberculosis or sarcoidosis. They can be clinically silent. Haemoptysis which can be occasionally life-threatening is a frequent occurrence in these patients.

3. *Invasive pulmonary aspergillosis*

This occurs in neutropenic patients with an absolute neutrophil count (ANC) of less than 500/cumm. Risk factors for invasive pulmonary aspergillosis are haematopoietic stem cell transplant, solid organ transplant, and corticosteroid therapy.

Fungal hyphae proliferate within the airspaces in the lung and invade the pulmonary arteries leading to pulmonary haemorrhage, pulmonary arterial thrombosis, tissue necrosis, and systemic dissemination.

Clinical features of invasive pulmonary aspergillosis are fever, cough, chest pain, and haemoptysis.

Chest X-ray usually shows nodules that are surrounded by ground glass opacities that are known as the 'halo sign'. Cavitation may occur in the nodules that are known as the 'air crescent sign' on X-ray[17].

Definitive diagnosis is by demonstration of the branching hyphae on tissue examination or culture of the organism from lung biopsy specimens. Enzyme immunoassay (EIA) for galactomannan can be performed in the serum and BAL fluid. Galactomannan is a cell wall component of aspergillus species[18].

Another diagnostic technique is the use of real-time polymerase chain reaction (RT-PCR) on serum and BAL fluid.

Treatment

1. ABPA: It is managed with a combination of corticosteroids and itraconazole.
2. Aspergilloma: Surgical resection of aspergilloma is recommended followed by itraconazole therapy.
3. Invasive pulmonary aspergillosis: Voriconazole is now considered to be the drug of choice for invasive aspergillosis due to better tolerance and improved survival with its use. It is used in the dose of 4 mg/kg intravenously twice daily till the patient becomes clinically stable. Voriconazole is then given orally as 200 mg tablets twice daily till radiologic resolution of lesions occur.

b) Cryptococcosis

It is a rare infection caused by *Cryptococcus neoformans*. Pulmonary infection can occur in both immunocompetent and immunocompromised hosts. Pulmonary involvement due to cryptococcosis is common in immunocompetent patients with chronic lung diseases[19].

The infection can be asymptomatic in immunocompetent adults or can present with fever, cough, and chest pain. In immunocompromised hosts, the infection is more severe and can lead to acute respiratory distress syndrome (ARDS).

Chest X-ray can show large, nodular densities, or diffuse bilateral pulmonary infiltrates[20].

Culture of the organism in sputum or BAL fluid is the definitive method of diagnosing pulmonary cryptococcal infection. Cryptococcal antigen test is useful in the diagnosis of cryptococcal meningitis. The test is highly sensitive and specific.

Treatment of cryptococcal infection depends upon the immune status of the patient. Lumbar puncture is indicated in immunosuppressed and immunocompromised patients to rule-out cryptococcal meningitis.

Treatment with oral fluconazole for a period of 6 - 12 months is indicated in patients with mild-to-moderate pulmonary infection[21]. In patients with severe pulmonary involvement or disseminated infection, treatment is started with liposomal amphotericin B 3 - 5 mg/kg/day intravenously along with flucytosine 25 mg/kg in four divided doses orally for 2 - 4 weeks. This is followed by fluconazole in the dose of 400 mg orally for another 8 - 10 weeks. After its completion, fluconazole is continued in the dose of 200 mg orally for a period of 6 - 12 months.

c) Mucormycosis

It is a severe opportunistic pulmonary infection caused by fungi belonging to the order Mucorales. The fungi show broad, non-septate hyphae with an irregular, branching pattern.

Infection with this fungus commonly occurs in patients with poorly controlled diabetes mellitus, leukaemias, or those on chronic steroid therapy.

The fungus has a tendency to cause invasion of the blood vessels that leads to tissue necrosis. Pulmonary involvement commonly occurs in patients with haematological malignancies having severe neutropenia and in stem cell transplant recipients[22].

Rhino-orbital-cerebral mucormycosis is seen in patients with uncontrolled diabetes mellitus.

The clinical manifestations of pulmonary mucormycosis

are similar to that of invasive aspergillosis due to the angio-invasive behaviour of the fungus in the lung. Patients commonly present with cough, haemoptysis, chest pain, and dyspnoea.

CT scan of the lungs in mucormycosis shows multiple nodules and 'reverse halo sign'. Reverse halo sign is a ground-glass attenuated appearance in the centre of a nodule with surrounding consolidation.

Mucormycosis can be diagnosed by identifying broad, non-septate hyphae that shows tissue invasion along with a positive culture.

Amphotericin B in the dose of 5 mg/kg intravenously daily is recommended in the treatment of mucormycosis for a period of 90 days along with surgical resection of the infected tissue. Posaconazole is used orally in the dose of 400 mg twice daily as a step-down therapy till complete resolution of lesions occur.

d) Pneumocystis jirovecii pneumonia

Pneumocystis jirovecii is a common opportunistic fungal pathogen that is responsible for causing pneumonia in patients with HIV infection. The fungus has a trophic form and cystic form during the stages of development.

Risk factors for developing pneumonia due to pneumocystis infection are HIV-infected patients with CD_4 cell count below 200 cells/µl and patients on immunosuppressive drugs (corticosteroids). Reactivation of latent pulmonary infection occurs in patients who are immunosuppressed.

Patients present with fever, dry cough, and dyspnoea. Patients with HIV infection have a sub-acute presentation with low grade fever while HIV negative patients present acutely with high grade fever. Physical examination reveals cyanosis, tachypnoea, and tachycardia.

Chest X-ray shows bilateral diffuse infiltrates. High-resolution CT (HRCT) thorax may show ground-glass opacities. Arterial blood gas (ABG) analysis shows reduced arterial oxygen pressure (PaO_2) and an increased alveolar-arterial oxygen gradient (PAO_2-PaO_2).

The organism can be demonstrated in broncho-alveolar lavage (BAL) fluid. Polymerase chain reaction (PCR) can also be used to detect *P. jirovecii* DNA in clinical specimens.

For the treatment of *P. jirovecii* pneumonia, a combination of trimethoprim and sulphamethoxazole (5 mg/kg + 25 mg/kg) 6 - 8 hourly orally daily is used for a period of 3 weeks in patients with HIV infection. The drug is given for a period of 2 weeks in non-HIV-infected patients. Prednisolone is indicated in patients who have features of desaturation on ABG analysis.

Other drugs which are useful in management of pneumocystis infection are trimethoprim-dapsone combination and clindamycin-primaquine combination.

Prophylaxis with trimethoprim-sulphamethoxazole combination is indicated in HIV-infected patients with CD count < 200 cells/µl or a history of oropharyngeal candidiasis or a past history of infection with *P. jirovecii*. Prophylaxis can be discontinued in these patients after the CD_4 count is greater than 200 cells/µl for a period of at least 3 months.

3. PARASITIC PNEUMONIAS

The common parasitic pneumonias are given below:-

a) Pulmonary amoebiasis
b) Malarial lung
c) Pulmonary ascariasis
d) Strongyloidiasis

a) Pulmonary amoebiasis

Pleuro-pulmonary involvement is a common manifestation of extra-intestinal amoebiasis. Pulmonary involvement usually occurs due to direct spread of liver abscess through the diaphragm.

Patients usually present with fever, cough, dyspnoea, pleuritic chest pain, and weight loss. The presence of hepato-bronchial fistula is associated with production of chocolate coloured (anchovy sauce) sputum if rupture of pulmonary amoebic abscess occurs.

Chest X-ray shows elevation of the right hemidiaphragm, pleural effusion, or abscess formation in the right lower lobe of lung. Amoebic serology and antigen detection in pleural fluid are helpful in the diagnosis of pulmonary amoebiasis.

Metronidazole is given in the dose of 750 mg intravenously 8 hourly along with an intra-luminal amoebicide like diloxanide furoate for 10 days to eradicate the parasite completely.

b) Malarial lung

Adult respiratory distress syndrome (ARDS) is the primary manifestation of lung involvement by *Plasmodium falciparum*. Pulmonary involvement is

commonly associated with cerebral disease and a high parasite burden.

Initially, patients present with cough and dyspnoea. Later, hypoxaemic respiratory failure occurs due to ARDS.

Chest X-ray shows the presence of non-cardiogenic pulmonary oedema.

Artesunate combination therapy (ACT) for eradication of the parasite along with mechanical ventilation and exchange transfusion can improve survival of patients with ARDS due to falciparum malaria. However, prognosis is poor and the condition is commonly fatal.

c) Pulmonary ascariasis

Ascaris lumbricoides is the most common cause of peripheral blood eosinophilia with pulmonary opacities (Loeffler's syndrome).

Patients present with chest pain, productive cough, haemoptysis, dyspnoea, and wheezing.

Chest X-ray shows the presence of unilateral or bilateral patchy pulmonary infiltrates.

Mebendazole 100 mg orally twice daily for 3 days is given for eradication of the parasite. Bronchodilators and corticosteroids can be used in the presence of bronchospasm.

d) Strongyloidiasis

Human beings are the primary host of Strongyloides stercoralis. Infective larvae present in the soil can invade the lungs through the skin.

Disseminated strongyloidiasis or hyper-infection syndrome is seen in patients with HIV infection and patients on corticosteroid therapy. It is a continuous auto-infection that can lead to a massive and life-threatening parasitic infestation.

Patients commonly present with cough, haemoptysis, dyspnoea, and wheezing. Diagnosis can be done by sputum or stool examination for the parasite.

The drug of choice for treatment of strongyloidiasis is Ivermectin that is given as a single dose of 200 µg/kg orally for a period of 7 days. The alternative drug is thiabendazole that is given in the dose of 25 mg/kg in two divided doses orally for 2 days.

4. LIPOID PNEUMONIA

It results from lipid accumulation in alveoli and can be divided into exogenous or endogenous types based on the source of lipid.

a) Exogenous lipoid pneumonia

It is caused by inhalation or aspiration of mineral oil or animal fat.

1. Acute exogenous lipoid pneumonia: It does not occur commonly. It is typically caused by an episode of aspiration of a large amount of a petroleum-based product.
2. Chronic exogenous lipoid pneumonia: It occurs due to use of oral laxatives or nasal decongestants. The lipids present in laxatives or decongestants get emulsified by lipase in the alveolar spaces of the lung and lead to a foreign body reaction. Histopathologic examination of lung tissue can show large amounts of foamy, vacuolated material in the alveoli seen as oil droplets within alveolar macrophages.

   Common symptoms that occur are cough, dyspnoea, chest pain, and haemoptysis and weight loss.

   Chest X-ray shows involvement of both lower lobes of the lungs. It can show presence of consolidation, pulmonary infiltrates, or pleural effusion. BAL fluid can be examined for fat containing macrophages with the help of special stains.

   Discontinuation of the offending agent helps in the resolution of symptoms.

b) Endogenous lipoid pneumonia

It is usually associated with bronchial obstruction and so it is an obstructive pneumonitis.

It has been typically reported to be caused by non-small cell lung cancers.

Histopathologic examination shows the presence of small fat droplets that show bi-refringence under polarised light microscopy.

Summary and conclusion

There is a need to understand the pathophysiology, diagnosis, and treatment of pneumonias caused by viruses, fungi, and parasites. This can help in the management of patients with non-bacterial pneumonias. Viral and fungal pneumonias are commonly encountered in clinical practice. Fungal pneumonias usually occur in immunocompromised patients.

Parasitic and chemical pneumonias are less commonly found in routine clinical practice. Diagnosing them poses a clinical challenge. This review has tried to give a clinician's

perspective in the diagnosis and management of non-bacterial pneumonias.

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"Righteousness and unrighteousness, pleasure and pain
are purely of the mind and are no concern of yours.
You are neither the doer nor the reaper of the consequences;
you are always free."

– ASHTAVAKRA SAMHITA.

CASE REPORT

JIACM 2016; 17(4): 303-06

Dark urine and pain abdomen: An odyssey of two cases of acute intermittent porphyria (AIP)

RN Das, Nabin Adhikari**

Abstract

A teenage girl was admitted with vomiting, abdominal cramps, and fits. All relevant physical examinations and laboratory investigations for common medical, surgical, and gynaecological causes of acute abdomen were ruled-out. After 2 days, the patient developed quadriplegia and seizure followed by aspiration pneumonia. She had AIP, SIADH, sepsis, and peripheral neuropathy. She died of acute respiratory failure due to respiratory muscle paralysis, and raised intracranial pressure. One year later, the deceased patient's female cousin was admitted with acute abdomen, vomiting, and recurrent fits. The meticulous clerking and skilful observation of the dark-coloured urobag prompted the principal author to do urinary porphobilinogen test. The test was positive and all her sibs were found to be negative. Timely appropriate treatment was given. She was discharged with a medic-alert bracelet, list of porphyria precipitating drugs and advice related to predisposing conditions.

Conclusion: Here, the secrets of diagnosis of AIP were traditional and meticulous clerking of family history, clinical examination, and keen observation of the surroundings including urobag which had prevented the iatrogenic death of the second female cousin.

Key words: abdominal pain, dark urine, peripheral neuropathy, fits, porphyria.

Introduction

Acute intermittent porphyria (AIP) is a dominantly inherited rare disorder of haeme biosynthesis due to porphobilinogen deaminase (PBG) deficiency. The majority of subjects with PBG deaminase deficiency remain asymptomatic, but occasionally present with various neurovisceral crises, triggered by hormones, drugs, infection, and fasting resulting in accumulation of toxic porphyrin precursors, δ-amino-laevulinic acid (δ-ALA) and PBG in serum, urine, and tissues[1]. Failure to recognise AIP, frequently delays effective treatment, leads to misdiagnosis and institution of improper treatment like unwarranted laparotomy, and occasionally, can lead to iatrogenic death.

The present study reports two cases of never documented AIP in the two female cousins in Nepal with a brief resume of relevant literature search to highlight the importance of diligent clerking and observation of the patient's surroundings. In a poor country like Nepal where quantitative and costly investigations are a mere luxury, Sir William Osler's dictum of "Observe, record, tabulate, and communicate" become an astute medical detective like Sherlock Holmes, which was imperative in the diagnosis of AIP-like mimicking disease[2].

Case 1

A 17-year-old girl was admitted with vomiting and abdominal cramps since 12 hours following a religious fast. Physical, gastroscopic, and sonographic examinations were unremarkable. Besides Na^+ 125 and K^+ 3.1 mEq/l, all biochemical tests were normal. She was treated with hyoscine, diclofenac sodium, fluid and electrolyte infusion. On the 2nd day morning, she had weakness of all four limbs. At noon she became drowsy. In the evening she had generalised tonic-clonic seizures and incontinence of urine. She was treated with oxygen and phenytoin. On the 3rd day morning, she developed fever, cough, and purulent expectoration. She became comatose and had high BP (160/100), pulse 120/min, respiratory rate 28/min, temperature 104°F, right basal crepitations, and dullness. Neurologically, all four limbs had 2/5 power (arms > legs; proximal > distal), reflexes diminished and bilateral plantars were flexor. Computerised tomography of brain was normal. On the 4th day morning round, the principal author noticed sun-exposed cola-coloured urine in the urobag (Fig. 1) which prompted porphobilinogen screening that turned-out to be positive (Fig. 3). Immediately

Fig. 1: *Cola-coloured urine in the urobag.*

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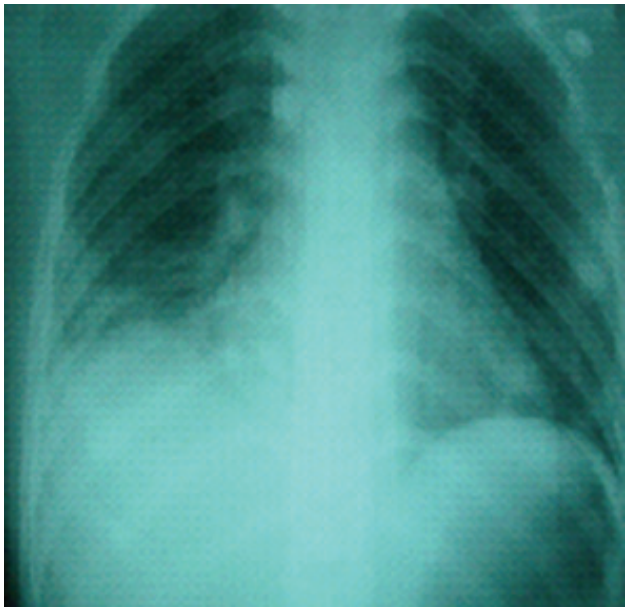

Fig. 2: *Right basal aspiration pneumonia.*

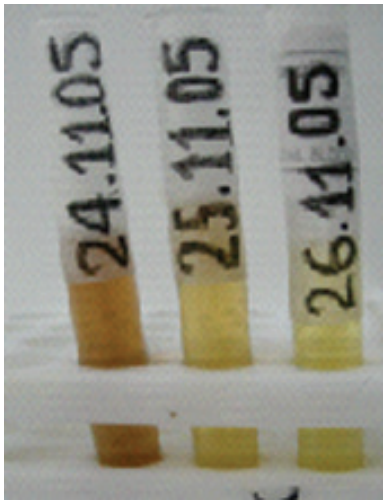

Fig. 3: *Urine colour change.*

diclofenac, phenytoin, and hyoscine were stopped, and concentrated dextrose (25%) drip was started. Repeat laboratory investigations showed high WBC count of 24,560/cumm with 90% neutrophils. Other results showed serum Na^+ 118 mEq/l, K^+ 5.2 mEq/l, Ca^{++} 9.2 mg% (albumin 4.2 mg%), urea 138 mg% and creatinine 4.6 mg%, sugar 86 mg%, aspartate and alanine aminotransferases 120 IU /l and 88 IU/l respectively. Arterial blood gas revealed PaO_2 76 mmHg, $PaCO_2$ 56 mmHg and pH 7.28. Chest imaging showed right basal pneumonia and cardiomegaly (Fig 2). Aspiration pneumonia was treated with amoxicillin-clavulanic acid and metronidazole, and BP was controlled with amlodipine and atenolol. Urine colour became normal within two days and it was free of porphobilinogen (Fig. 3). She had assisted ventilation and continuous diazepam drip for uncontrollable seizures. Despite intensive medical management, she died on the 28th day. She was diagnosed to have AIP with SIADH, type II respiratory failure, peripheral neuropathy, quadriplegia, and intractable seizures.

Case 2

One year later, another 15-year-old menstruating girl presented with fever, abdominal pain, persistent vomiting, anuria for 12 hours, and weakness of arms and legs on both sides. She was treated with oxygen, intravenous fluid, Foley's catheterisation and Ryle's tube feeding besides diclofenac, hyoscine, and pantoprazole. Next morning she became drowsy and threw fits. Her history revealed that she had a similar episode of weakness and seizures 6 months ago which had subsided spontaneously.

The principal author recalled a similar case and noticed the cola-coloured urobag in this case also. Immediately, hyoscine and diclofenac were discontinued, and urinary porphobilinogen test was requistioned.

Our drowsy patient had high BP (160/100) and rapid pulse (120/min). General and systemic examinations were unremarkable. In all four limbs, the power was reduced (3 - 4/5), reflexes were depressed and plantars were bilaterally flexor without any sensory impairment. Fundi were normal.

Laboratory investigations revealed WBC 16,500/cu mm with 80% neutrophils, urea 58 mg%, creatinine 1.6 mg%, uncuffed Ca^{++} 10.2 mg% (albumin 4.8 mg%), plasma glucose 78 mg%, Na^+ 130 mEq/l and K^+ 3.2 mEq. Routine urine: pus cells 10-12/hpf, RBC 8-10/hpf, and trace of protein. Computerised tomography of brain and spinal fluid were normal. Her urinary porphobilinogen was positive but two of her brothers were negative. She was treated with oxygen, intravenous 25% dextrose, gentamicin, diazepam, and esmolol. She recovered gradually within a fortnight with residual weakness of both arms and legs and was discharged with a medic alert bracelet, a list of incriminating porphyric drugs and advise for implementing some changes in her lifestyle. She was followed-up for one year without any more such attack.

