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VIEWPOINT

JIACM 2008; 9(2): 92-5

Where the Mind is Free!

*BM Hegde**

"Where the mind is without fear and the head is held high;
Where knowledge is free……..;
Where words come out from the depth of truth…;"

– Rabindranath Tagore.

Where is that world that Gurudev Rabindranath Tagore was talking about? I wonder if the world will ever be truthful! "Truth", wrote Aristotle, "could only influence half-a-score of men in a century, while falsehood and mystery will drag millions by the nose". How very true? I had a good demonstration of this today while reading the day's newspaper, one of the leading ones by the numbers sold, about the enigma called AIDS, today being the 20th of May when in 1983, the writer claims, that the virus, now called HIV virus, was discovered as the cause of AIDS – almost within two years after AIDS in its present *avatar* made its presence felt. The writer also claims that Luc Montagnier, the French scientist working at the Pasteur Institute, found out that the HIV virus caused AIDS. The author claims, in addition, that Robert Gallo, an American scientist, agreed with Luc and they together went on to describe the cause etcetera. The article claims that this great discovery was first reported on the 20th May, 1983, in the prestigious American journal *Science*. The article goes on and on to describe the various falsehoods and claims that have been made ever since about this poor virus and that killer disease connecting the two in a cause-effect relationship.

Let us examine the truth behind all those claims. In the first place, AIDS was not a new disease. Even as early as 1959 when a few people died of a mysterious pneumonia in Lester General Hospital, some curious doctors had taken the patients' blood and kept them deep frozen. The blood now shows HIV antibodies. Be that as it may, let us see how HIV and AIDS are connected? The first paper in the journal *Science* written by Luc Montagnier's group in Paris is only a case report of a patient with symptoms and signs suggestive of immune deficiency whose bone marrow had a retrovirus which then was supposed to be HTLV virus (the same became HIV later).

Let me give you the original abstract of the paper in *Science* of the 20th May, 1983 issue.

Science. 1983 May 20; 220 (4599): 868-71.

Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS).

Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dauguet C, Axler-Blin C, Vézinet-Brun F, Rouzioux C, Rozenbaum W, Montagnier L.

"A retrovirus belonging to the family of recently discovered human T-cell leukaemia viruses (HTLV), but clearly distinct from each previous isolate, has been isolated from a Caucasian patient with signs and symptoms that often precede the acquired immune deficiency syndrome (AIDS). This virus is a typical type-C RNA tumour virus, buds from the cell membrane, prefers magnesium for reverse transcriptase activity, and has an internal antigen (p25) similar to HTLV p24. Antibodies from serum of this patient react with proteins from viruses of the HTLV-I subgroup, but type-specific antisera to HTLV-I do not precipitate proteins of the new isolate. The virus from this patient has been transmitted into cord blood lymphocytes, and the virus produced by these cells is similar to the original isolate. From these studies it is concluded that this virus as well as the previous HTLV isolates belong to a general family of T-lymphotropic retroviruses that are horizontally transmitted in humans and may be involved in several pathological syndromes, including AIDS."

By no stretch of imagination this could be taken as proof of HTLV virus being the cause of AIDS. None of the scientific criteria for assigning a causative role for that virus had been satisfied. Nor were the Koch's postulates satisfied. Any person with severe immune deficiency would have

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multiple germs invading his/her body. There is no surprise that this poor HTLV virus was found there. If a patient with AIDS has tubercle bacilli in him, does it mean that tubercle bacillus is the cause of AIDS?

Three years later, an African researcher injected the blood of AIDS patients to normal human beings and produced a similar disease. While this "research" is inhuman, it does not show that HTLV virus is the cause of AIDS. Both these reports only show that the two are associated with one another but the 'cause-effect' relationship is yet to be established. Let me hasten to add that our present effort to treat HIV virus with very, very powerful drugs might help the patients as these drugs could temporarily suppress most of the germs – known or unknown – although there are Nobel Laureate researchers like Kary Mullis and Walter Gilbert who feel that the drugs are dangerous in immune compromised patients.

People are worried stiff about the positive HIV test results in healthy people. To reassure them let me quote just one of the hundreds of such studies: "In a population with low probability of infection, the false-positive HIV test is very high. According to a study by Burke *et al* of routine HIV testing of US army recruits, 83% of those that initially tested positive by ELISA was false-positive[1]!"