Discussion

Many fascinating stories of Dracula to the episodic madness of King George III (1738 - 1820) have been connected with porphyrias[3]. AIP is the commonest and severest among acute porphyrias with episodic attacks and spontaneous remissions, and occasional deaths have also been recorded.

AIP occurs due to PBG deaminase deficiency. When the demand for hepatic haeme biosynthesis is increased by drugs, hormones, fasting, menstruation, or infection, the deficient enzymes can become a limiting step for haeme biosynthesis[4]. Reduced caloric intake induces δ-ALA synthase, and accumulation of δ-ALA and PBG in blood and tissues precipitate acute porphyrias[5].

Table I: Common unsafe and safe drugs in porphyria.

Class of drugs	Unsafe drugs	Safe drugs
Anticonvulsants	Carbamazepine, phenytoin, valproic acid, phenobarbital, fosphenytoin, topiramate, primidone	Diazepam, paraldehyde, levetiracetam, gabapentin, lamotrigine
Antiemetics	Metoclopramide, hyoscine	Cyclizine, ondansetron, chlorpromazine
Antibiotics	Chloramphenicol, co-trimoxazole, ceftriaxone, oxytetracycline, metronidazole, clindamycin, erythromycin, tinidazole, nitrofurantoin	Aminoglycoside, azithromycin, carbapenem, aztreonam, cefalosporin, co-amoxyclav, vancomycin, doxycycline, penicillin, linezolid
Cardiovascular	Hydralazine, methyldopa, diltiazem, clonidine, nifedipine, nimodipine, verapamil, simvastatin, atorvastatin, cerivastatin	ACE-inhibitors, ARBs, amlodipine, beta-blockers, dopamine, dobutamine
Analgesics	Diclofenac, tramadol	Aspirin, celecoxib, codeine, morphine, indomethacin, pethidine, paracetamol

The first case was calorie-deficient due to religious fasting, and the second case had the stress of menstruation which precipitated a porphyric attack.

Toxic accumulation of δ-amino-laevulinate or secondary local deficiency of haeme may be responsible for neurovisceral crises in AIP as evidenced by abnormal neurotransmitter function, increased serotonin and direct interference of γ-amino-butyric acid (GABA) function[6].

AIP occurs mainly in young adults with a female: male ratio around 5:1 owing to oestrogenic influence[7]. Both of our patients were teenage females. In European ancestry, 2/ 10^5 population has some form of porphyrias with a predominance of AIP. In many cases, there is no family history; AIP having remained latent or unrecognised for generations which requires screening of leucocyte amino-laevulinic acid and erythrocyte uroporphyrinogen-L-synthase activities[8].

An increased level of PGC-1 has led to increased production of ALAS-1 and consequently accumulation of haeme molecule precursors, which causes acute attacks of porphyria in mice.This discovery has revealed why dextrose administration is beneficial, since dextrose can return PGC-1 to normal level if infused adequately. Here, the first case had fasting induced porphyric attack while the same was ameliorated by 25% dextrose drip in the second case[9].

Neurological manifestations in AIP comprise of flaccid paralysis, neuropsychiatric disturbances and rarely epileptic fits triggered by fasting or drugs. Altered mental status during acute episodes are of metabolic origin (hyponatraemia and SIADH, i.e., syndrome of inappropriate anti-duiretic hormone secretion) while neurological weakness of the extremities is due to focal demyelination and/or axonal degeneration of peripheral nerves[10]. Both of our patients had motor neuropathy without any sensory loss. Epileptic fits in AIP have been reported in about 15 to 20% cases. Here both patients had seizures with abdominal pain.The first patient had also developed flaccid quadriplegia and urinary incontinence. Seizures may occur in AIP from hyponatraemia resulting from vomiting, diarrhoea, poor intake, excess renal loss, overzealous fluid administration, SIADH, or hypothalamic involvement [11].

Here, in Nepal, with are limited resources, the diagnosis of AIP was based mainly on meticulous clerking, astute clinical examination, skilful observation of the surroundings, and simple urinary PBG screening. Quantitative estimation of porphyrin level in urine and serum was not available. In the first case, all common surgical, gynaecological, and medical causes of acute abdomen were excluded but inappropriate treatment with hyoscine and phenytoin caused her untimely death. In the second case, the sun-exposed dark-coloured urobag and recollection of a similar case in the previous year actuated the principal author to order for urinary porphobilinogen test.

Approximately 25% sibs of AIP patients may be expected to have PBG in urine and therefore screening of sibs and other family members should be done. We had done the urinary screening for the relatives of the second case.

As there is no specific treatment of AIP, avoidance of the triggering factor is mandatory. Early infusion of haemin prevents synthesis of porphyrin by negative feedback. Intravenous glucose alone is recommended only for mild attacks when weakness or hyponatraemia is absent or until haemin is available. Unfortunately haemin is not available in Nepal. Other treatments during acute episode are usually symptomatic and supportive. Opioids for abdominal pain, chlorpromazine for nausea and vomiting, beta-blockers for tachycardia and hypertension are safe drugs. Epileptic fits are controlled with diazepam or gabapentin safely[12]. Urinary and serum electrolytes should be checked daily to correct inappropriate ADH secretion which requires fluid restriction.

Conclusion

This paper depicts the significance of medical documentation, astute clinical examination and skilful

observation of patient's surroundings. In Nepal, urinary PBG screening can be done easily in any hospital. AIP diagnosis is not difficult, but its awareness among attending physicians is required to prevent many cases of premature death in adolescence.

Acknowledgement

We are grateful to Prof. KJ Shetty, Dean, Manipal Teaching Hospital, Pokhara, Nepal, for his permission, valuable guidance, and suggestions in preparing this manuscript.

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"We are born of love; love is our mother.
Through love all that is bitter will be sweet,
through love all that is copper will be gold,
through love all dregs will become wine,
through love all pain will turn to medicine."

– Jalaluddin Rumi.

CASE REPORT

JIACM 2016; 17(4): 307-08

Autoimmune hypoglycaemia and anti-insulin antibodies

Rambabu, Komal Arora**, Priyanka Singh****

Abstract

Insulin autoimmune disease (IAS) is an uncommon cause of hyperinsulinaemic hypoglycaemia characterised by auto-antibodies to endogenous insulin in individuals without previous exposure to exogenous insulin. IAS is the third leading cause of spontaneous hypoglycaemia in Japan, and is increasingly being recognised worldwide in non-Asian population. Exact aetiology remains unknown but some causative agents are known. Its presentation closely resembles insulinoma. We are hereby reporting a case of 49 years female patient with recurrent episodes of hypoglycaemia due to anti-insulin antibody.

Key words: Recurrent hypoglycaemia, anti-insulin antibodies, insulin autoimmune disease.

Introduction

Insulin auto-immune disease is a rare disorder – the first case being detected in Japan by Hirata *et al* in 1970. It is the third leading cause of spontaneous hypoglycaemia in Japan after insulinoma and extrapancreatic malignancy. Although the cause of auto antibody formation without a history of medication for diabetes mellitus is not clear, it is known to be related to autoimmune disease or with medications that include sulphydryl group and a strong association is seen with HLA-DR 4.

Case report

A 49-years-old obese woman, a known case of hypertension from the past one year, presented in the OPD with complaints of recurrent episodes of giddiness and generalised weakness from the past 3 days. She had one episode of sweating and uneasiness 3 days back early morning which was not associated with any convulsions, headache, nausea/vomiting, or chest pain.

On examination, the patient was conscious, oriented to time, place and person, with no evidence of any focal neurological deficit. She was afebrile; pulse rate 84/min, regular; blood pressure 140/80 mm Hg; respiratory rate 18/min; RBS 48 mg/dl. ECG and all other systemic examinations were normal. She was therefore advised to take an oral glucose drink, after which she felt better.

Our patient was not a known case of diabetes, and she did not give any history of taking oral hypoglycaemic drugs or any exposure to exogenous insulin, but she gave history of feeling of uneasiness and weakness off-and-on since the past one month which used to resolve on its own. For the above-mentioned complaints, she went to the nearest lab to get her fasting blood sugar levels checked twice without taking dinner. Both times it was unrecordable with the glucometer. On the third visit, she got her fasting blood sugar level checked after taking dinner and the level was found to be 54 mg/dl. The patient was documented to be hypoglycaemic three times before she came to our OPD. She was advised hospitalisation for further detailed evaluation.

Our patient was showing Whipple's triad (symptoms of hypoglycaemia, documented evidence of low blood sugar, and improvement in symptoms after glucose administration); so we strongly suspected an insulinoma. Samples for fasting serum insulin and C-peptide levels were sent. Fasting serum cortisol levels and four-hourly blood sugar charting with a glucometer was advised along with other routine investigations. The patient showed symptoms of hypoglycaemia, viz., giddiness and uneasiness after 8 hours of admission; and at 6 am her blood sugar level was 55 mg%.

Results of routine investigations, including haemogram and renal, liver, and thyroid function tests, were not significant. Lipid profile, fasting serum cortisol level, serum procalcitonin and X-ray cervical spine were within normal limits. Fasting blood sugar in the lab sample was 41 mg/dl, post-prandial 103 mg/dl, HbA1C 6.5 (normal 4 - 6), serum insulin levels > 600 µU/ml (normal 2.00 - 25.0 mU/l) and serum C-peptide level was 6.65 (normal 0.81 - 3.85 ng/dl). This was strongly suggestive of an insulinoma. In view of this, imaging studies were done for localisation of the insulinoma. USG whole abdomen showed mild hepatomegaly with mild fatty infiltration. CT abdomen with triple-phase contrast was normal, and no pancreatic or extra-pancreatic mass was detected. CT scan has a sensitivity of 82 - 94% for detection of insulinoma[1]. MRI abdomen with pelvis also came out to be normal. Endoscopic USG was also normal. Endoscopic ultrasonography detects 77% of insulinoma in the pancreas[2].

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As there was no sign of pancreatic or extra-pancreatic tumour and our patient was getting persistent early morning hypoglycaemia during hospital stay, we suspected some autoimmune aetiology. ANA and ANA profile and anti-insulin antibody were advised. SS-B/La antigen in ANA profile was positive (marker for Sjögren's syndrome, also in SLE) but anti-ds DNA was negative. Serum anti-insulin antibodies level was >300 U/ml.

Based on all workup, diagnosis of insulin autoimmune disease – Hirata's disease – was made. The patient was treated with tablet prednisolone 5 mg twice a day with advice of having small frequent meals and complex carbohydrates in diet. Patient responded within 24 hours; no early morning hypoglycaemia was noted. Patient was discharged after two days observation with the said advice. Reviewed after 1 month, the patient showed decrease in serum insulin levels along with disappearance of hypoglycaemic phase, but the complained of weight gain with the treatment.

Discussion

Insulin autoimmune syndrome (IAS), or Hirata disease, is most commonly seen in Asians. The first case was described by Hirata *et al* in 1970. It is the most common cause of spontaneous hypoglycaemia in Japan after insulinoma and extra-pancreatic malignancy. It is increasingly being recognised in non-Asian populations – both in Europe and the United States (USA) also[3]. Patients with IAS usually present in adulthood (typically after 40) without any gender predilection. IAS typically presents with fasting hypoglycaemia although post-prandial hypoglycaemia and exercise-induced hypoglycaemia has also been described. Over 380 cases have been reported in medical literature since, with majority (90%) depicted in the Japanese population[4].

Affected individuals may complain of marked neuroglycopenic symptoms of confusion and an altered level of consciousness, and may even be in comatose state on initial presentation[7]. Half of IAS patients report recent exposure to medications, with over 90% of offending agents containing a sulfhydryl group[7]. Methimazole is the most commonly implicated drug. Others include carbimazole, glutathione, tiopronin, tolbutamide, gold thioglucose (auro thioglucose), interferoná, captopril, diltiazem, hydralazine, procainamide, isoniazid, D- penicillamine, imipenem and penicillin G[5,6,8]. Alpha-lipoic acid, a popular health supplement for the treatment of diabetic neuropathy and obesity, has been linked to IAS in recent years.

Although the precise mechanism for hypoglycaemia in IAS is unknown, the most widely accepted hypothesis is a mismatch between glucose and free insulin concentration, secondary to the binding and release of secreted insulin by autoantibodies[6]. Following a meal or oral glucose load, glucose concentration in the blood stream rises, providing a stimulus for insulin secretion. Autoantibodies bind to these insulin molecules rendering them unavailable to exert their effects. The resultant hyperglycaemia not only promotes further insulin release, but may also explain the increased HbA1c often seen in IAS patient[5]. Insulin molecules spontaneously dissociate from autoantibodies at this time, giving rise to raised free insulin level inappropriate for the glucose concentration, evoking hypoglycaemia[6]. Medications containing sulfhydryl group have been proposed to induce autoantibody formation by interacting with the disulfide bonds of the insulin molecule and augmenting its immunogenicity; however, true underlying pathophysiology remains unclear at this time.

More than 80% of patients require no treatment and spontaneous remission is seen. In symptomatic individuals strategies used are stopping the culprit drug and change of food habits (small frequent meals). Therapy with prednisone appears to alleviate the hypoglycaemia rapidly, usually within 24 hours. This effect of prednisone appears to result from antagonism of effects of antireceptor antibodies without actually lowering the titre.

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"It is a capital mistake to theorise before one has data."

– Sir Arthur Conan Doyle.

CASE REPORT

JIACM 2016; 17(4): 309-11

Metastatic adenocarcinoma presenting as acute liver failure

R Dewan, S Anuradha**, P Sethi***, N Nischal***, Pranav Ish****, S Agarwal*****

Abstract

A 14-year-old male single child presented with complaints of abdominal pain and distension for past 1 month. There was no history of jaundice, haematemesis, malena, vomiting, altered bowel habits. On day 5 of admission patient became drowsy (in early hepatic encephalopathy), ALT rose to 1,040 U/L, AST to 1,298 U/L, total bilirubin to 6.8 mg/dl (conjugated 4.1), and prothrombin time to 22 seconds (INR 3.8). The patient expired on day 8. Post-mortem liver biopsy showed extensive hepatocyte necrosis and diffuse infiltration of the liver parenchyma with tumour cells. Immunohistochemistry features were suggestive of metastatic adenocarcinoma probably colorectal in origin.

Background

Acute liver failure (ALF) is defined as hepatic encephalopathy developing within 8 weeks of the onset of jaundice in a patient with no previous history of liver disease[1]. ALF is often due to viral infection, toxins and drug-induced hepatotoxicity. ALF is a rare complication of metastatic liver disease and is associated with a high mortality[2]. We present a case of acute liver failure caused by the metastatic infiltration of adenocarcinoma of unknown primary.

Case

A 14-year-old male single child presented with complaints of abdominal pain and distension for the past 1 month. There was no history of jaundice, haematemesis, malena, vomiting, altered bowel habits. On examination, the patient was conscious, oriented, and afebrile. There was no pallor, icterus, lymphadenopathy, or asterixis. On abdominal examination there was ascites and liver was palpable 4 cm below costal margin. There was no splenomegaly or dilated veins on abdomen. Rest of the systemic examination was unremarkable.

Investigations on admission: haemoglobin 10.8 g/dl, total leukocyte count 15×10^9/l, and platelet count 290×10^9/l; liver functions tests – total serum bilirubin 1.8 mg/dl, conjugated bilirubin 1.3 mg/dl, ALT 73 IU/L, AST 313 IU/L, alkaline phosphatase 656 IU/L, total protein 8.1 gm/dl, serum albumin 2.6 gm/dl, and international normalised ratio of prothrombin time 1.28; serum LDH 1,134 IU/L; serum creatinine 0.6 mg/dl. Ascitic tap showed high SAAG (> 1.1), and blood and urine cultures were sterile. Serologic test for hepatitis B revealed HBsAg and HBeAg positive. Other viral markers and human immunodeficiency virus (HIV) were negative; laboratory tests excluded copper-related metabolic disorders and autoimmune liver disease. USG abdomen revealed liver 18 cm size, coarsened echotexture, with multiple nodule formation. Portal vein, spleen, and other organs were normal.

On day 5 of admission, the patient became drowsy (in early hepatic encephalopathy), ALT rose to 1,040 U/L, AST to 1,298 U/L, total bilirubin to 6.8 mg/dl (conjugated 4.1), and prothrombin time to 22 seconds (INR 3.8). Despite supportive care that included transfusions of fresh frozen plasma, hepatic function deteriorated in the next 48 hours with mental status changes consistent with hepatic encephalopathy and patient went into respiratory failure requiring mechanical ventilation and expired on day 8.

Post-mortem liver biopsy on haematoxylin and eosin study showed extensive hepatocyte necrosis and diffuse infiltration of the liver parenchyma with tumourcells (Fig. 1). Immunohistochemistry was positive for cytokeratin (CK) 20 (Fig. 2), and negative for CK 7 (Fig. 3), CK19, MCEA, vimentin. Immunohistochemistry features were

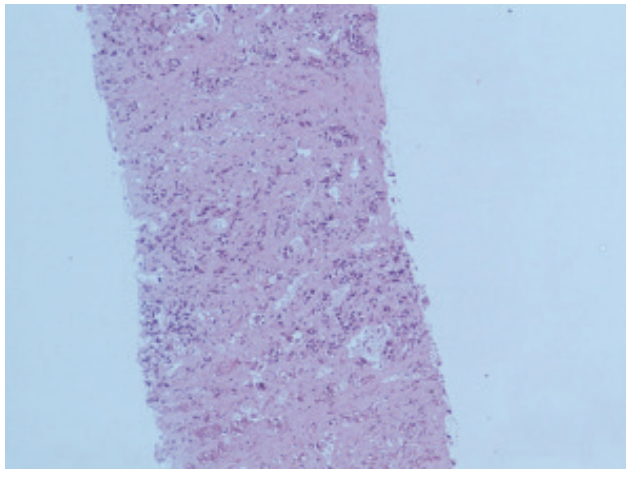

Fig. 1: *Tumour cells showing glandular formation.*

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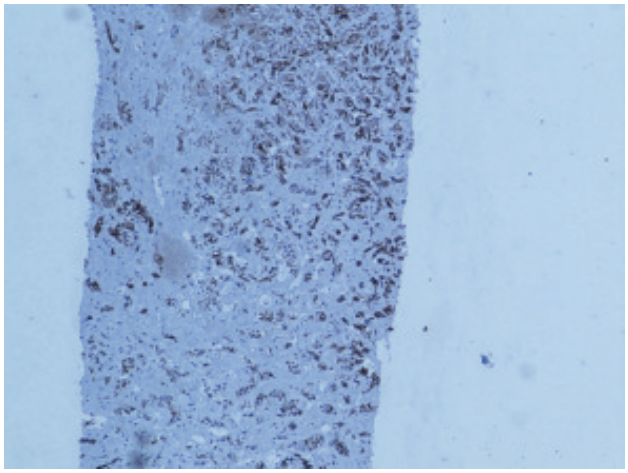

Fig. 2: *Tumour cells CK 20 positive.*

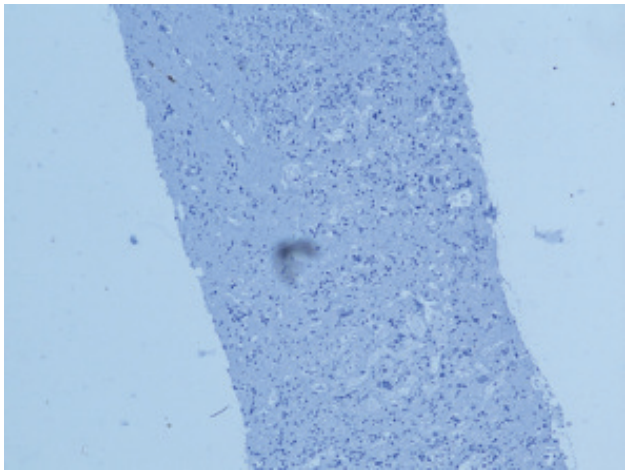

Fig. 3: *Tumour cells CK 7 negative.*

suggestive of metastatic adenocarcinoma probably colorectal in origin.

Discussion

Acute liver cell failure can occur by diffuse infiltration of malignant cells in the liver parenchyma. In a series of 4,020 cases with ALF, of various causes, malignant hepatic infiltration accounted for 0.44% (18 cases)[2]. Haematological malignancy was the underlying cause in the majority of cases while solid tumor was implicated in only 4 of the 18 patients described[2].

The malignant cells might be either primary hepatocellular carcinoma or metastatic liver disease[3]. Most of the cases of acute liver failure due to malignant infiltration are seen in adults with very few cases in children. Haematologic malignancies (non-Hodgkin's and Hodgkin's lymphoma[2]), acute and chronic leukaemia[4,5], and rarely multiple myeloma[6] are the most common metastatic malignancies responsible for liver failure. Non-haematologic malignancies that may present in this manner include adenocarcinoma breast[7], prostate cancer[8], small-cell carcinoma lung[9], carcinoma urinary bladder[10], and malignant melanoma[11]. In more than half of the cases with ALF due to malignant liver infiltration reported to date, cancer was not diagnosed before the development of ALF[12].

Colorectal cancer is exceedingly rare in the paediatric age group, with an estimated annual incidence of approximately 1 case per million individuals[13]. A recent study of the Italian TREP project on rare paediatric tumours[14], using data from the Italian network of cancer registry, estimated a colorectal cancer incidence rate of 0.09 and 0.72 per million person-years for children ages 10 to 14 years and 15 to 17 years, respectively. Advanced stage at diagnosis, high occurrence of aggressive histologic subtypes (poorly differentiated, signet ring, and mucinous adenocarcinoma), and poor survival are the hallmarks of paediatric colorectal cancer[15].

In patients of ALF due to malignant infiltration of liver, hepatomegaly was present in almost all cases but is a non-specific finding[12]. The transudate character of the ascitic fluid implies that the pathogenic mechanism of ascites is the acute increase in sinusoidal pressure due to the diffuse and massive infiltration of the sinusoids by malignant cells. High levels of aminotransferases, particularly AST, may occur in malignant infiltration[12]. Disproportionately raised LDH and high uric acid had been reported previously as common findings in haematological and non-haematological malignant infiltration. Radiological findings can be negative in more than half of the cases because of the histological pattern of micro-invasion. Liver metastasis and fulminant hepatic failure can mimic cirrhosis on USG[16].

The underlying pathogenic mechanism of ALF due to malignancy is hypoxic hepatocellular necrosis due to massive sinusoidal infiltration and obliterative invasion of the hepatic vessels by tumour cells. Secondly, cytokine release by the tumour cells, particularly in haematological malignancies cause damage to the bile ducts and activation of leukocytes and sinusoidal cells, impeding the sinusoidal microcirculation. Rapid replacement of vast areas of hepatic parenchyma by malignant cells may lead to a critical mass of hepatocyte destruction and subsequent ALF[2,12].

In summary, we conclude that non haematologic as well as haematologic tumour metastasis must be included in the differential diagnosis of ALF, particularly when usual viral, toxic, and metabolic causes have been excluded. Although not without risk in patients with coagulopathy, transjugular liver biopsy may be necessary to confirm the diagnosis and verify the futility of liver transplantation in a patient with ALF.

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"Twenty years from now you will be more disappointed by the things you didn't do than by the ones you did do.
So throw off the bowlines.
Sail away from the safe harbour.
Catch the trade winds in your sail.
Explore ... Dream ... Discover."

– MARK TWAIN.

CASE REPORT

JIACM 2016; 17(4): 312-14

Achondroplasia and pregnancy

Richa Sharma, Arvind Kumar***

Abstract

Achondroplasia is a genetic disorder of bone growth occurring in 1:10,000 to 1:40,000 in all races and sexes. A 32-year-old primigravida with achondroplasia presented to our obstetrics and gynaecology casualty with labour pains at 31 weeks gestation. LSCS was done in view of contracted pelvis. Baby also had achondroplasia and expired on the 5th neonatal day due to prematurity. Prenatal and preimplantational diagnostic tools are available regarding termination of pregnancy, rearing of affected child at home, foster care, or adoption.

Introduction

Achondroplasia is a genetic disorder of bone growth occurring in 1:10,000 to 1:40,000 in all races and sexes[1]. This is the most common growth disorder characterised by short stature with disproportionate short limbs[1,2]. Because of rarity of this condition and its adverse impact on obstetrical outcome, we felt justifiable to report this case of achondroplasia with pregnancy.

Case report

A 32-year-old unbooked primigravida at 31 weeks gestation presented to our obstetries and gynaecology casualty with history of show and labour pain. It was a spontaneous conception, her antenatal period was unsupervised, although uneventful. She was a disproportionate dwarf with a height of 44 inches, upper span 30 inches, lower span 14 inches, arm span 35 inches and her weight was 48 kgs (Fig. 1). Age of her husband was 36 years and his height was 5 ft 5 inches. Abdominal examination revealed fundal height of 30 weeks, cephalic presentation with good contractions, and foetal heart sound was 132/min regular. PV examination indicated advanced labour and contracted pelvis, LSCS was done and 1.08 kgs male baby was delivered with APGAR score of 4 and 6 at 1 minute and 5 minutes respectively. The baby had a relatively large head circumference, normal length of trunk, short limbs, and broad hands and feet (rhizomelic) – an appearance which is pathognomic of achondroplasia.The baby expired on the 3rd neonatal day due to prematurity and very low birth weight.The mother was discharged on the 5th post-op day after complete evaluation and genetic counselling.

Maternal growth hormone, thyroid function test, and X-rays were done. GH = 1.17 µg (normal), TFT (N), X-ray of

Fig. 1:

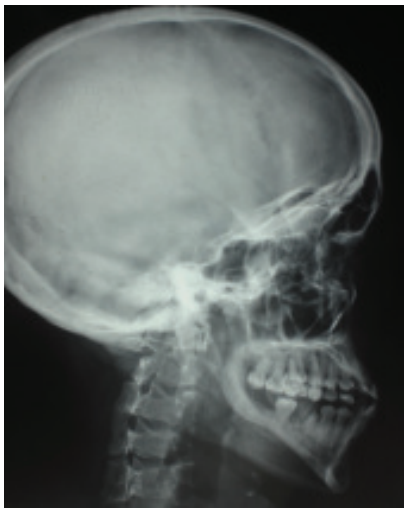

Fig. 2: *Relatively large calvaria, prominent forehead, depressed nasal bridge, small skull base and foramen Magnum.*

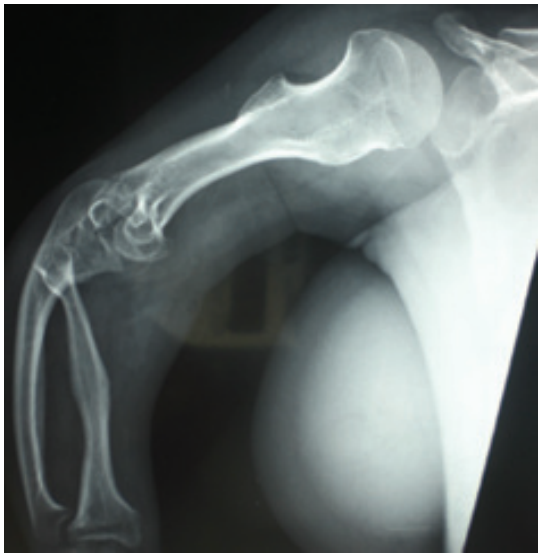

Fig. 3: *Markedly shortened humerus.*

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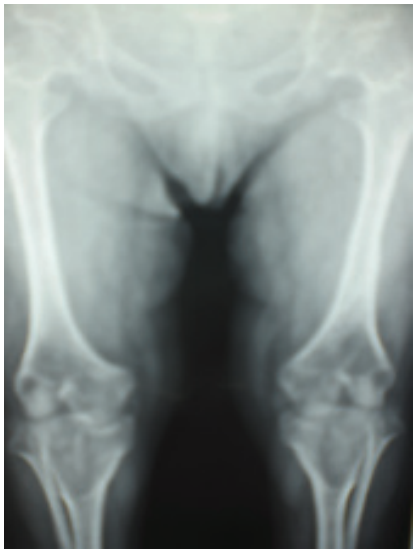

Fig. 4: *Short femoral neck.*

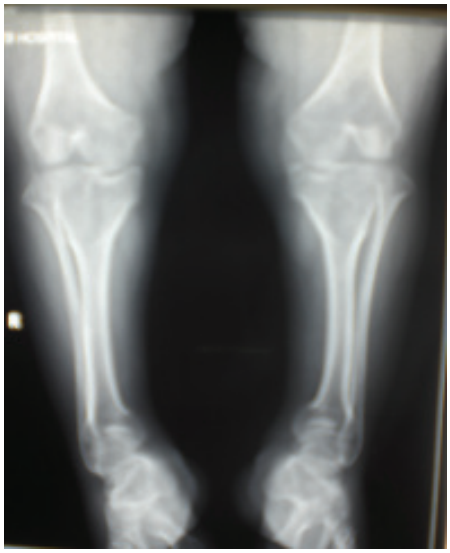

Fig. 5: *Disproportipmate long fibula in relation to tibia.*

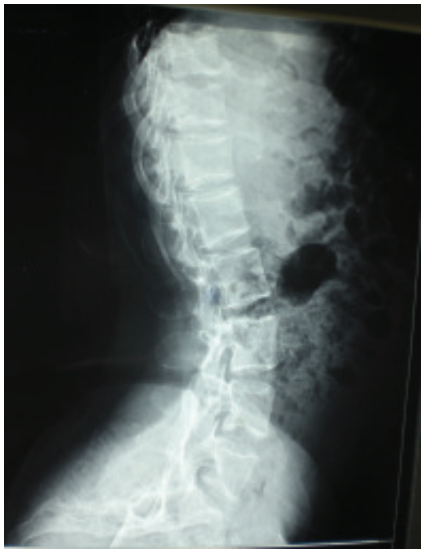

Fig. 6: *Caudal narrowing of interpedicular distances in lower lumbar spine and different degrees of anterior wedging of vertebral bodies causing gibbus.*

skull showed a relatively large calvaria, prominent forehead, depressed nasal bridge, small skull base and foramen Magnum (Fig. 2). X-rays of limbs indicated markedly shortened humerii (Fig. 3), short femoral neck (Fig. 4), and disproportionately long fibula in relation to tibia (Fig. 5). Spine X-ray (Fig. 6) showed caudal narrowing of interpedicular distances in lower lumbar spine and different degrees of anterior wedging of vertebral bodies causing gibbus. Therefore, a diagnosis of achondroplasia was made.

Discussion

Achondroplasia is inherited as an autosomal dominant trait with complete penetrance, caused by mutation in a gene fibroblast growth factor receptor 3 (FGR3) located on ch locus 4p16.3. Mutation leads to increased tyrosine kinase activity in the cartilaginous growth plate, thus inhibiting bone growth[5]. All bones that are formed by endochondral ossification are affected, but bones that are formed by membrane ossification are not affected, thus allowing the skull vault to develop normally[3,4]. More than 80% of the cases are not inherited, but results from a new de-novo dominant mutation that occurs in egg, or sperm cell that form the embryo and its mutation rate is estimated to be 0.000014 per gamete per generation[2,5]. Risk of recurrence in a family with sporadic cases is 1:443. Parents of achondroplasic child resulting from a new mutation are of normal height and chances of having second child affected is < 1%[6,7]. If one parent is affected, then the risk of recurrence in the offspring is 50% for either sex.

Advanced paternal age of more than 35 years strongly correlates with achondroplasia[8]. Affected people are at risk of corticomedullary compression, spinal stenosis, obesity, and obstructive sleep problems. They have increased incidence of menstrual complaints, leiomyomata and premature menopause. Decreased fertility and problems with certain contraceptions. Delivery should almost always be by caesarean section under GA[9]. Obstetric problems encountered are preeclampsia, polyhydramnios, respiratory compromise, contracted pelvis requiring LSCS, prematurity, and foetal wastage. Increased neonatal mortality due to hydrocephalus and thoracic cage abnormality.

Prenatal diagnosis

In high-risk pregnancy, prenatal diagnosis is possible by analysis of DNA for FGRF3 gene mutation of the foetal cells obtained by chorionic villus sampling (CVS) at 10 - 12 weeks and by amniocentesis at 15 - 18 weeks[10]. Preliminary evidence suggests that diagnosis may be possible by detection of FGFR3 mutation in foetal DNA in maternal serum[11].

In low risk pregnancy, level-II ultrasound may identify short foetal limbs. Krakow *et al* (2003) described the use of 3D USG at 16 - 18 weeks to identify facial features and relative proportions of appendicular skeleton and limbs. Ruano *et al* (2004) used 3D USG and intrauterine 3D helical computer tomography (3D HCT) to enhance diagnostic accuracy for skeletal defects[12].

Preimplantation genetic diagnosis (PGD) may be an option for some families in which disease causing mutation has been identified.

Conclusion

Affected individuals (heterozygous) have 50% risk of transmitting the disorder to their offspring, like our case. Prenatal diagnostic tools are available and the obstetrician should explore the options available to the family for the management of such a foetus using non directive approach which includes discussion of pregnancy termination as well as continuation and rearing of the affected child at home, foster care, or adoption.

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"Mukti or liberation is possible because it is within you.
No one is stopping you. The only barrier is you.
If you are willing, who can stop you?
So, all the sadhana is just to make you willing.
Sadhana is not for enlightenment."

– SADHGURU JAGGI VASUDEV.

CASE REPORT

JIACM 2016; 17(4): 315

Chronic mesentric ischaemia due to diffuse atherosclerosis

Parveen Malhotra, Ajay Chugh*, Hemant Dahiya*, Jeetender*, Yogesh Sanwariya*, Naveen Malhotra**

Case

We present the case of a 76-years diabetic male who was on treatment for ischaemic heart disease for the last five years. He presented with recurrent, dull, diffuse post-prandial abdominal pain for two years. The pain was classical of mesenteric ischaemia, used to occur after half to one hour after taking of meals, reached its peak in the next one hour and used to subside within 3 - 4 hours. There was no history of diarrhoea, weight loss, abdominal distension, upper gastrointestinal bleed or fever. On detailed evaluation, his clinical examination, labs tests, UGIE, colonoscopy, and USG abdomen were normal. In view of his classical clinical presentation and normal examination and investigations, chronic mesenteric ischaemia was kept as the diagnosis and CT angiogram was done which revealed diffuse atherosclerosis of abdominal aorta with plaques obstructing the origin of the superior mesenteric artery and extending into bilateral common iliac arteries (Fig. 1). Atherosclerosis is the most common cause of chronic mesenteric ischaemia (CMI), but such diffuse involvement is rare.

Discussion

In more than 95% of patients, the cause of mesenteric ischaemia is diffuse atherosclerotic disease which decreases the flow of blood to the bowel. As the atherosclerotic disease progresses, symptoms worsen. Usually, all three major mesenteric arteries are occluded, or narrowed. Patients with chronic mesenteric ischaemia often present with malnutrition secondary to their fear of post-prandial abdominal pain. These patients may have a prolonged hospital course due to their chronic malnourished state. Some studies show an increased prevalence in females compared with males, while other studies show equal distribution. The average age at presentation is 60 years. Patients typically present with a history of weight loss, post-prandial pain, sitophobia and history of vascular disease involving other organs such as myocardial infarction (MI), cerebral vascular disease or peripheral vascular disease.

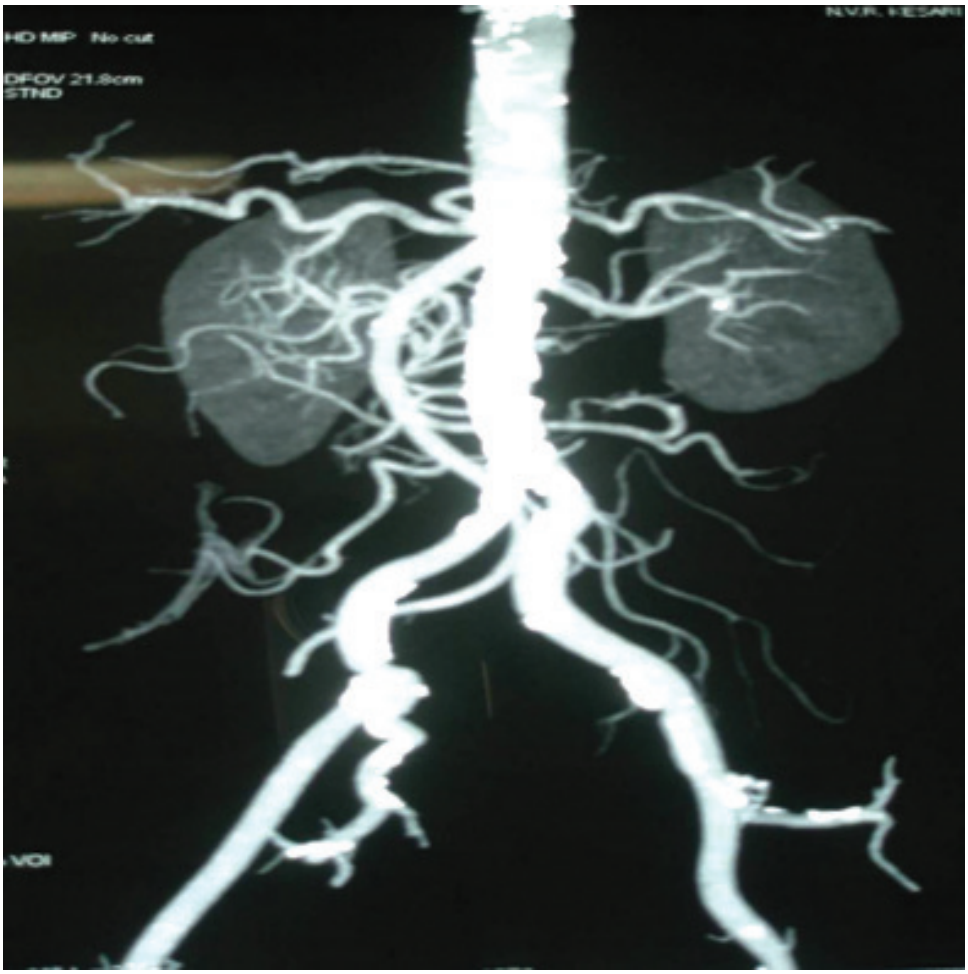

Fig. 1: *CT angiogram showing diffuse atherosclerosis.*

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CASE REPORT

JIACM 2016; 17(4): 316-18

Scorpion sting envenomation presenting with pulmonary oedema and subconjunctival haemorrhage

Kripa Shanker Jhirwal, Hemant Mahur**, DP Singh****

Abstract

Scorpion sting is a common problem in villages of underdeveloped countries like India. It may present with mild local pain to severe systemic symptoms related to respiratory, neurologic, and cardiovascular systems. The life-threatening complications like myocarditis and pulmonary oedema are known to occur with red scorpion sting in India. This condition requires urgent attention and ICU care from few hours to days. Delay in recognition and the hypoxaemia increase the morbidity and mortality. Illiteracy, ignorance, poverty, traditional faith healers trying treatment in remote areas, lack of transport in difficult terrains, and the non availability of ventilation facility in the nearby hospital, add to delay in appropriate treatment. A young adult female patient was admitted in MB Government Hospital and RNT Medical College, Udaipur (Rajasthan) with a history of scorpion sting. She presented with pulmonary oedema and hypotension and required ICU care. She was successfully managed with O_2 inhalation, cardiac support with inotropics, fluid balance, and careful monitoring. The magnitude of this problem, clinical presentation, and management done is emphasised.