More intriguing is the presence of HIV negative AIDS patients. Though the CDC reports in the US do not record these cases, by 1993, there were 4,621 cases of HIV-free AIDS which had been documented in the US, Europe, and Africa, with clinical AIDS definition according to the records maintained by Peter Duesberg and quoted in his book cited elsewhere in page 645. Walter Gilbert, a Nobel laureate in Chemistry had this to say: "Duesberg is absolutely correct in saying that no one has proven that AIDS is caused by HIV virus. And he is absolutely correct that the virus cultured in the laboratory may not be the cause of AIDS."

While I do not know what causes AIDS, one could possibly surmise that this is a multi-factorial disease where many of the human activities might depress the immune system singly or collectively, the notable among them being homosexuality, multiple sex partners even in bisexual individuals, many of the habit forming drugs that people take for a kick, alcohol in excess, tobacco, artificial food additives and preservatives and, many of our therapeutic drugs in addition to poverty and malnutrition. Extensive research in the field of viruses and cancer, even in laboratory animals, has shown that the viruses could provoke a disease, including cancer, only in those that have their immune systems compromised by other means. Laboratory animals that are inbred and made to deliver offsprings quickly by artificial means alone respond to viral challenge while the normal animals in the wild do not seem to suffer! It is very premature to think, therefore, that AIDS is caused by that poor virus HIV.

Kary Mullis, the father of the PCR test that detects viruses and a Nobel Laureate professor of chemistry at Berkeley, went in search of the first scientific paper that showed that the HIV (HTLV) virus causes AIDS. Mullis's PCR test is the vital link in the identification of any virus. Kary did not succeed. He contacted many virologists all over the world to know the truth but could not get any response from any of them. All that he found out was that Robert Gallo and Luc Montagnier called a press conference jointly to announce the "so called" discovery that HTLV (HIV) virus as the cause of AIDS. Karry feels that this was the first time an earth shaking scientific discovery was made in a press conference having not been published earlier in any peer reviewed scientific journal! I feel sorry for both of them as they did not get the Nobel!

Peter Duesberg is a world famous virologist at Berkeley and a colleague of Kary Mullis. When Peter wrote a treatise on *Inventing the AIDS virus*, Kary Mullis wrote the foreword from which I quote the following sentence for the benefit of the readers: "We have not been able to (Peter and I) discover any good reasons *why most of the people on earth believe that AIDS is a disease caused by a virus called HIV*. There is simply no scientific evidence demonstrating that this is true[2]." Shocking statement indeed, but a true one to date, to the best of my knowledge. Breaking the tradition, the publishers of the book Regenery Inc. write a foreword in addition to the one by Kary Mullis from which I have quoted the following sentence that tells it all: *"AIDS is the first major political disease, the disease that consumes more government research money, more press time, and indeed probably more heartache – much of it unnecessary – than any other. Duesberg tells us why. If Duesberg is right, we believe he is, he documents one of the greatest scientific scandals of the century."*

This is not an isolated instance of falsehood in medical

science. When SMON (sub-acute myelo-optico neuropathy) surfaced in Japan for the first time killing many patients a few years prior to the Tokyo Olympics, the *Sarkari* scientists in Japan were under great pressure to find a cause and suppress the disease as the Japanese government was worried that they might have to abandon the Olympics. The disease did spread to other areas as well. Lo and behold, the scientists came up with a *slow virus* as its cause which they announced in a press conference. This slow virus, they claimed, was a close cousin of the *Kuru* virus in Africa! They retained their jobs but patients kept dying regularly and many were paralysed totally.

It was a good family physician, Dr. Kono, in one of the Tokyo suburbs, who was very vigilant, that noticed that SMON would hit only those of his patients who took a new quinoline derivative in large doses for their diarrhoea on a long-term basis. His ideas were soon shot down by the virus lobby. After many more deaths and no clue, a professor in Niigta University, Tadao Tsubaki, went on to prove by prospective studies that the quinoline, *clioquinol* (brand name entero-vioform and Emoform) in larger doses was responsible for the syndrome. To cut the long story short, SMON was found to be a dangerous adverse drug reaction of clioquinol. The drug was withdrawn from the market and the deadly disease disappeared, allowing the Olympics to be held in Tokyo[3]. It is worth noting that while the virus lobby could get acceptance within a few months of their hypothesis, it took several bold scientists to work for years to refute that hypothesis. This story is relevant to AIDS saga.