Introduction

Scorpion sting is common in the rural population of India. Scorpion sting, commonly being less fatal than snake bite[1], gets less attention in health setups. Mostly being non-fatal, the victims present with mild-to-moderate symptoms and are attended to by the traditional healers in villages.

Scorpion envenomation in humans is manifested as pain at the local site, hypertension in mild cases, and in its severest presentation it leads to respiratory distress. Mortality is related to the development of myocarditis and pulmonary oedema[2-5]. The treatment of patients with hypotension, and pulmonary oedema in particular, is not clear[6].

We report a patient who developed clinical and radiographically documented acute pulmonary oedema, hypotension and subconjunctival haemorrhage after scorpion envenomation.

Case report

A 17-year-old female with complaints of shortness of breath, cough and drowsiness, attended the emergency block of the Maharana Bhopal Government Hospital, Udaipur at 11:17 pm on 27/9/2010 (around 35 hours after receiving scorpion sting on the middle finger of her right hand, while working in a grass field). She was having only mild local symptoms like pain, burning and local tenderness for 7 - 8 hours following scorpion envenomation. After that she developed some difficulty in breathing and restlessness. She was brought to a local hospital in the village where she received IV antibiotic, deriphyllin, dopamine, hydrocortisone and IV fluids. Next day her shortness of breath increased markedly and blood pressure started falling despite pressure support, so the attending doctor referred her to our hospital which is a tertiary care centre.

She came with pulse: 140/min; BP: 90/66 mm Hg on dopamine support; SaO_2: 78%; RR: 28/min. She was having subconjunctival haemorrhage in the right eye's bulbar conjunctiva, local swelling and tenderness over the right middle finger due to scorpion sting, and bilateral crackles heard in the chest.

Chest X-ray revealed diffuse, fluffy, bilateral infiltrates in the lungs; ECG showed sinus tachycardia, left axis deviation, ST elevation of > 1 mm in all chest leads.

She was admitted in the ICU and received inj ceftriaxone,

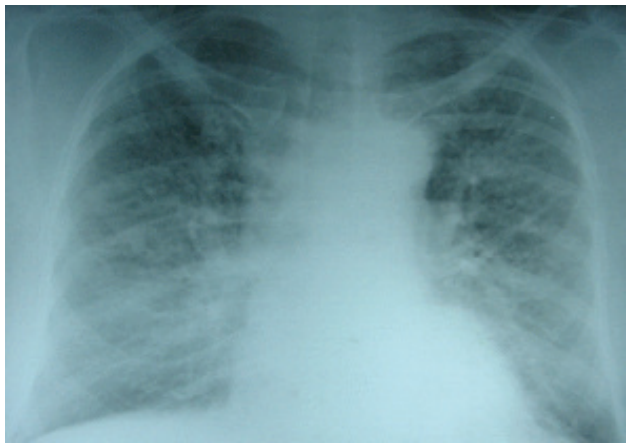

Fig. 1: *Chest X-ray showing diffuse, fluffy, bilateral infiltrates in lungs.*

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inj hydrocortisone, inj dobutamine, inj furosemide, inj rabeprazol, oxygen inhalation through oxygen mask, tab digoxin, and continuous monitoring of blood pressure, heart rate, ECG, SaO_2. Prazocin and NTG were not used as the patient was in hypotension.

2D echocardiography showed global hypokinesia of left ventricle, severe left ventricular dysfunction (ejection fraction 25%), mild MR, and mild TR.

Her Hb: 15.8 gm/dl; TLC: 27,300/cu mm; blood sugar: 163 mg/dl; blood urea: 41.2 mg/dl; serum creatinine: 0.62mg/dl; SGOT: 101 IU/L; SGPT: 70 IU/L; ALP: 100 IU/L; serum Na^+ 139 meq/lit; K^+ 4.6 meq/lit; urine complete: NAD; bleeding time: 3 min; clotting time: 4 min 30 seconds; PT: 16.2 seconds (INR: 1.39).

The patient's blood pressure continued to fall in the initial 2 hours of admission, and once it was even non recordable. But after increasing the rate of infusion of dobutamine, the patient's BP started to recover and came within normal range by the next morning, and after that dobutamine infusion was tapered off and then stopped. Patient was maintaining SaO_2 in the range of 85% - 92% with oxygen inhalation through oxygen mask, so endotracheal intubation and mechanical ventilation were not considered. The patient recovered from the stage of acute pulmonary oedema and hypotension within a period of 48 hours after admission. Repeat ECG and chest X-ray on the 4th day of admission were within normal limits. Patient was discharged on the 6th day of admission (on 2/10/2010) without having any residual morbidity.

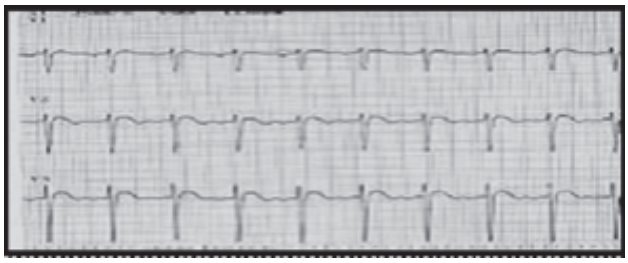

Fig. 2: *ECG showing sinus tachycardia, left axis deviation, ST elevation of >1 mm in all chest leads.*

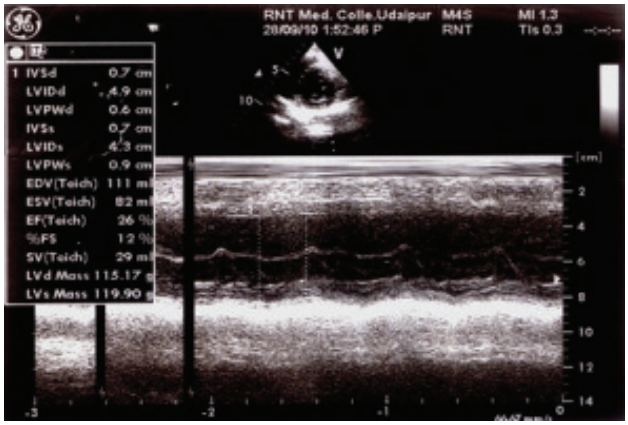

Fig. 3: *Echocardiography showing global hypokinesia of left ventricle, severe left ventricular dysfunction (ejection fraction 25%), mild MR, and mild TR.*

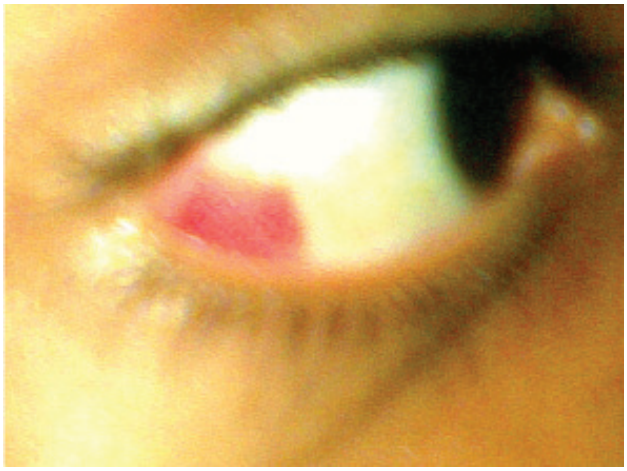

Fig. 4: *Sub-conjunctival haemorrhage in the right eye of the patient.*

Discussion

Scorpion stings are a major public health problem in many tropical countries. Out of 1,500 scorpion species, 50 are dangerous to humans. Scorpion stings cause a wide range of manifestations, from several local skin reactions to neurologic, respiratory, and cardiovascular collapse.

Scorpion venom contains neurotoxins, haemolysins, agglutinins, haemorrhagins, leucocytolysins, coagulins, ferments, lecithin, and chloesterin[7]. This venom is a species specific complex mixture of short chain neurotoxic proteins, serotonin, hyaluronidase, and various enzymes that act on trypsinogen[8,9]. The toxin binds at the cell membrane level to the voltage gated K^+ channels, Ca^{2+} activated K^+ channels, and Na^+ channels[9].

Scorpion venom is a powerful stimulant of autonomic nervous system. The primary action of venom is through both sympathetic and parasympathetic post-ganglionic stimulation. In most of cases the sympathetic response predominates, resulting in "sympathetic storm"[10], or "autonomic storm"[11]. Cardiovascular manifestations are due to direct effect of excess circulating catecholamines and cholinergics from autonomic hyper-stimulation. The sympathetic system of the autonomic nervous system usually predominates, resulting in hypertension and tachycardia and in case of severe envenomation, dysrhythmias, left ventricular failure, and pulmonary oedema. Parasympathetic predominance may result in bradycardia, various grades of AV blocks, and non-cardiovascular manifestations such as priapism and

hypersalivation.

Late onset pulmonary oedema is due to acute myocardial injury and LVF caused by the toxin-induced autonomic storm. This has been reported in 17% - 34.8% cases from Saudi Arabia and India[12].

Factors like hypoxaemia and hypercarbia contribute to pulmonary hypertension. Hyperoxygenation by positive pressure ventilation at high FiO_2 reduces pulmonary hypertension and pulmonary oedema[13]. PEEP helps by alveolar recruitment and by shifting oedema fluid away from alveoli. Haemodynamic control with adequate fluid replacement and inotropic support (dobutamine) treats hypotension and improves cardiac function. Dopamine is not used because it further increases the catecholamine induced cardiac damage[14]. Prazosin and NTG infusion with CVP guided fluid are given to reduce afterload and better cardiac output along with dobutamine infusion as recommended by Biswal *et al*[15]. Bawaskar and Bawaskar (2000) also recommended prazosin medication to prevent and treat pulmonary oedema, as prazosin (a post-synaptic alpha-1 blocker) has the pharmacological properties that counteract the effects of excessive catecholamines[16]. Antivenom therapy was not used because it is species specific and works only when it is given immediately after the sting[17].

Delayed hospitalisation is associated with severe life-threatening complications. This report emphasises the complexity of clinical picture and need of intensive approach to timely diagnosis of pulmonary oedema and initiation of respiratory and inotropic support in the ICU for better outcome.

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"If you translate every mistake of your life into a positive one,
you will never be a prisoner of your past;
you will be a designer of your future."

– Brahma Kumaris.

CASE REPORT

JIACM 2016; 17(4): 319-21

Vanishing lung syndrome: A rare case managed conservatively

B Malhotra, N Pandhi**, NC Kajal***, R Prabhudesai****, A Kumar****, CL Nagaraja*****

Abstract

A distinct clinical syndrome, giant bullous emphysema (GBE) or vanishing lung syndrome (VLS), primary bullous disease of the lung, or type 1 bullous disease is defined as a large bulla occupying at least one-third of a hemithorax. We report a rare case of VLS with giant bullae occupying almost both lungs. Patient was a 45-year-old chronic smoker with breathlessness at rest. His Computed Tomography (CT) scan of chest revealed multiple bullae in both hemithorices with collapse of both upper lobes and encysted pneumothorax on left side. His alpha-1 antitrypsin levels were within normal limits. He was managed conservatively with oxygen inhalation, bronchodilators, and antibiotics. We are reporting this case because the patient was relieved of symptoms just with conservative management without undergoing surgery.

Keywords: Vanishing lung syndrome, giant bullae, pneumothorax.

Introduction

A distinct clinical syndrome, giant bullous emphysema (GBE) or vanishing lung syndrome (VLS), primary bullous disease of the lung, or type 1 bullous disease, is defined as a large bulla occupying at least one-third of a hemithorax[1-3]. In 1937, Burke described a case of "vanishing lungs" in a 35-year-old man who experienced progressive dyspnoea, respiratory failure, and radiographic and pathologic findings of giant bullae, which occupied two-thirds of both hemithorices[1]. Since Burke's original description, scattered cases have been reported. Roberts described radiographic criteria for this entity: the presence of a giant bulla in one or more upper lobes (mostly unilateral), often asymmetrical, occupying at least one-third of the hemithorax and compressing surrounding normal lung parenchyma[2].

The condition has clearly been associated with smokers, alpha-1 antitrypsin deficiency and marijuana abuse[4]. Surgery is indicated to treat the complications related to GBE or on preventive basis when lesions occupy more than one-third of the hemithorax, when there is a compression of healthy adjacent lung tissue, and when size of a bulla shows to have been increased at follow-up. Generally resection of small bullae has no effect on lung function[5,6]. Also auto-bullectomy has been reported[7].

The case described below is one of the first in literature to be managed successfully conservatively without surgery.

Case history

A 45-year-old male was referred to our hospital for breathlessness with an abnormal chest radiographic finding. He was a current smoker with 25 pack year with no other addictions. On physical examination pulse rate was 90/min, blood pressure was 120/84 mm Hg, respiratory rate of 18/min, and oxygen saturation of 89% on room air. Chest examination revealed decreased breath sounds bilaterally, but more so on the left. Other systems examination was within normal limits.

Routine lab investigations showed Hb of 16.5 gm/dl, TLC of

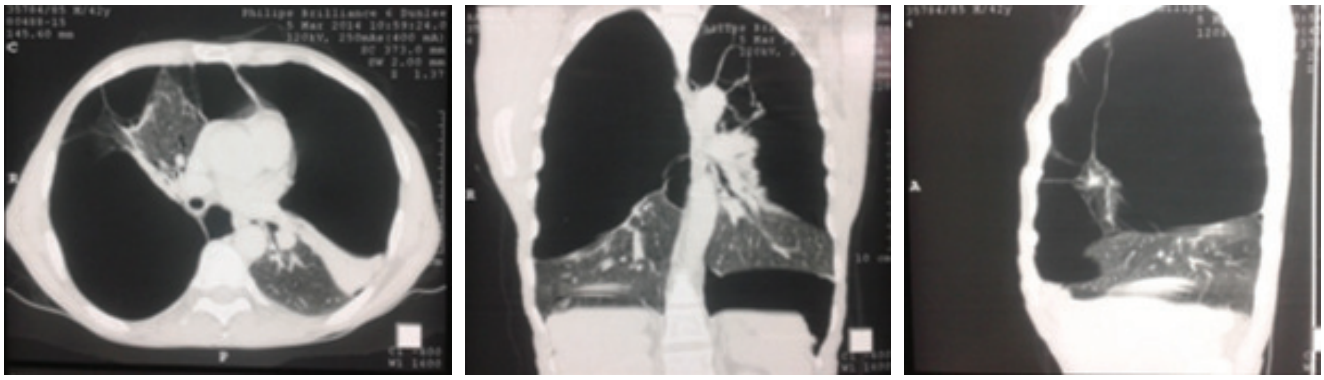

Fig. 1A, B, C: *CECT chest showing multiple bullae in both hemithorices with collapse of both upper lobes and encysted pneumothorax on the left side.*

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15,200/mm^3 with N 80, L 17, M 2, E 1,B 0. ESR was 12 mm/hour random blood sugar was 175 mg/dl. LFTs and RFTs were within normal limits. Sputum for AFB was negative. HIV test was also negative. Arterial blood gas analysis showed normal PO_2 with slightly raised PCO_2 and HCO_3 25 mmol/L. Patients alpha one antitrypsin levels were within normal limits (174 mg/dl).

Chest X-ray showed hypertranslucent areas bilaterally. Chest computed tomography (CT) scan was done which revealed multiple bullae in both hemithorices with collapse of both upper lobes and encysted pneumothorax on left side (Fig. 1A, B, C).

After the patient was stabilised on inhaled oxygen, two days later a PFT was undertaken which showed forced vital capacity (FVC) of 1.23 L (30% of predicted), forced expiratory volume in 1 second (FEV_1) of 1.1 L (32.6% of predicted), FEV_1/FVC ratio of 0.89 . Chest X-ray was repeated after 7 days which showed resolution of pneumothorax (Fig. 2).

Discussion

Giant bullous emphysema appears to be a distinct clinical syndrome. The disease usually afflicts young male smokers and is characterised by large bullae in the upper lobes of the lungs[2]. In 1937, Burke described the first case of "vanishing lungs". Since these descriptions, scattered reports have been described in young male smokers and this entity has been referred to as the vanishing lung syndrome, type 1 bullous disease, or primary bullous disease of the lung[8,9]. Roberts *et al* established the radiologic criteria for the syndromes as the presence of giant bullae in one or both upper lobes, occupying at least one-third of the hemithorax and compressing the surrounding normal lung parenchyma[2].

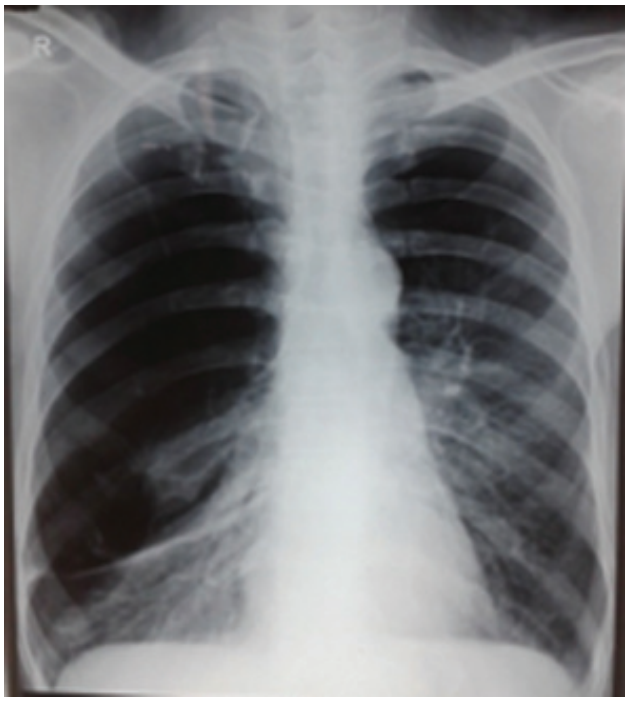

Fig. 2: *Chest X-ray PA view showing resolution of pneumothorax.*

A major complication of VLS is pneumothorax, which classically involves a history of acute deterioration in respiratory function associated with chest pain. In our case the patient had developed sudden onset breathlessness with chest pain secondary to left-sided pneumothorax. High resolution computerised tomography (HRCT) is used for preoperative assessment and shows the extent and distribution of the bullous disease to accurately determine the possible cause of the symptoms. HRCT also allows assessment of coexisting conditions such as infected cysts, bronchiectasis, pulmonary artery enlargement, and pneumothorax[10,11].

According to the protease-antiprotease theory, cigarette smoke attracts alveolar macrophages which release chemotactic factors that provoke leukocytes to release neutrophil elastases entering secondary pulmonary lobule causing unrestricted elastase activity in the lung with destruction of the alveolar walls. These effects are usually balanced by alpha-1 antitrypsin. However, it can be oxidized by chemicals in cigarette smoke and leukocytes. Hereditary deficiency of alpha-1 antitrypsin can lead to elastolytic, panlobular emphysema in nonsmokers[8]. In our case, the patient did not have alpha-1 antitrypsin deficiency, but he was a heavy smoker which is why he presented at an early age.

Bullae are thought to be in contact with the bronchial tree; they are preferentially filled during inspiration, causing collapse of the adjacent normal lung parenchyma. Because their space occupancy interferes with normal respiratory mechanics and thus, normal gas exchange, bullae lead to increased work of breathing with associated exercise limitation and dyspnoea[8]. The natural history of VLS is one of progressive enlargement of bullae, resulting in worsening dyspnoea; the rate of expansion; however, is unpredictable. In patients with GBE, bullectomy is the treatment of choice. Patients have reported early improvement of dyspnoea. Hypoxaemia and hypercapnia usually improve. Further, there is a rise in pulmonary function (FEV_1/FVC), and diffusing capacity of the lung for carbon monoxide (DLCO). In this respect, the preoperative size of bullae is the most important factor in determining the extent to which pulmonary function improves after surgery. Specifically, determination of the preoperative bulla volume allows the prediction of the expected increase of post-operative FEV_1. Bullectomy causes significant improvements in dyspnoea, gas exchange, pulmonary function, and exercise capacity, with the best

results being obtained in the more significant VLS cases. On an average, improvements persist for approximately 3 to 4 years, but begin to decline thereafter. This may be secondary due to decompression of the functioning lung and the ipsilateral bronchi following bullectomy[6]. Our patient did not undergo bullectomy for financial reasons, but luckily he responded to conservative management.

Although reported early mortality rates after bullectomy are low (from 0% to 2.5%), surgery is not without risk in these patients. Complications include prolonged air leak for > 7 days (53%), atrial fibrillation (12%), need for post-operative mechanical ventilatory support (9%), and pneumonia (5%)[10]. Safer alternative treatments, therefore, would be welcomed. In the last decade, the application of video-assisted thoracoscopy (VATS) bullectomy with endoscopic staple resection emerged, and is considered as a suitable and safe treatment of choice[11].

Conclusion

Vanishing lung syndrome is a rare condition which becomes clinically evident in a much advanced stage. Patients should be strongly counselled against any further tobacco use. These patients should be referred to pulmonology and cardiothoracic surgery to further delineate plans for surgery at the appropriate time. Patients who are not fit for surgery or cannot afford surgery shall be given a trial of conservative management.

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"Humility is the mother of all virtues.
... If you are humble, nothing will touch you, neither praise or disgrace,
because you know what you are.
... If they call you a saint, you will not put yourself on a pedestal."

– Saint Teresa.

CASE REPORT

JIACM 2016; 17(4): 322-23

Occurrence of malignancy in SLE: A rare association between SLE and adenocarcinoma of colon

Prashant Shringi, SR Meena**, Manoj Saluja***, SB Meena****, Naveen Seervi*, Pankaj Saini**

Abstract

SLE is an autoimmune disease in which organs and cells undergo damage by tissue binding autoantibodies and immune complexes. Lupus patients have an increased risk of malignancy. SLE is usually associated with haematological malignancies like lymphoma. Here we present a case in which there is a rare occurrence of adenocarcinoma of colon in a patient of SLE.

Background: SLE is an autoimmune diease which usually manifests in women of child-bearing age group, and is commonly associated with haematological malignancy. Here we present a case in which there is SLE associated with adenocarcinoma of colon.

Case report: This case is of a woman of child bearing age in which SLE was associated with adenocarcinoma of ascending colon. This woman fulfilled 7 criteria out of 11 which are required for SLE. Adenocarcinoma of colon was confirmed by CECT abdomen.

Conclusion: The overall cancer risk in SLE is only about 10% - 15% more as compared to the general populations. Some studies suggest that together it is controversial whether the risk of all cancers is increased in SLE patients compared with the general population. Pathogenic mechanisms involved with the development of lymphoproliferative malignancies in association with SLE include some common aetiologic agents for diseases, environmental factors, the use of cytotoxic or immunosuppressive agents, genetic variables, and immunologic factors such as immunoregulatory disturbances of the immune system.

Keywords: Systemic lupus erythematosus (SLE), adenocarcinoma colon, CA19 - 9 cold antibody.

Introduction

SLE is an autoimmune disease which usually manifests in women of child bearing age group. SLE is an autoimmune disease in which organs and cells undergo damage by tissue binding autoantibodies and immune complexes. Systemic lupus erythematosus ("lupus" or "SLE") and other autoimmune diseases are linked to an increased risk of certain types of cancer. Specifically, lupus patients may experience an elevated risk of lymphoma and other cancers such as cancer of the cervix, breast, and lung[1]. Researchers have elucidated certain connections between lupus and cancer. For example, it is widely accepted that immunosuppressive medications such as azathioprine and mycophenolate mofetil contribute to elevated cancer risk. However, one of the largest studies to investigate this connection suggests that the risk of cancer is actually greatest during the earlier stages of lupus indicating that exposure to immunosuppressive therapy is not the only link between lupus, and cancer. Physicians do not yet understand the precise relationship between lupus and cancer[2].

Case report

A 45-year-old female was admitted in our hospital with complaints of fever (low grade), malaise, fatigue, anorexia since three months. Skin rashes, malar rashes, alopecia since three months, pain abdomen and altered bowel/bladder habits since one month. She had complaints of cough since ten days, and also the complaint of photosensitivity in the sun-exposed area.

On general physical examination, there are photosensitive hyperpigmented erythematous rashes on the cheeks and nose (butterfly rashes), upper back, and extensor surfaces of arm. Oral ulcers were present, and pallor was also present (Fig. 1).

On systemic examination, mild hepatomegaly was present

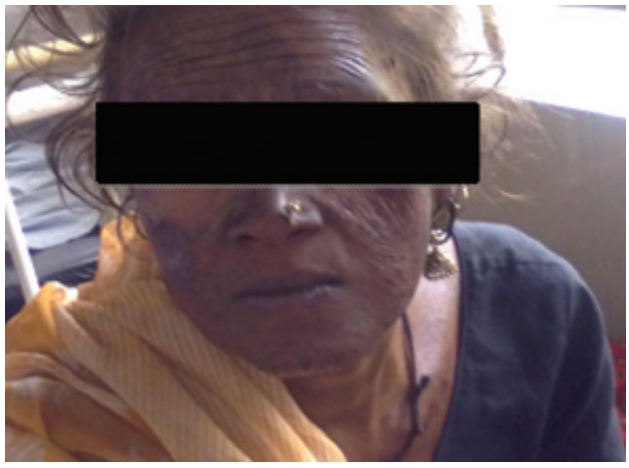

Fig. 1: *Hyperpigmented erythematous rash on the cheeks and nose.*

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6 cm below the costal margin, air entry was decreased on the right side of the chest; rest of the systemic examination was normal. Investigations showed pancyotopenia (Hb - 7.9 gm%, TLC - 1,870/cu mm, platelets 69,000/cu mm), ANA (ELISA) positive 118 IU/ml, anti-ds DNA positive 133 IU/ml. Rest of the biochemical and pathological examinations were normal. Urine analysis shows proteinuria (+1). USG showed hepatomegaly and right pleural effusion.

CECT abdomen showed irregular, mild circumferential soft tissue dense poor contrast-enhanced lesion in ascending colon and hepatic flexure with mucosal irregularity suggestive of adenocarcinoma of ascending colon with a right lobe heptic lesion (metastasis).

For diagnosis of SLE, 4 out of 11 criteria should be fulfilled[5]. In our patient, 7 criteria were fulfilled. The following criteria were present in our patient:-

1. Malar rashes\discoid rashes
2. Photosensitivity
3. Oral ulcers
4. Serositis (pleural effusion)
5. Proteinuria – albumin present, cellular casts present
6. Leukopenia +thrombocytopenia
7. ANA+, anti dsDNA Ab +.

Initially she was treated with oral and topical steroids, and correction of anaemia was done; then she was transferred to the cancer department where she was treated with azathioprine. Her cutaneos symptoms were relieved, and then she was dischared and referred to a higher centre.

Discussion

The overall cancer risk in SLE (that is, all cancer types considered together) is only about 10% - 15% more as compared to the general population. In fact, some cancers are more common in SLE than the general population (for example, lymphoma, a cancer of blood cells), and some cancers are less common in SLE than the general population (for example, breast cancer)[3] so it almost evens out that overall there is only a slight increase in cancer for people with SLE versus the general population. The frequency of cancer in patients with SLE is between 2.5 and 13.8%. A literature review has identified nine full-length studies, that estimated the overall risk of cancer in SLE patients compared with the general population; five of them have not noted an increased risk for the development of overall cancers among SLE patients compared with the general population. One study identified a 30% increased risk for occurrence of cancer among 1,585 SLE patients followed over 10,807 patient-years. Taken together it is controversial whether the risk of all cancers is increased in SLE patients compared with the general population.

Increased risk of lymphatic malignancies has been shown in multiple large series of SLE patients, but SLE is usually not associated with an increased risk for the development of most of the solid tumours.

Pathogenic mechanisms involved with the development of lymphoproliferative malignancies in association with SLE include a common aetiologic agent for diseases, environmental factors, the use of cytotoxic, or immunosuppressive agents, genetic variables, and immunologic factors as immunoregulatory disturbances of the immune system[4]. SLE is associated with increased risk of lymphoma and leukaemia. Our case is different because here SLE is associated with solid tumour adenocarcinoma of colon. Tumour-associated antigen cold antibody (CA) 19 - 9 which is a fairly specific marker for gastrointestinal adenocarcinomas was positive in 6 of 19 patients with SLE in one report, and tumour-associated antigen CA 125 was present in active SLE in another study.

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"I attribute my success to this –
I never gave or took any excuse."

– FLORENCE NIGHTINGALE.

CASE REPORT

JIACM 2016; 17(4): 324-26

Nocardia and Pseudomonas co-infection complicating allergic bronchopulmonary aspergillosis

Prabhat Kumar, Nitin Sinha**, Gurmeet Kaur**, RS Tonk***, Nupoor Acharya*****

Abstract

Nocardia is an ubiquitous organism and often causes serious fatal infection in immunocompromised individuals. Patients on steroids and immunosuppressants are particularly at risk. We present the case of a middle-aged lady who was taking oral and inhalational steroids for asthma and allergic bronchopulmonary aspergillosis (ABPA). She came to us with complaints of cough, fever and breathlessness for a week. We suspected nocardiosis based on her co-morbidities and chest X-ray findings. Sputum examination by modified acid-fast staining demonstrated Nocardia and culture showed Pseudomonas aeruginosa. She was given appropriate antibiotics and other supportive treatment, but she did not show any improvement and succumbed to her illness.

Introduction

Nocardia is an ubiquitous organism causing infection in immunocompromised individuals. Risk of acquiring nocardiosis is significantly increased in patients of ABPA who are on steroid therapy. Pulmonary infection is the most common manifestation of nocardiosis and diagnosis is often missed leading to significant morbidity and mortality. Nocardiosis should be strongly suspected in patients who are immunocompromised and have features of severe pneumonia with nodular or fluffy infiltrates on the chest X-ray. Modified acid-fast staining is an easy way to diagnose Nocardia infection and the microbiologist should be asked to look for Nocardia in case of strong suspicion. Often, polymicrobial pneumonia is seen in patients of ABPA taking steroids and with underlying lung pathology.

Nocardiosis is under-reported in ABPA patients and there are only a few cases reported so far in the medical literature[4,5]. We report this case of Nocardia and Pseudomonas co-infection in an ABPA patient so as to make the treating physician more vigilant – as an early diagnosis and treatment of nocardiosis has a better prognosis.

Case report

A 46-year-old nurse presented with complaints of high-grade fever, productive cough with black-brown coloured thick sputum and progressive breathlessness since the last seven days. She was a known case of bronchial asthma since childhood and was diagnosed as having allergic bronchopulmonary aspergillosis (ABPA) one-and-a-half month back by serological and radiological criteria. She was on inhalational steroids with long-acting beta agonists, oral steroids, and voriconazole. She had significant improvement in her symptoms and was doing well. She also had a history of pulmonary tuberculosis 14 years back and had taken a complete course of anti-tubercular therapy and was declared cured.

On presentation, she had fever of 102°F, pulse of 106/minute and blood pressure of 140/80 mmHg. She was tachypnoeic with a respiratory rate of 30/min and was using accessory muscles of respiration. Oxygen saturation was 90% on room air. Mild pallor, facial puffiness, and buffalo hump were present with the rest of her general physical examination being normal. Respiratory system examination showed bilateral coarse crepitations and rhonchi in all the chest areas. Rest of the systemic examination was essentially normal.

Her investigations revealed anaemia (Hb 9.8 gm/dl) with normal total leukocyte count (8,600 cells/cu mm), and normal platelet count (2,50,000/cu mm), deranged random blood sugar (278 mg/dl) with HbA1c of 8.1% and low serum albumin (2.6 gm/dl). Renal function tests, liver function tests and serum electrolytes were normal. Chest X-ray done 10 days prior to her admission was normal (Fig. 1), but the chest X-ray done on the day of admission showed bilateral fluffy nodular opacities (Fig. 2). A repeat chest X-ray on the third day of admission showed bilateral fluffy infiltrates with possible cavitation (Fig. 3).

HRCT chest done one-and-a-half months earlier showed bilateral central bronchiectasis without any cavitation. However, CECT chest during her present illness revealed multiple areas of peribronchial consolidation, ground glass opacities, and bronchiectasis in bilateral lung fields with multiple cavitatory lesions in the posterior segment of the right upper lobe (Fig. 4).

Sputum microscopy showed acid-fast filamentous branching hyphae suggestive of Nocardia by modified acid-

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fast staining (Fig. 5) and sputum culture showed *Pseudomonas aeruginosa* which was sensitive to amikacin, ciprofloxacin, and piperacillin and tazobactam. Sputum KOH preparation did not show any fungal hyphae.

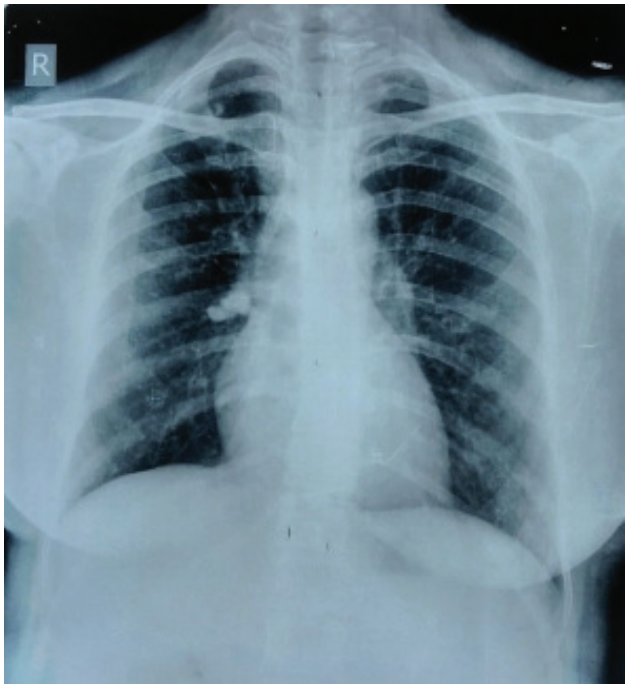

Fig. 1: *Normal chest X-ray done 10 days prior to her admission.*

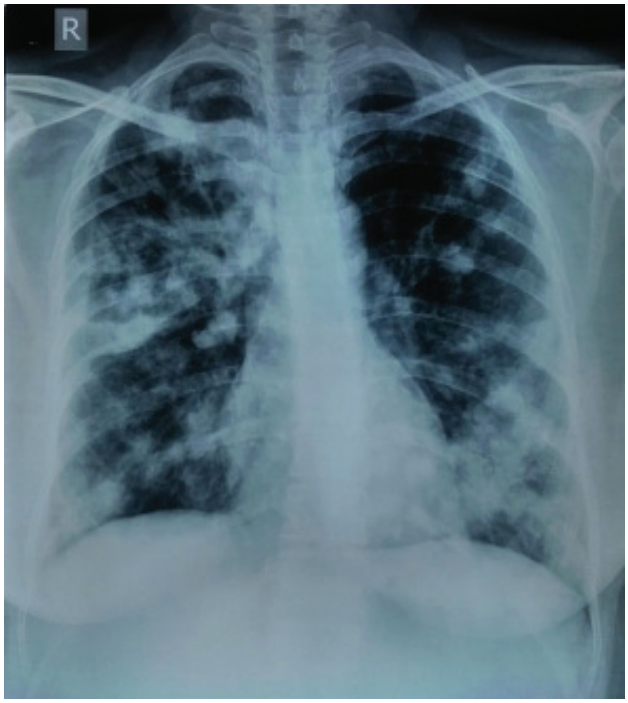

Fig. 2: *Chest X-ray on the day of admission showing bilateral fluffy nodular opacities.*

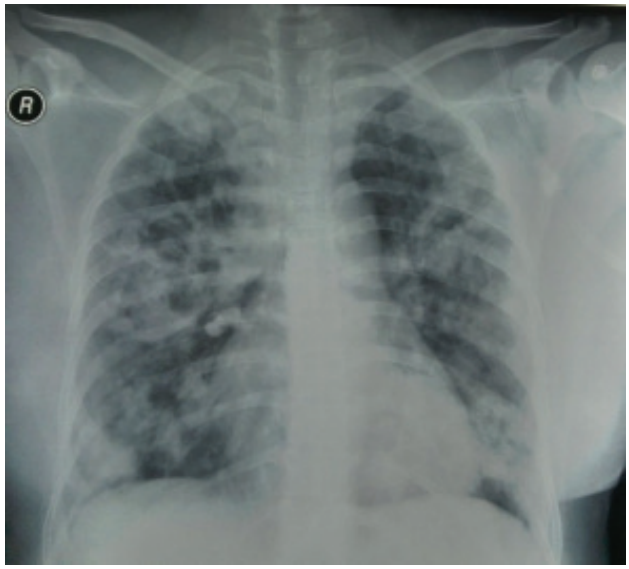

Fig. 3: *Chest X-ray on the third day of admission showing infiltrates with possible cavitation.*

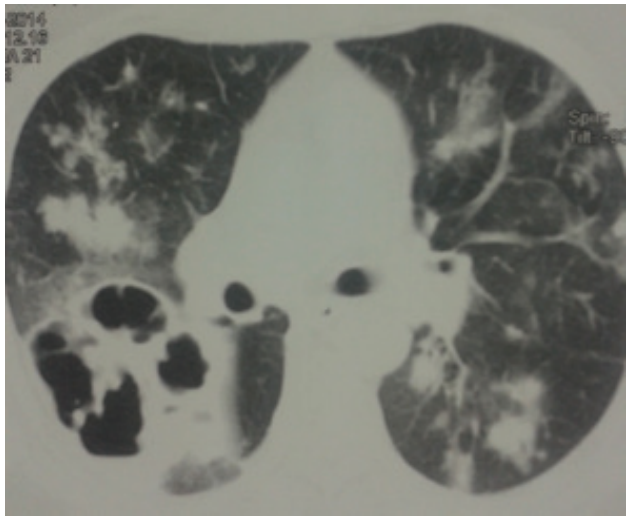

Fig. 4: *CECT Chest showing consolidation and bronchiectasis in bilateral lung fields with multiple cavitations.*

Serum IgE level was 1403 IU/ml and had decreased significantly from its previous value of 7,243 IU/ml done at the time of ABPA diagnosis. Serum galactomannan for invasive aspergillosis was negative. 2-D echocardigraphy was normal. HIV was nonreactive.

The patient was treated with imipenem, amikacin, cotrimoxazole, itraconazole, and insulin. Oral steroids alongwith nebulisation with beta-agonists and steroids were also administered.

She did not respond to the treatment and developed type 1 respiratory failure followed by altered sensorium. She was put on mechanical ventilation, but despite our best efforts she succumbed to her illness after ten days of admission.