Similarly, medical textbooks even today write that Edward Jenner was the father of vaccination that eradicated the only deadly disease from Planet Earth. The truth is otherwise! Jenner used the cow pox virus to vaccinate against small pox. Today we know that the two are totally different viruses when they are finger-printed! It was TZ Holwell, FRS, FRCP (London) that came to India in a team of twenty scientists sent here by the East India Company to study Indian science and technology in the 18th century. While the rest left after a couple of years, Holwell stayed on for twenty years in *The Bengall* of those days to study a very effective Indian system of small pox vaccination that was being practised by *pundits* from the great Indian universities of yore[4].

Holwell studied the Indian vaccination and its effect on the vaccinated and the unvaccinated segments of society each year prospectively for twenty long years and came to the conclusion that those that were vaccinated had survived ninety per cent while the unvaccinated died ninety per cent in each epidemic. Holwell did what we call today the gold standard of medical research-randomised controlled studies (RCTs). It was in the year 1747 that Holwell went back to England to present his paper to the Royal College of Physicians, strongly recommending that universal vaccination could now be recommended to the King. He wrote that this very successful vaccination used the smallpox virus specially attenuated by the native method and had been in practice since "times out of mind". Holwell's report is displayed in a glass case in the Royal College library for those that want to check the veracity of these statements. Edward Jenner's anecdotal experience of one human being – his errand boy, James Phipps – an orphan aged thirteen years, today would have sent him to the gallows. This is akin to the African scientists injecting AIDS blood to normal subjects.

History is replete with instances where dangerous treatments were administered to hapless patients with this kind of scientific data. Pellagra and Beriberi were both treated as bacterial diseases for decades with powerful antibiotics like arsenic and mercury. Gastric ulcers were treated with milk drips into the stomach. Now we know that milk is a strong stimulator of gastric acid secretion, thanks to its calcium content. Upper GI surgery was very fashionable even until the late 60s. *Doctors Dilemma* by George Bernard Shaw is a good play that unmasks the darker side of the medical moon. Many of the present day illustrated methods of treatment – both medical and surgical – have been found out to be counter-productive and risky by the painstaking research of a former professor of cardiac surgery at Stanford, David Eddy, who now has become a mathematician telling the world that medical science is using the wrong mathematical basis of linear laws in a non-linear dynamic system[5]. There is no space to go into the details here. Such of those readers that want to get to the root might find a goldmine at www.archimedesmodel.com

If the mind is free and the head is held high one can get at the truth, but, it is hard work before that happens. In any

debate, said Acharya Charaka that the truth could come out only when people argue without animosity and with compassion giving authentication for their views. Let the scientific community put their heads together to get at the root of this enigma, AIDS. For all we know it might not be a disease at all, but a conglomeration of many immune deficiency states due to multiple causes. The immune system, the *soil*, as enunciated by Louis Pasteur, could be more important than the *seed*.

Theobald Smith, a thinking American physician, had written way back in 1915 AD that while any disease could be directly proportionate to the virulence of its cause, it is certainly inversely proportionate to the resistance of the host. In the ancient Indian system of Ayurveda, immune boosting is a very important part of health management. There are many powerful immune boosting drugs and techniques mentioned. While modern medicine should have a very strong foundation of emergency care and corrective surgery, it must keep its windows and doors open to wisdom to flow from all sides as Gurudev Tagore had rightly said about his new educational system at Shanthi Niketan. That will only make modern medicine more effective, less dangerous and in addition, it could become patient friendly – the need of the hour.

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ORIGINAL ARTICLE

JIACM 2008; 9(2): 96-9

Trends in Aetiology and Outcome of Patients with Pericardial Effusion: a Five-Year Experience

Yogendra Singh, Sohaib Ahmad**, Saurabh Srivastava**, SK Verma***, Nadia Shirazi****, Anant Dev Surya******

Abstract

Aim: This study aimed to evaluate the aetiology, clinical characteristics, and the outcome of patients of pericardial effusion presenting at Himalayan Institute of Medical Sciences, Dehradun, India over a period of five-years.

Methods: All in-patients and out-patients between January 2002 and January 2007 with a diagnosis of pericardial effusion were studied after excluding post-cardiopulmonary bypass grafting effusion and that associated with Dressler's syndrome. Demographic and clinical characteristics, echocardiographic parameters, laboratory investigations, treatment, and outcomes were retrospectively reviewed using a standardised data collection form.