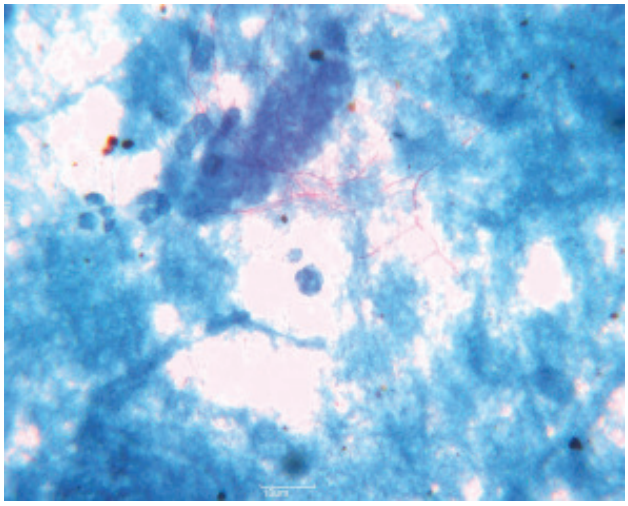

Fig. 5: *Sputum microscopy showing acid-fast filamentous branching hyphae of Nocardia.*

Discussion

Nocardia species are ubiquitous soil borne Gram-positive aerobic actinomycetes. Nocardia causes either localised, or disseminated disease and presentation can be acute, sub-acute, or chronic. It affects all age groups; however, it is two to three times more common in males[1].

Nocardiosis is an opportunistic infection and occurs in individuals with a suppressed cell-mediated immunity. The risk is increased several-fold in people who are on steroids or immunosuppressants, in patients of COPD, cystic fibrosis, haematological malignancy, HIV, and diabetes[2].

Patients with COPD, cystic fibrosis, and bronchiectasis have recurrent lower respiratory tract infections that cause epithelial damage which facilitates growth of nocardia. Further, intake of steroids by these patients impair cell mediated immunity which results in survival and dissemination of Nocardia[3]. Nocardiosis in an ABPA patient is not so well documented in medical literature with only a few case reports published so far[4,5]. ABPA is a lung disease due to hypersensitivity to aspergillus leading to pulmonary infiltrates, worsening of asthma, and often bronchiectasis. Therapy of ABPA includes long-term steroid therapy alongwith antifungal drugs.

Pulmonary involvement is most common in nocardiosis and is acquired through direct inhalation of soil contaminated with Nocardia. Symptoms include productive cough with thick purulent sputum associated with fever, dyspnoea, anorexia, and pleuritic chest pain. Chest X-ray is non specific and may show bilateral infiltrates which are dense with nodules which often cavitate. Diagnosis is made by demonstration of filamentous hyphae on modified acid-fast stain with 1% sulphuric acid. Nocardia can be cultured on various media, but the isolation may take four days to six weeks.

Pulmonary nocardiosis has a high mortality rate ranging from 14 - 40% and about 60 - 100% in patients with dissemination to CNS[6].

Sulfonamides are the drug of choice. Many patients do not show adequate response to combination therapy of sulfamethoxazole (SMX) and trimethoprim (TMP). There are reports of emerging drug resistance in Nocardia to co-trimoxazole[7]. For severe and disseminated disease, a combination of TMP-SMX, amikacin, imipenem, or cephalosporin is recommended[8]. Total duration of therapy is prolonged and ranges from 6 to 12 months depending upon the site and severity of infection.

Polymicrobial infection of lung can occur alongwith Nocardia in immunocompromised individuals and those with underlying lung pathology; however, the incidence is not known yet.

Our patient had multiple risk factors for nocardiosis as she was an asthmatic with ABPA on oral steroids and she was also diagnosed to be having diabetes during her hospital stay. Co-infection with Pseudomonas probably further worsened the clinical condition of our patient.

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CASE REPORT

JIACM 2016; 17(4): 327-28

Non-fatal myocardial damage in zinc phosphide poisoning: A rare manifestation

Neha Sharma, Alok Gupta**, Priyanka P*, Rajkumar Sehra***, Deepak Sharma***, Puneet Nag****

Abstract

Zinc phosphide poisoning is one of the easily accessible, lethal rodenticide presenting with varied manifestations such as nausea, vomiting, circulatory collapse, metabolic, cardiac complications, and multisystem inolvement: (1) Direct myocardial damage in the form of ST elevation myocardial infarction (STEMI) and fatal arrhythmia although rare have been reported; (2) Inadvertant thrombolysis in such patients with streptokinase have been fatal in aluminium phosphide poisoning; (3) Our case presented with history of zinc phosphide ingestion in a state of circulatory collapse with dyselectrolytaemia and ECG showed sequential changes suggestive of ST elevation myocardial infarction which persisted after correction of electrolytes. Cardiac markers were positive. 2D ECHO and TMT were normal. Patient was treated symptomatically and discharged. This is a rare case of non fatal, reversible myocardial damage caused by zinc phosphide ingestion.

Key words: STEMI, thrombolysis, acute pulmonary oedema, phosphine.

Introduction:

Zinc phosphide, a rodenticide is one of the common poisonous agents easily available at home all over world. Intoxication occurs following ingestion or inhalation. After interaction with water or acid (ideal pH 2 - 4), its active metabolite is released:-

$Zn_3P_2+6H_2O \rightarrow 3Zn(OH)_2+2PH_3$

$Zn_3P_2+6H^+ \rightarrow 3Zn_2++2PH_3$

It is rapidly absorbed and affects the mitochondrial cytochrome coxidase enzyme leading to oxidative respiration inhibition at the cellular level causing widespread tissue damage mainly in the heart and lungs.

Patients usually develop circulatory collapse, acute pulmonary oedema, arrhythmias, garlic odour breath, gastrointestinal manifestations such as vomiting, nausea, diarrhoea, acute kidney injury, hepatotoxicity, severe metabolic acidosis, electrolyte disturbances, hypoglycaemia, altered mental status, generalised tonic clonic seizures[1,2,3,4]. The mortality rate is 37 - 100% with no specific antidote[5].

Case report

A 40-year-old male presented to the emergency with history of rodenticide ingestion compound being zinc phosphide in dissolved form with water and of unknown amount after 2 hours with complaints of nausea, vomiting (4 to 5 episodes), non blood stained. At presentation, the patient was drowsy GCS - 11/15 having vitals – PR - 90/min, BP - 70 systolic mmHg, RR - 16/min with no other findings on clinical examination. ECG showed dome-shaped ST segment elevation with T wave inversion in V2 - V4. There was no history of chest pain suggestive of angina.

The patient was treated with gastric lavage, resuscitated with IV fluids and vasopressor support.

On investigation, haemogram, RFT, LFT, serum electrolytes, CPK MB were within normal limits. Troponin I was positive.

Serial ECG showed ST elevation in precordial leads V2 - V5, T-wave inversion in leads I, II, III, avL, avF, V1 - V6 which progressed to sequential changes suggestive of myocardial infarction as shown in Fig. 1. On day 2, the patient was haemodynamically stable without any vasopressor support, GCS being 15/15 with no history of chest pain. ABG revealed compensated respiratory alkalosis with hypokalaemia and hypocalcaemia, which were corrected over 24 hours. 2D echo did not reveal any regional wall motion abnormality and LVEF was 60%. The patient's attendants refused permission for coronary angiography.

The patient was clinically stable and all investigations were within normal limits. He was discharged on day 9 in a satisfactory and stable condition.

Discussion

Zinc phosphide is one of the fatal poisons whose symptoms vary from nausea, vomiting, diarrhoea, pain abdomen, skin burning, altered mental status, respiratory distress, hypotension at the time of presentation, later progressing on to jaundice, decreased urine output, bleeding manifestations[1-5].

According to Chug *et al*, it commonly presents with vomiting (100%), pain abdomen (100%), palpitations, sweating (80%), dyspnoea (75%), metabolic acidosis (60%), shock (40%) in

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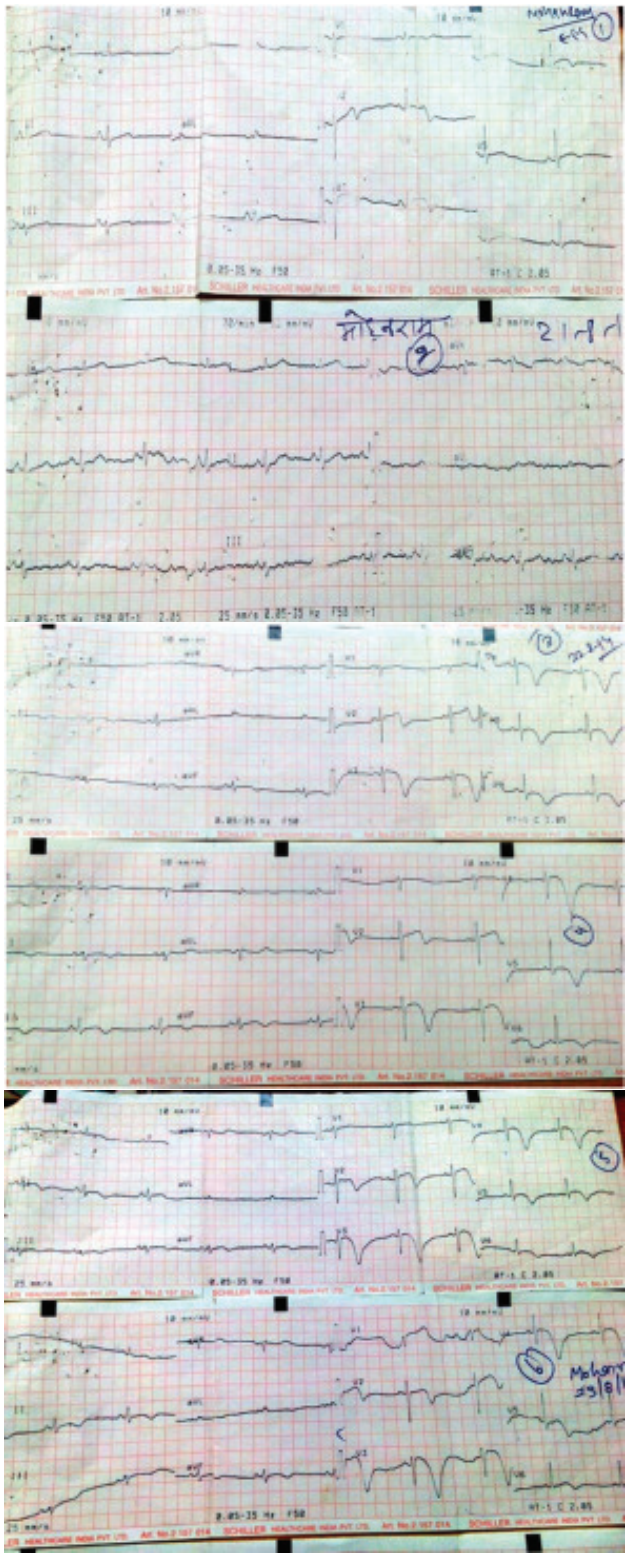

Fig. 1: *ECGs showing sequential ST-T changes mimicking STEMI in the anterior chest leads.*

a study of 20 patients with a mortality of 25% which was due to irreversible shock[6].

The lethal dose for humans in various studies was found to be around 5 - 20 g via ingestion. Various literatures have reported the lethal oral dose as 20 - 40 mg/kg[7].

Table I: Toxic inhalation doses of phosphine gas.

Dose (ppm)	Effects
100 - 190	Serious after 30 - 60 mins
290 - 430	Dangerous after 30 - 60 mins
400 - 600	Death after 30 - 60 mins
2,000	Death after 30 - 60 mins

Cardiac manifestations of zinc phosphide poisoning are arrhythmias, acute pulmonary oedema, and circulatory collapse. Direct cardiac toxicity in the form of myocardial damage although reported is a rare manifestation which is usually fatal[1].

Our case presented with circulatory collapse, altered mental status without any history of chest pain, but developed sequential ECG changes suggestive of myocardial infarction with positive cardiac biomarkers suggestive of myocardial damage. 2D echo revealed no RWMA with normal EF of 60%.

Coronary angiography was not feasible in our patient due to financial constraints. The patient was treated symptomatically and discharged on day 9. Follow-up ECHO was normal and TMT was negative.

Phosphine's toxicity on heart and lungs has been described in a case report by Marino *et al* showing signs and symptoms of myocardial damage in the form of ST elevation mimicking acute MI developing arrhythmia, acute pulmonary oedema, and cardio-respiratory failure which was fatal inspite of intensive care treatment. Inappropriate thrombolysis in such patients has been hazardous.

Thus this case is reported for its rarity – being non-fatal reversible myocardial damage secondary to zinc phosphide ingestion.

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CASE REPORT

JIACM 2016; 17(4): 329-231

Haemodialysis catheter causing internal jugular vein thrombosis and infective endocarditis of tricuspid and mitral valve

Prabhat Kumar, Anand Vishal**, Vaibhav Tandon***, Varsha Ambwani****

Abstract

Infective endocarditis (IE) in a haemodialysis patient is an emerging problem and results in significant mortality and morbidity. We present the case of a young lady who was supposed to get a renal transplant for ESRD (end-stage renal disease) and a double-lumen dialysis catheter was inserted in her right internal jugular vein to provide her maintenance haemodialysis till then. She presented with complaints of fever and palpitation and further investigations showed vegetations on both mitral and tricuspid valves. Multiple valve involvement in catheter-associated IE is unusual and not frequently reported.

Introduction

End-stage renal disease (ESRD) is a major public health problem in a developing country like India. In India the incidence of ESRD has been reported to be 160 - 232 per million population[1]. Approximately 30% patients of diabetes have nephropathy, and with a significant increase in the diabetic population in India, the incidence of ESRD is expected to rise further. Cardiovascular diseases are the most common cause of mortality in these patients, accounting for almost 43% of all cause mortality in patients on haemodialysis (HD)[2].

Infective endocarditis (IE) in HD population was first reported in 1966[3] and now it is one of the leading cause of mortality and morbidity in HD patients. We present a case of tricuspid and mitral valve endocarditis in a patient of ESRD who had a double-lumen dialysis catheter placed in her right internal jugular vien.

Case report

A 25-year-old lady presented with the chief complaints of intermittent fever for 2 weeks, palpitations, and progressive breathlessness since the last 1 week. She was a diagnosed case of ESRD, aetiology of which was not known. She was on maintenance haemodialysis for the last 6 months and a permcath was inserted in her right internal jugular vein four months back. She was doing well and was scheduled for renal transplantation before development of these symptoms. She was admitted to a private hospital for 2 days prior to coming to our institute and had received intravenous antibiotics there.

On presentation, she was febrile, pulse rate was 110/minute, and blood pressure was 140/100 mmHg. She had respiratory rate of 20/min and oxygen saturation was 99% on room air. Mild pallor, facial puffiness were present with the rest of her general physical examination being normal. Cardiovascular system examination showed a muffled first heart sound with a grade 4 pan-systolic murmur in the mitral area which was radiating to the axilla. Respiratory system examination showed bilateral basal crepitations. Rest of the systemic examination was essentially normal.

Her investigations revealed anaemia (Hb 7.0 gm/dl) with a normal total leukocyte count (7,000 cells/cu mm) and normal platelet count (2.0 lacs/cu mm), deranged renal function tests (urea 67 mg/dl and creatinine 4.6 mg/dl) with raised serum potassium and low serum albumin (2.6 gm/dl) levels. Liver function tests were normal. Urine routine and microscopy revealed 2 - 4 pus cells with proteinuria (3+) and 0 - 1 granular casts with no hematuria. Two blood culture samples sent one hour apart before starting antibiotics were sterile. Rheumatoid factor was positive and serum complement level was normal.

Chest X-ray done showed permcath in situ with no cardiac and lung parenchymal abnormalities (Fig. 1).

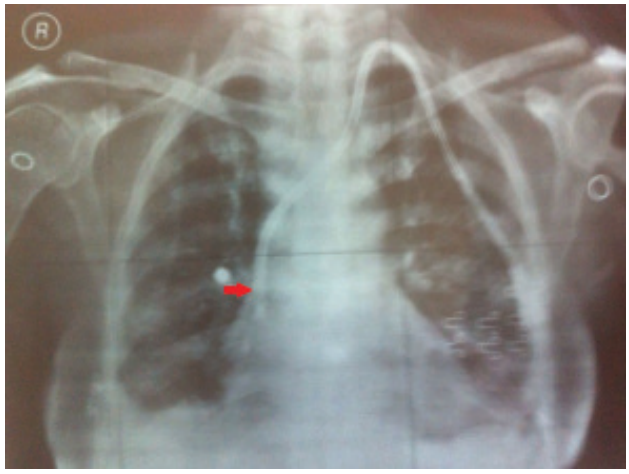

Fig. 1: *Chest X-ray showing permcath in the right internal jugular vein.*

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Ultrasound abdomen showed bilateral shrunken kidneys with ascites and multiple hypoechoic areas in the spleen which were suggestive of splenic abscess or infarction.

2D echocardiography was done which showed severe mitral and tricuspid regurgitation with vegetations on both tricuspid and mitral valve leaflets (Fig. 2 and 3). There was moderate pulmonary arterial hypertension and ejection fraction was 55%. A baseline 2D echocardiography done 6 months back was normal.

Doppler of neck veins showed chronic thrombus with partial recanalisation in the right internal jugular vein.

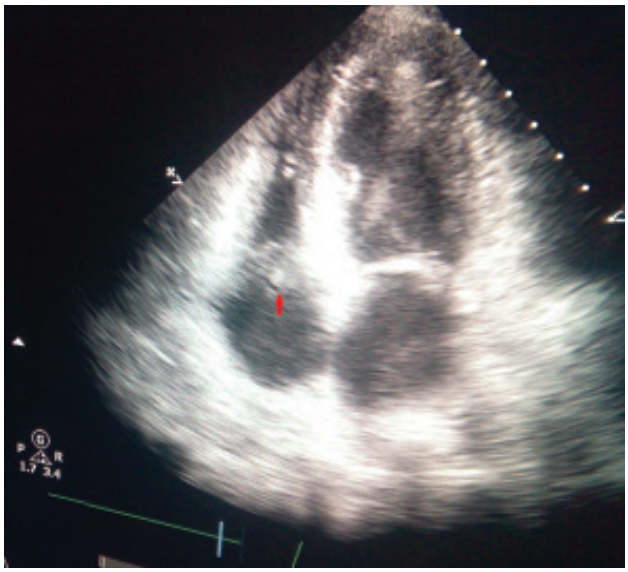

Fig. 2: *Echocardiography showing vegetation on tricuspid valve (red arrow).*

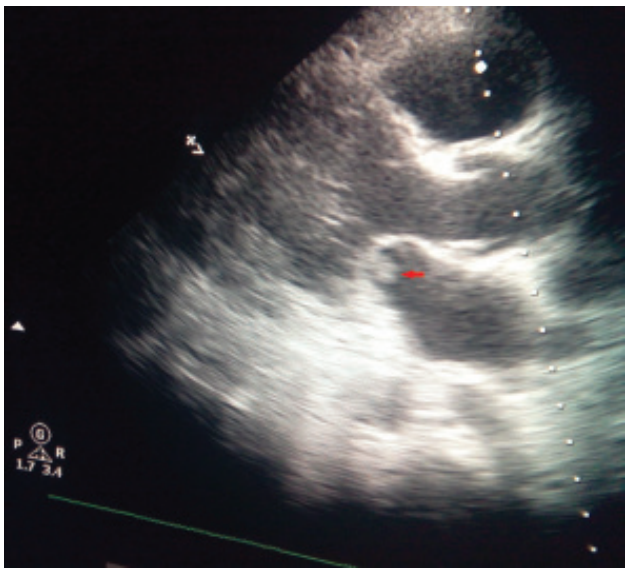

Fig. 3: *Echocardiography showing vegetation on mitral valve (red arrow).*

A diagnosis of infective endocarditis was made as per modified Duke's criteria for IE.

The patient was started empirically on injection ceftriaxone, gentamycin in renal modified dosage, and vancomycin was administered in conjunction with haemodialysis to facilitate its excretion and prevent toxicity. Oral beta-blocker and intravenous loop diuretic were given for heart failure.

As patient had permcath-induced IE, it was removed and its tip culture showed growth of *Stenotrophomonas maltophilia*.

Her symptoms gradually improved and she was given antibiotics for six weeks before discharging from hospital.

Discussion

In the USA, IE is the fourth leading cause of life-threatening infection and 7% - 29% cases of IE are healthcare associated endocarditis[4]. Traditionally, there are four categories of IE – namely, native valve, prosthetic valve, IE in IV drug abusers, and nosocomial IE. However, due to significant rise in cases of healthcare associated IE, it has been proposed to add a fifth category (healthcare associated IE and HD associated IE). In a French study, the incidence of IE in HD patients was found to be 50 - 60 times higher than the general population[5].

There are several possible explanations for increased incidence of IE in HD patients. Degenerative heart valve disease is more common in HD patients due to abnormalities of calcium-phosphorus homoeostasis and chronic inflammatory state due to uraemia[6]. Frequent episodes of bacteraemia are common in HD patients due to dialysis catheters and less frequent in patients with AV fistulas. Often, thrombi are found along catheters which are a predisposing factor for bacteraemia and sepsis[7]. Also, the immune system is often weak in HD patients due to dialysis, malnutrition, and diabetes.

Mitral valve is commonly involved, followed by aortic valve. Isolated involvement of tricuspid valve is unusual. Multiple valve involvement is uncommon[8]. Vegetation can embolise also to distant sites like brain, kidneys, lungs and spleen. Our patient had internal jugular vein thrombosis due to dialysis catheter and vegetation on both tricuspid and mitral valves which also embolised to spleen causing splenic infarction.

Staphylococcus is the most common organism isolated (40%) followed by enterococcus (33%) and streptococcus (17%). Almost 10% patients are culture-negative – posssibly due to prior antibiotic administration. In this case, culture was negative as she had received antibiotics prior to visiting us. Transoesophageal echocardiography TEE (81%) has higher sensitivity than transthoracic

echocardiography TTE (30%) to visualise vegetation. Treatment includes removal of dialysis catheter and appropriate antibiotic coverage as per the culture report. Antibiotics are given for an average duration of 4 - 6 weeks, and often surgery is needed in acute conditions. Since staphylococcus is the most common organism isolated, an empirical regime in culture negative patients should include vancomycin. The mortality rate from HD-associated IE is almost 30% in the next 30 days, whereas cure rate of IE in non-dialysis patient is 90 - 95%[9]. IE can be prevented by using aseptic techniques while manipulating the catheter, topical application of antibiotics at the exit site and using antibiotic lock solution to fill catheters.

Infective endocarditis should be suspected in a patient of ESRD on HD, especially those having double lumen dialysis catheter who present with complaints of prolonged fever, palpitations, or breathlessness. Blood culture should be drawn and sent before starting antibiotics and TEE should be done preferably to look for vegetations. Removal of dialysis catheter and administration of appropriate antibiotics for at least 6 weeks is needed. All dialysis units should have a written protocol to prevent bacteraemia and subsequent development of IE.

Acknowledgement

We are thankful to the Departments of Nephrology and Cardiology, PGIMER and Dr RML Hospital for their support.

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"Everyone of us is, in the cosmic perspective, precious.
If a human disagrees with you, let him live.
In a hundred billion galaxies, you will not find another."

– Carl Sagan.

CASE REPORT

JIACM 2016; 17(4): 332-33

Isoniazid-induced gynaecomastia

*NS Neki**

Abstract

Gynaecomastia due to anti-tubercular therapy (ATT) especially isoniazid is a rarely reported drug reaction. We report a 24-year-old, unmarried, HIV negative male patient of pulmonary tuberculosis who was started on antitubercular treatment (ATT) with rifampicin (R), isoniazid (H), pyrazinamide (Z), ethambutol (E) in combination: RHEZ for initial two months and RHE thereon. After four-and-a-half months of treatment with RHE, he developed painful bilateral gynaecomastia. So isoniazid was withdrawn and the patient asked to continue on R and E up to nine months. On stopping isoniazid, his breast enlargement subsided and became non-tender. On follow-up at 8 months, after withholding isoniazid, the patient became asymptomatic.

Key words: Antituberculosis treatment, isoniazid, adverse drug reaction, gynaeacomastia.

Introduction

Side-effects induced by anti-tubercular drugs are fairly common but few side-effects occur rarely. Since the introduction of isoniazid in 1952, it has remained a key drug in all chemotherapeutic regimens against *Mycobacterium tuberculosis*. Isoniazid is the cheapest and most effective among anti-tuberculous drugs. It is bactericidal against metabolically active bacilli and bacteriostatic against resting bacilli. It is well tolerated at the recommended dose. Rarely, it may cause serious adverse effects in the form of hepatitis, peripheral neuropathy, optic neuritis, optic atrophy, psychosis, seizures, leucopenia, thrombocytopenia, cutaneous changes, high blood sugar, impaired memory[1]. Gynaecomastia due to isoniazid is a rare and nonserious side-effect[2,3]. Only few cases of isoniazid-induced gynaecomastia have been reported in the literature[4,5]. The rare occurence of this side-effect prompted us to report this case.

Case report

A 24-year-old unmarried male patient, non smoker, non alcoholic, was admitted to our hospital with complaints of cough and expectoration, evening rise of temperature, 2 episodes of haemoptysis, and loss of appetite since 3 months. On examination, he was conscious, oriented, anaemic, weight 45 kg, temp 99.9 °F, pulse rate 104/min, regular, with no special character, BP 130/80 mm Hg, no cyanosis, JVP not raised. Examination of the chest revealed crepitations in the left supramammary and upper axillary areas. CVS, CNS and abdominal examination was unremarkable. His genitalia and secondary sexual characters were normal. Laboratary investigation revealed Hb 9.2 g/dl; TLC 11,200/mm^3; DLC N - 82, L - 20, M - 0; urine examination NAD; B. urea 30 mg/dl, S. creatinine 0.8 mg/dl with normal liver and thyroid function tests. ESR was 62 mm at the end of the first hour. ECG showed tachycardia, chest X-ray revealed Koch' lesions in the left upper lobe. The sputum was positive for acid-fast bacilli. Endocrinological investigations including hormonal profile revealed no abnormality. He was diagnosed as a case of sputum-positive pulmonary tuberculosis and was initiated on ATT with rifampicin 450 mg, isoniazid 300 mg, pyrazinamide 1,500 mg, and ethambutol 800 mg once daily for 2 months, followed by HRE for the next 4 months. The patient responded well to the treatment and gained 5 kg weight during the initial intensive phase of treatment. Under treatment follow-up at four-and-a-half months, while continuing with rifampicin, isoniazid and ethambutol, the patient complained of swelling and pain in both breasts. On examination, he had bilateral tender mobile breast lump, about 4 x 3 cm in diameter, not fixed to the underlying structures. The temporal association with ATT led to the presumptive diagnosis of isoniazid-induced gynaecomastia. Hence isoniazid was stopped immediately from the treatment, but R and E were continued with further investigations of the patient to know the cause of gynaecomastia. His mammogram showed features suggestive of bilateral benign mammary tissue hyperplasia indicating true gynaecomastia. On stoping isoniazid – further at one month – the swelling and pain subsided in both breasts and a repeat chest X-ray showed resolution of lesions. Follow-up at six months after the prescribed 9 months of treatment revealed an asymptomatic patient with non-tender slighted enlarged breasts.

Discussion

Gynaecomastia is a benign enlargement of the male breast[3]. It was first described by Paulus Aegineta (AD 625 - 690), who thought it to be due to formation of fat[6].

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Clinically significant gynaecomastia caused by drugs may be due to increase in plasma oestrogen activity, inhibition of testosterone synthesis ratio, or a rise in prolactin level, or by other unkown mechanisms[5]. A large number of drugs are known to cause gynaecomastia[7] and they are diethyl-stilboesterol, digitalis, clomiphine, phenytoin, spironolactone, ketoconazole, metronidazole, cisplatin, diazepam, methyldopa, finesteride, phenothiazines, cimetidine, captopril, metoclopramide, methotrexate, etc. Most of these drug-induced gynaecomastias have been reported by means of case reports[5]. In addition to drugs, gynaecomastia can occur due to various causes including developmental gynaecomastia, congenital causes like Klinefelter syndrome, hermaphroditism, enzyme defects of testosterone production, acquired causes like trauma, infection, torsion, radiation, mumps, chemotherapy, malignancies like bronchogenic carcinoma, alcoholism, congenital adrenal hyperplasia, liver cirrhosis, renal failure, thyrotoxicosis, etc.

In 1953, an year after isoniazid became an integral component of ATT (year 1952), a report from France documented this drug responsible for causing gynaecmastia, then one report from Italy in 1957, and another French report came in 1976[8]. The French report described bilateral gynaecomastia in a 52-year-old man who was receiving 600 mg of isoniazid daily for 4 months along with rifampicin and ethambutol[9]. On investigation, he had a slow acetylator status.

Gynaecomastia is a very rare side-effect of isoniazid. The exact cause is not known, but it is postulated that disturbance in vitamin B6 complex activation in the liver leads to altered oestrogen-androgen metabolism. Another hypothesis is that isoniazid may act by means of a re-feeding mechanism in men with tuberculosis known as 'Re-feeding gynaecomastia', which is supposed to be caused by restoration of weight, gonadotrophin secretion, and gonadal functions[10]. Among anti-tubercular drugs, isoniazid, thioacetazone, and ethionamide have been implicated as a cause of gynaecomastia[11]. Isoniazid-induced gynaecomastia has also been reported in a few Indian reports[2,12,13,14]. As of now there are no reports implicating rifampicin and ethambutol causing gynaecomastia which prompted us to attribute isoniazid as the sole inciting aetiology. Most patients with gynaecomastia require no treatment other than the removal of any inciting cause. Specific treatment of enlarged breast tissue is indicated if it is causing sufficient pain, embarrassment, or emotional discomfort. If surgery is not possible, anti-oestrogens (tamoxifen), or aromatase inhibitors (testolactone) can be tried[15].

Conclusion

The present case highlights a need for the healthcare providers to keep in mind the possibility of occurrence of the rare adverse effect, i.e., gynaecomastia, during the course of isoniazid containing ATT, which may be very embarrasing to the male patient.

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"There are worse crimes than burning books.
One of them is not reading them."

– RAY BRADBURY.

CASE REPORT

JIACM 2016; 17(4): 334-37

Rhabdoid tumour of the brain

Gaurav Jain, Ajay Gaurav Sharma**, Zahid Khan**, Sandeep Chopra***, Varun Jain****, Subimal Roy******

Abstract

Malignant rhabdoid tumour (MRT) most commonly occurs in the kidney. In the central nervous system, cerebellum is the most common site of occurrence. CNS rhabdoid tumours typically occur in small children, do not respond favourably to treatment, and are usually fatal within one-year. Here is reported an eighteen month old child who presented with features of raised intracranial pressure. Apart from papilloedema, there were no neurological signs. Imaging revealed a right temporal SOL with mass effect. He underwent right pterional craniotomy and decompression of tumour. Histopathology revealed rhabdoid tumour. The tumour has a particularly poor prognosis and is largely considered incurable at present, though few cases of long-term survival with aggressive multimodality treatment have been reported.

Key words: Rhabdoid tumour, brain.

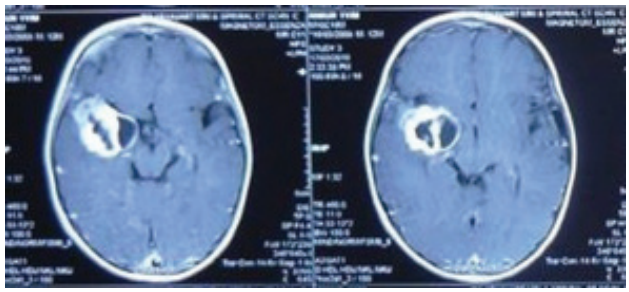
Malignant rhabdoid tumour (MRT) is a rare aggressive childhood neoplasm, predominantly of renal origin. Beckwith and Palmer described a group of renal neoplasms with unique histological features while reviewing a large number of Wilms' tumours for the Children's Cancer Study group in 1978.They considered it a type of Wilms' tumour with rhabdomyosarcomatoid features because of abundant eosinophilic cytoplasm and virulent biological behaviour[1]. However, neither immunohistochemical nor electron microscopic features of the tumour supported this diagnosis and they were named malignant rhabdoid tumour of the kidney by Haas *et al* in 1981[2]. It has been reported at several extra-renal sites, including the brain. They most frequently involve the posterior fossa but have been documented in the supratentorial compartment as well[3,4]. Clinical features are non specific and depend upon the site of occurrence. MRT of brain occurs usually in children and carries a poor prognosis with frequent local recurrences and dissemination through CSF pathways[5,6]. However no established protocol is available for treatment of rhabdoid tumour patients as yet. Here is a rare presentation of this tumour diagnosed as tuberculoma, but on surgery it was revealed to be a rhabdoid tumour.

Case report

This 18-month-old male child presented with a one-week history of headache and vomiting. He had one episode of focal seizure one day prior to admission. On examination, there was no motor, sensory, or cranial nerve deficit. His chest X-ray, ultrasound of abdomen, and urine routine and microscopic examinations were within normal limits.

Contrast-enhanced CT scan showed a well-defined heterogeneous conglomerate mass in the right temporal lobe diagnosed as tuberculoma. Magnetic resonance imaging (MRI) revealed a large heterogeneous mass in the right temporal lobe.The tumour was isointense on T1 and hyperintense on T2-W images, with cystic areas. Mild heterogeneous enhancement was seen on contrast administration (Fig.1A and 1B).The child underwent right temporal craniotomy and gross total excision of the tumour. The tumour was highly vascular, greyish-pink, firm and suckable with Cavitron ultrasonic aspirator (CUSA) with cystic area. On a post-operative CT scan (Fig. 1C), there was no evidence of residual tumour or haematoma.

Histopathology revealed sheets of typical rhabdoid cells with abundant cytoplasm and eccentric vesicular nuclei with prominent nucleoli (Figs. 2A and B). Immunohistochemistry revealed tumour cells to be strongly positive for vimentin (VIM) (Figs. 2C), epithelial membrane antigen (EMA) (Figs. 2D), smooth muscle actin (SMA), focal positivity for glial



Figs. 1A:

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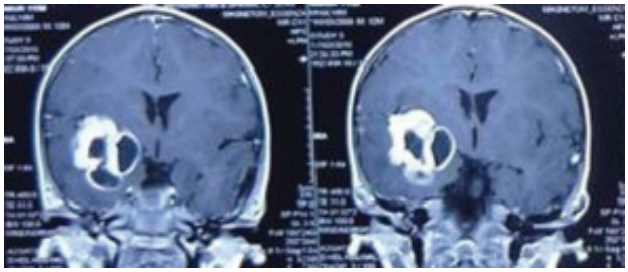

Fig. 1B:

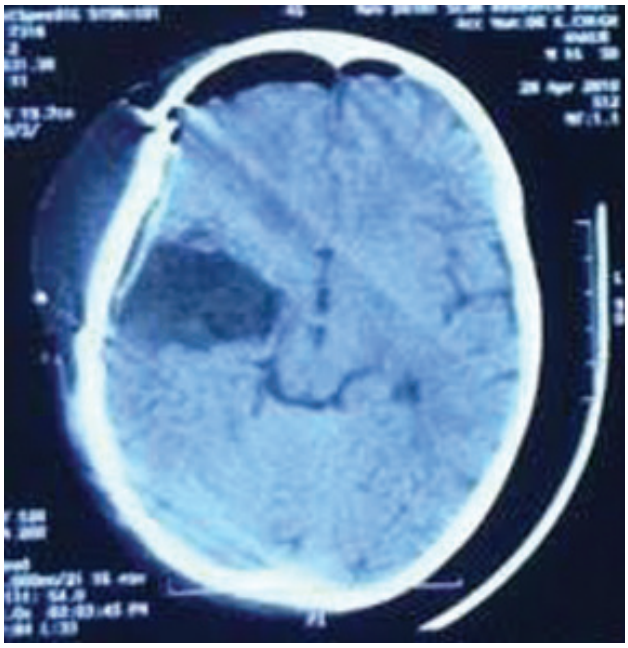

Fig. 1C:

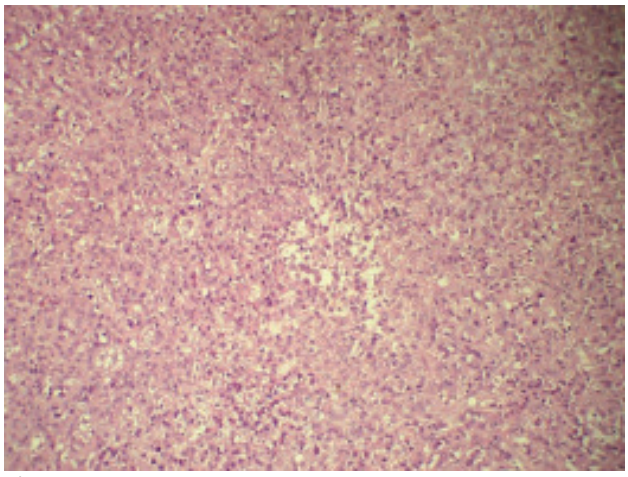

Fig. 2A:

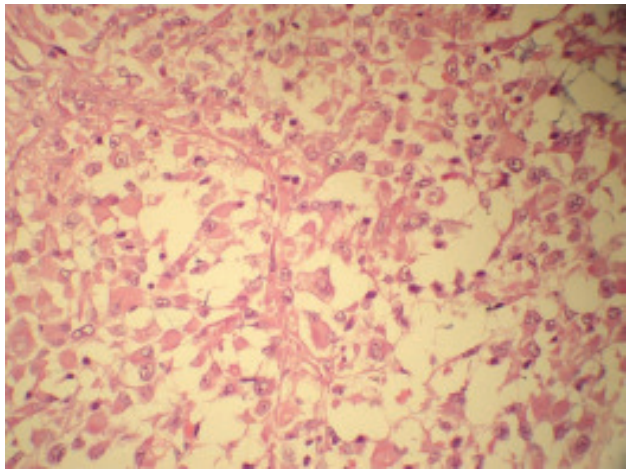

Fig. 2B:

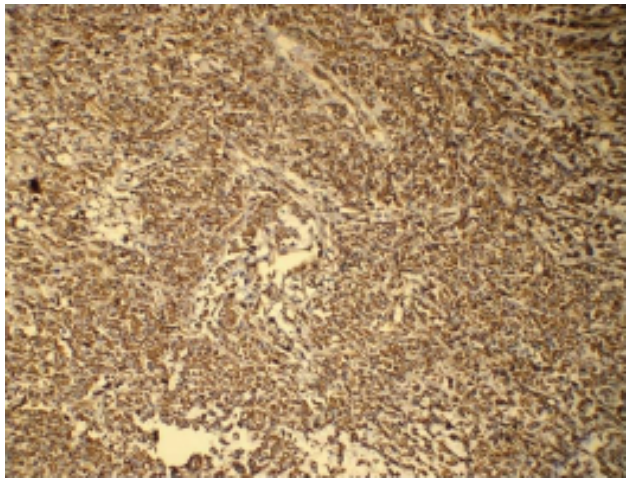

Fig. 2C:

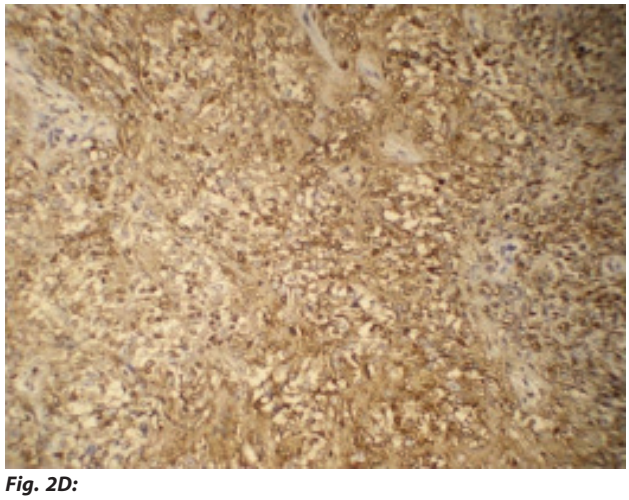

Fig. 2D:

Fig. 2A - D: *Photomicrograph showing sheets of polygonal cells (Fig. A, H and E × 100). On higher magnification, the cells show a distinct cytoplasmic outline, abundant eosinophilic cytoplasm and vesicular nucleus with a prominent nucleolus (Fig. B, H and E × 400). Immunohistochemical staining shows the tumour cells to be positive for Vimentin and EMA (Fig. C, D × 200).*

fibrillary acid protein (GFAP) and synaptophysin, thus confirming the diagnosis. Electron microscopy showed perinuclear aggregates of intermediate filaments.