Results: Of the ninety patients with pericardial effusion, a mild, moderate, and large pericardial effusion was determined echocardiographically in 55 (61.1%), 18 (20%) and 17 (18.8%) patients, respectively. The most frequent aetiologies were tuberculous pericarditis (n = 38, 42.2%), malignancy (n = 13, 14.4%) and idiopathic pericarditis (n = 13, 14.4%). Large effusions were more likely to be associated with malignancy. Thirty-seven patients underwent pericardiocentesis, 2 required pericardiectomy, while five patients died during hospitalisation despite treatment.

Conclusion: Tuberculosis remains the major cause of pericardial effusion; however, pericardial effusions of malignant origin are on the rise.

Keywords: Pericardial effusion, Malignancy, Tuberculosis, Pericarditis.

Introduction

Pericardial effusion can develop in patients with acute pericarditis or may be seen as an incidental and silent finding in a variety of systemic disorders, the frequency varying with respect to geographical regions[1]. The precise aetiology of pericardial effusion remains elusive in a large proportion of patients and may prove to be crucial in certain instances. In developing countries, tuberculosis and viral infections have been recognised as the major cause of pericardial effusion with constrictive pericarditis being a dreaded complication[2]. Malignancy as a cause of pericardial effusion is becoming increasingly common and pericardial involvement is often the sentinel presentation[3].

We retrospectively reviewed the clinical characteristics, management, and outcome in all patients presenting with pericardial effusion to this tertiary care hospital over a period of five years.

Materials and methods

Hospital data of patients with pericardial effusion (both in-patients and out-patients) presenting between January 2002 to January 2007 was analysed and ninety patients (males = 53, females = 37) with a diagnosis of pericardial effusion/constrictive pericarditis were included in the study. Patients with pericardial effusion resulting from cardiopulmonary surgery and Dressler's syndrome were excluded. Demographic and clinical features, laboratory findings, echocardiographic parameters, as well as the outcomes were recorded and analysed using a standardised form.

Following the criteria of Weitzman *et al*, the diagnosis of pericardial effusion was established echocardiographically by the presence of an echo-free space anterior to the right ventricle and posterior to the left ventricle by the commercially available HP Image Point machine. The echo-free spaces were measured at the onset of the QRS complex in diastole and effusion was labelled mild (echo-free space – anterior plus posterior < 10 mm), moderate (10 to 20 mm), or large (> 20 mm). Pericardial tamponade was diagnosed by the presence of *pulsus paradoxus* with right ventricle diastolic collapse on echocardiography.

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Acute pericarditis was diagnosed by clinical features like fever, chest pain – with or without pericardial friction rub, generalised ST elevation on ECG, and subsidence of clinical features with bed rest and non-steroid anti-inflammatory drugs[5]. The diagnosis of viral pericarditis was made in patients with a history of upper respiratory tract infection two weeks prior to the onset of pericardial effusion after excluding other aetiologies.

Tuberculous pericarditis was diagnosed by the identification of acid-fast bacilli or presence of caseating granulomas or positive PCR for tuberculosis in pericardial fluid, evidence of tuberculosis elsewhere in the body, and response to anti-tuberculous chemotherapy (four first-line ATT) and steroids[6]. A pericardial effusion was considered to be of malignant origin on the basis of elevated pericardial fluid CEA (chorio-embryonic antigens) levels or positive cytology or biopsy results. Effusion in patients of collagen vascular diseases was considered secondary to the disease.

Diagnostic pericardiocentesis was performed in 21 patients, while therapeutic drainage was undertaken in 16 patients presenting with tamponade. All the patients received treatment according to the aetiology of pericardial effusion and the in-hospital and follow-up outcomes were analysed as per the hospital records.

Results

From January 2002 to January 2007, there were 53 men (58.8%) and 37 women (41.1%) diagnosed with pericardial effusion, with a median age of 35-years (range 12 – 86 years). The clinical and investigative profile of the study group is shown in Table I and the aetiological distribution is depicted in Table II. A mild, moderate, and massive pericardial effusion was detected in 55 (61.1%), 18 (20%) and 17 (18.8%) respectively.

Acid-fast bacilli were observed in pericardial fluid in two cases, caseating granulomas in 3, PCR positivity in 4, and evidence of tuberculosis elsewhere in the body in 10 of the 38 diagnosed cases of tuberculous pericarditis. Cardiac tamponade was the primary presentation in 7 (18.4%) patients. All patients received four drug anti-tuberculous therapy (ATT) with steroids for a period not less than nine-months, and as per the records, 37 patients improved in relation to clinical and echocardiographic parameters.