Discussion

Malignant rhabdoid tumour (MRT) is a rare and highly malignant childhood neoplasm. Several cases of primary intracranial MRT have been reported since its recognition as a separate entity in 1978[1]. The term "rhabdoid" was used due to its similarity with rhabdomyosarcoma under the light microscope. The exact pathogenesis of MRT is unknown, although a possible neuroectodermal origin for renal MRT has been proposed[2]. The cerebellum is the most common location for primary intracerebral MRT. Biggs *et al* were the first to report a primary intracranial MRT[6]. A case of primary renal and brain MRT occurring concomitantly has also been reported[3]. Its highly invasive nature may, in part, be explained by the over-expression of type-IV collagenases relative to tissue inhibitors of metalloproteases (TIMPs)[11]. The average age of presentation of primary MRT of brain is two years (with a range of one month to twelve years) with 1.9:1 male predominance[12]. However, such tumours have also been described in the adults[13]. Though the tumours were located in the supratentorial compartment, among 6 out of 11 patients reviewed from literature by Kumar[14], most of the authors agree that the posterior fossa is the most common site of occurrence[7,8,10,12,13,15-17]. Clinical features depend upon the location of the tumour, though features of raised intracranial pressure are common. Lethargy, ataxia, vomiting, headache, squint, seizures and irritability are the common presenting features[14].

MRT has a marked tendency for subarachnoid dissemination[10], which may be due its spread along the Virchow-Robin spaces[3] and one-third of tumours already have CNS dissemination at presentation[12]. Pathologically, all tumours have rhabdoid cells with abundant eosinophilic cytoplasm, well-defined round nuclei and prominent nucleolus. There are abundant mitosis, and foci of necrosis are common. Reactive inflammatory cells are present in the background. Two-third of such tumours contain areas that, taken in isolation, would be classical primitive neuroectodermal tumours. The most common chromosomal abnormality involves chromosome 22[12].

The imaging features usually are non-specific, showing zones of iso or slight hyperdensity alternating with cystic and necrotic hypodense areas, together with the occasional hyperdensity because of presence of calcification or haemorrhage. Contrast administration causes irregular enhancement pattern, which probably parallels the varied cellular composition of these neoplasms. On magnetic resonance imaging, they are hypointense on T1WI and iso-to-hyper intense on T2WI, with inhomogeneous enhancement on contrast administration. Its heterogeneous appearance is because of presence of cystic and necrotic areas with occasional haemorrhagic changes and moderate-to-marked surrounding oedema. Obstruction of CSF pathways can lead to hydrocephalus. The differential diagnosis must include ependymoma, choroid plexus papilloma, teratoma, and especially PNET/medulloblastoma[15]. The earlier age of onset, larger size and polymorphic appearance help in differentiating MRT with PNETs[16].

Prognosis for MRT is very poor despite surgical excision, irradiation, and extensive chemotherapy. Median survival is six months[12]. However, aggressive multimodality treatment including radical surgery, multi-agent chemotherapy, radiotherapy, intrathecal chemotherapy, and stem cell rescue has prolonged the natural history in a subset of children[18,19]. The authors conclude that the possibility of primary intracranial MRT should be kept in the differential diagnosis of large malignant intracranial childhood neoplasms, especially if they have non-specific imaging findings and are present in the posterior fossa. Final diagnosis can only be made pathologically. The tumour has a particularly poor prognosis and is largely considered incurable at present, though few cases of long-term survival with aggressive multimodality treatment have been reported. As compared to primitive neuroectodermal tumours, MRT has an earlier age of onset, large size at presentation, varying density pattern and inhomogeneous enhancement on imaging, and a poorer prognosis.

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JIACM 2016; 17(4): 338

Hyperpigmentation in vitamin B12 deficiency mimicking Addison's disease

Prabhat Kumar, Gargi Sasmal**, Ratnakar Sahoo****

A 25-year-old student presented with complaints of progressive hyperpigmentation of fingers, nails, face, and lips for the last six months. This was associated with mild fatigue and generalised weakness. There was no history of loose stools, fever, drug intake, or tuberculosis in the past. He was a vegetarian by diet and was not even taking dairy products. On general physical examination, there was hyperpigmentation over both palmar and dorsal aspects of the hand including knuckles, fingers, and creases (Fig. 1). This was also noted over his lips, tongue, oral mucosa and feet (Fig. 2 - 3). Rest of the clinical examination was essentially normal. Blood investigation showed haemoglobin of 9 gm/dl, total leucocyte count was 4,200/cu mm, and platelet count was 100,000/cumm. MCV was 110 fl and peripheral smear showed macrocytic anaemia with thrombocytopenia. Serum bilirubin was mildly raised (2.4 mg/dl) with an indirect component of 1.9 mg/dl. Serum LDH level was also significantly raised (1,100 U/L) and serum ferritin level was normal. A possibility of megaloblastic anaemia was kept and serum vitamin B12 and folate levels were done. Serum B12 level was found to be 121 pg/ml (normal: 200 to 900 pg/ml) and folate level was normal. A serum cortisol level at 8 AM was also done to rule-out Addison's disease, which came normal. He was given vitamin B12 supplementation and after treatment his pigmentation improved considerably.

Vitamin B12 deficiency is a common clinical condition characterised by macrocytic anaemia, pancytopenia, neurological and cutaneous manifestations. Skin hyperpigmenation is a lesser known manifestation in megaloblastic anaemia and can masquerade Addison's disease[1]. Other cutaneous manifestations include glossitis, vitiligo, angular stomatitis, and hair changes[2]. Hyperpigmentation is primarily seen over the dorsum of the hands and feet, interphalangeal joints, oral mucosa, nails, and rarely on creases of palms and soles. Hyperpigmentation in Addison's disease is seen over the mucosa, skin, creases of body, areola and other pressure points. Mechanism of hyperpigmentation in vitamin B12 deficiency is believed to be due to increased melanin synthesis, whereas in Addison's disease it is due to increase in adrenocorticotrophin (ACTH) and melanocyte stimulating hormones[3]. Vitamin B12 deficiency is commonly seen in malabsorption diseases, vegans, pancreatic insufficiency, inflammatory bowel disease and in the elderly[4]. Correction of deficiency often leads to complete improvement in cutaneous manifestations. Therefore, in any suspected case of Addison's disease, a possibility of vitamin B12 deficiency should be always kept.

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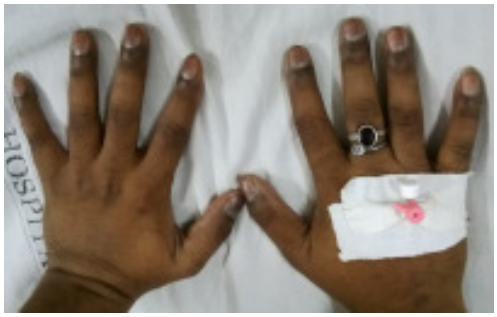


Fig. 1: *Hyperpigmentation of nails and knuckles.*

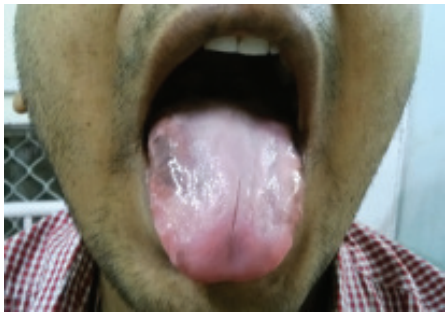
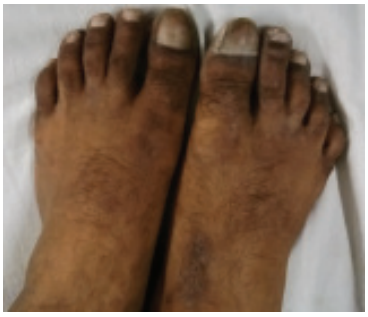


Fig. 2: *Tongue and oral mucosa hyperpigmentation.*



Fig, 3: *Feet hyperpigmentation.*

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† Williams JD. B-Lactamase Inhibition and *In Vitro* Activity of Sulbactam and Sulbactam/Cefoperazone. *Clinical Infectious Diseases.*1997; 24:494-7.

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DOSAGE GUIDELINES:

Usual Adult Dosage	Dosage in Renal Impairment		Dosage for Most Pediatric Patients
2 g to 4 g of the 1:1 ratio (Magnex®) or 3 to 6 g (Magnex® Forte) of the 1:2 ratio, per day IM or IV in equally divided doses every 12 hours. Maximum dosage: up to 8 g per day of the 1:1 ratio (Magnex®) or 12 g per day of the 1:2 ratio (Magnex® Forte). The recommended maximum daily dosage of sulbactam is 4 g.	Creatinine clearance recommended 15-30 mL / min <15 mL / min Please read full prescribing information for other important details on reconstitution, incompatibility, etc.	Sulbactam maximum dosage 2 g / day 1 g / day	Usual dosage of 1:1 ratio (Magnex®) is 40-80 mg / kg / day, in two to four equally divided doses, while that of 1:2 ratio (Magnex® Forte) is 60-120 mg / kg / day. In serious or refractory infections, dosage may be increased up to 160 mg / kg / day of the 1:1 ratio (Magnex®) or 240 mg/kg/day of the 1:2 ratio (Magnex® Forte), in two to four equally divided doses. The maximum daily dosage of sulbactam in pediatrics should not exceed 80 mg / kg / day. In cases where doses above 80 mg / kg / day of cefoperazone activity are necessary, additional cefoperazone should be administered separately or the 1:2 product (Magnex® Forte) may be used. See prescribing information for important additional information on dosage in neonates.

Adapted from approved local product document of Magnex® and Magnex® Forte version no 9.0 (LPDMGX032015)

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#Mean reductions from baseline in HbA1c are generally greater in drug naive patients, those with higher baseline HbA1c values. When given as an add on with metformin and in open label extension phases of trials.

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TRAJENTA™
Composition: 1 film-coated tablet contains linagliptin 5 mg Indications : Monotherapy and Combination Therapy: TRAJENTA™ tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. TRAJENTA™ should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis, as it would not be effective in these settings. Dosage and administration: Adults–The recommended dose is 5 mg once daily. TRAJENTA™ can be taken with or without a meal at any time of the day. Renal impairment –No dose adjustment is required for patients with renal impairment. Hepatic Impairment –No dose adjustment is required for patients with hepatic impairment. Elderly –No dose adjustment is necessary. Children and adolescents –TRAJENTA™ is not recommended for use in children below 18 years due to lack of data on safety and efficacy. Missed dose If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken at the same day. Contraindications: Hypersensitivity to the active ingredient or any of the excipients. Special warnings and precautions: General TRAJENTA™ should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Pancreatitis: There have been post-marketing reports of acute pancreatitis in patients taking linagliptin. If pancreatitis is suspected, TRAJENTA™ should be discontinued. Hypoglycaemia Linagliptin alone showed a comparable incidence of hypoglycaemia to placebo. Sulphonylureas are known to cause hypoglycaemia. Therefore, caution is advised when linagliptin is used in combination with a sulphonylurea. A dose reduction of the sulphonylurea may be considered. Side effects: Nasopharyngitis, cough. Hypoglycaemias in the placebo controlled studies (10.9 %; N=471) were mild (80% %; N=384) or moderate (16.6 %; N=78) or severe (1.9%;N=9). Post –marketing side effect include angioedema, rash and urticaria. Shelf Life: 36 Months. Storage: Store in a safe place out of the reach of children [Source: Trajenta™ PI Version dated June 2014]

TRAJENTA DUO™
Composition: 1 film-coated tablet contains linagliptin 2.5 mg and metformin hydrochloride 500 mg, 850 mg or 1000 mg
Indication: TRAJENTA DUO™ tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate. It should not be used in patients with type 1 diabetes, or for the treatment of diabetic ketoacidosis. It has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using TRAJENTA DUO™.
Dosage and administration: The dosage should be individualized on the basis of both effectiveness and tolerability, while not exceeding the maximum recommended dose of 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily. It should be given twice daily with meals. Dose escalation should be gradual to reduce the gastrointestinal (GI) side effects associated with metformin use. Recommended starting dose: In patients currently not treated with metformin, initiate treatment with 2.5 mg linagliptin/500 mg metformin hydrochloride twice daily. In patients already treated with metformin, start with 2.5 mg linagliptin and the current dose of metformin taken at each of the two daily meals (e.g., a patient on metformin 1000 mg twice daily would be started on 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily with meals). Patients already treated with linagliptin and metformin individual components may be switched to TRAJENTA DUO™ containing the same doses of each component. When TRAJENTA DUO™ is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia.
Pediatric Use: Safety and effectiveness of TRAJENTA DUO™ in pediatric patients under 18 years of age have not been established. Geriatric Use: Linagliptin is minimally excreted by the kidney; however, metformin is substantially excreted by the kidney. Considering that aging can be associated with reduced renal function, TRAJENTA DUO™ should be used with caution as age increases.
Pregnancy and Lactation: Trajenta DUO™ should be used during pregnancy only if clearly needed (Category B).Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
Contraindications: Renal impairment; Acute or chronic metabolic acidosis, including diabetic ketoacidosis; History of hypersensitivity reaction to linagliptin or metformin.
Special warnings and precautions: Lactic acidosis is a rare, but serious, complication that can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, sepsis, dehydration, excess alcohol intake, hepatic impairment, and acute congestive heart failure. If acidosis is suspected, TRAJENTA DUO™ should be discontinued and the patient hospitalized immediately. In addition, TRAJENTA DUO™ should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure necessitating restricted intake of food or fluids. It should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. It is contraindicated in patients with renal impairment. Before initiation of therapy with TRAJENTA DUO™ and at least annually thereafter, renal function should be assessed and verified to be normal. If pancreatitis is suspected, promptly discontinue TRAJENTA DUO™ and initiate appropriate management. Metformin may lower vitamin B12 levels. Monitor hematologic parameters annually. No conclusive evidence of macrovascular risk reduction with linagliptin or metformin or any other antidiabetic drug. There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.
Adverse reactions: Adverse reactions reported in >5% of patients treated with TRAJENTA DUO™ and greater than with placebo are nasopharyngitis and diarrhea. Hypoglycemia was more commonly reported in patients treated with the combination of TRAJENTA DUO™ and SU compared with those treated with the combination of SU and metformin. There have been postmarketing reports of hypersensitivity reactions and acute pancreatitis, including fatal pancreatitis and rash, severe and disabling arthralgia, mouth ulceration, stomatitis.
Shelf Life: 18 Months. Storage: Store in a safe place out of the reach of children.
Version 5 (Jan 2016): [Source: Trajenta DUO™ PI Version Jan 2016]

JARDIANCE™
Composition: 1 film-coated tablet contains empagliflozin 10 mg or 25 mg. Indication: JARDIANCE™ is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Dosage and administration: The recommended starting dose of JARDIANCE™ is 10 mg once daily. In patients tolerating empagliflozin 10 mg once daily and requiring additional glycemic control, the dose can be increased to 25 mg once daily. JARDIANCE™ can be taken with or without food. When JARDIANCE™ is used in combination with sulfonylureas or with insulin, a lower dose of the sulfonylurea or insulin may be considered to reduce the risk of hypoglycemia. Renal insufficiency: JARDIANCE™ is not recommended for use in patients with persistent eGFR <45 ml/min/1.73 m2. No dose adjustment is required for patients with eGFR ≥45 ml/min/1.73 m2. Hepatic insufficiency: No dose adjustment is recommended for patients with hepatic impairment. Elderly: No dosage adjustment is recommended based on age. Initiation of empagliflozin therapy in patients ≥85 years of age is not recommended. Missed dose: If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. Contraindications: Hypersensitivity to the empagliflozin or any of the excipients. This product contains 113 mg of lactose per maximum recommended daily dose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosemia should not take this medicine. Pregnancy, lactation and children: It is recommended to avoid the use of JARDIANCE™ during pregnancy unless clearly needed. It is recommended to discontinue breast feeding during treatment with JARDIANCE™ . Safety and effectiveness of JARDIANCE™ in children < 18 years of age have not been established. Special warnings and precautions: JARDIANCE™ should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. Assessment of renal function is recommended prior to JARDIANCE™ initiation and periodically during treatment, i.e. at least yearly. Caution should be exercised in patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or patients ≥ 75 years of age. In case of conditions that may lead to fluid loss (e.g. gastrointestinal illness), careful monitoring of volume status and electrolytes is recommended for patients receiving empagliflozin. Temporary interruption of treatment with empagliflozin should be considered until the fluid loss is corrected. Temporary interruption of empagliflozin should be considered in patients with complicated urinary tract infections. Side effects: The frequency of minor and major hypoglycemic events was similar for JARDIANCE™ and placebo as monotherapy, as add-on to metformin, and as add on to pioglitazone +/– metformin, but it increased with JARDIANCE™ compared to placebo, in the presence of sulfonylurea and insulin in the background therapy. The frequency of volume depletion was similar to placebo (JARDIANCE™ 10 mg 0.5%, JARDIANCE™ 25 mg 0.3% and placebo 0.3%). In patients ≥ 75 years of age, the frequency of volume depletion events was similar for JARDIANCE™ 10 mg (2.3%) compared to placebo (2.1%), but it increased with JARDIANCE™ 25 mg (4.4%). The frequency of urinary tract infections (UTIs) was similar in patients treated with JARDIANCE™ 25 mg and placebo (7.6%), and higher in patients treated with JARDIANCE™ 10 mg (9.3%). The intensity of UTIs was similar to placebo. The frequency of complicated UTIs was similar between empagliflozin and placebo. Vaginal moniliasis, vulvovaginitis, balanitis and other genital infections were reported more frequently for JARDIANCE™ 10 mg (4.1%) and JARDIANCE™ 25 mg (3.7%) compared to placebo (0.9%), and was reported more frequently for empagliflozin compared to placebo in female patients, and the difference in frequency was less pronounced in male patients. The genital tract infections were mild and moderate in intensity, none was severe. Increased urination was observed at higher frequencies in patients treated with JARDIANCE™ 10 mg (3.4%) and JARDIANCE™ 25 mg (3.2%) compared to placebo (1.0%). The frequency of reported nocturia was comparable between placebo and JARDIANCE™ (<1%). Shelf Life: 36 Months. Storage: Store in a safe place out of the reach of children API dated 19th August 2015
[Source: JARDIANCE™ India pack insert version - 16th June 2014] This is an abridged prescribing information for Jardiance® . It is recommended to refer to the full prescribing information before prescribing.

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