Table I: Clinical, radiographic and electro-cardiographic characteristics of patients with pericardial effusion.

Clinical features	
Dyspnoea	67 (74.4%)
Cough	26 (28.8%)
Weight loss/ night sweats	26 (28.8%)
Fever	25 (27.7%)
Hypertension	21 (23.3%)
Pulsus paradoxus	21 (23.3%)
Chest pain	21 (23.3%)
Oedema	9 (10%)
Radiological features	
Normal	41 (45.5%)
Cardiomegaly	28 (31.1%)
Calcification	8 (8.8%)
Pulmonary Koch's	7 (7.7%)
Neoplasm	6 (6.6%)
Electrocardiographic features	
Non-specific ST-T changes	55 (61.1%)
Sinus tachycardia	42 (46.6%)
Low voltage complexes	25 (27.7%)
Arrhythmias	5 (5.5%)

Table II: Aetiological profile of pericardial effusion.

Aetiologies	Total N = 90	Male N = 53	Female N = 37
Tuberculosis	38 (42.2)	25 (65.7)	13 (34.2)
Malignancy	13 (14.4)	7 (53.8)	6 (46.1)
Idiopathic	13 (14.4)	10 (76.9)	3 (23.0)
Collagen vascular diseases	12 (13.3)	2 (16.6)	10 (83.3)
Viral infection	6 (6.6)	4 (66.6)	2 (33.3)
Uraemia	3 (3.3)	2 (66.6)	1 (33.3)
Purulent	3 (3.3)	2 (66.6)	1 (33.3)
Thyroid insufficiency	2 (2.2)	1 (50.0)	1 (50.0)

Figures in parenthesis indicate percentage.

Cardiac tamponade as the primary manifestation was observed in 7 (53.8%) patients with malignant effusion; however, malignant cells were observed on cytology of fluid only in 8 (61.5%) cases. Malignant effusion was observed in 6 patients of carcinoma lung, 3 each in carcinoma breast and gastro-intestinal malignancy and in one patient of acute lymphoblastic leukaemia. Bacterial pericarditis was suspected in 3 patients; however, the

aerobic cultures were sterile in all.

A total of 37 (41.1%) patients underwent pericardiocentesis and 2 patients required pericardiectomy. All but one patient each with tuberculous and idiopathic pericardial effusion became asymptomatic at discharge, despite continuous need for medications. Three patients with malignancy died of severe bacterial infection during hospitalisation.

Table III: A comparison of case series of pericardial effusion in term of aetiology.

Aetiology	Corey 1993 N = 75[10]	Sagrista 2000 N = 322[9]	Tsang 2003 N = 1127[5]	Ours N = 90
Tuberculosis	NA	NA	NA	42.2
Idiopathic	7	29	8	14.4
Malignancy	23	13	33	14.4
Collagen vascular diseases	12	5	4	13.3
Iatrogenic	0	16	35	0
Uraemia	12	6	NA	3.3
Infection	27	2	6	6.6
Post-MI	0	8	3	NA
Hypothyroidism	0	0	NA	2.2
Purulent	0	0	0	3.3
Others	19	21	11	0

All values are expressed in percentage; NA: Not assessed.

Discussion

The pattern of aetiology of pericardial effusion may vary depending on the geographical location, the population studied, and the manner in which the diagnosis is established[2, 7]. The common causes of pericardial effusion worldwide are malignancy, tuberculosis, and a group of idiopathic, viral, and immunological diseases. In developed countries, malignancy is the most common cause of pericardial effusion, while tuberculosis and bacterial infections have been implicated in the pathogenesis in the developing countries although the literature is meager from such countries[3, 8].

The present study demonstrated tuberculosis as the most common aetiology of pericardial effusion, followed by malignancy. An increasing incidence of HIV is a threat for increase in the tuberculous pericardial effusion all over the globe. Already, the incidence of tuberculous pericarditis has shown an increase in Africa as a result of the human immunodeficiency virus (HIV) epidemic[6]. In developed countries, tuberculous pericarditis is less frequent, but a possible increase may be expected in the near future as a result of resurgence of tuberculosis with co-existence of HIV-infection; moreover, large scale immigration from areas of high prevalence may also contribute.

In our study, malignancies emerged as the second most common cause of pericardial effusion, whereas previous studies from this part of the world have shown malignant pericardial effusion being less common[2]. Tsang *et al* reported 1,127 cases of pericardial effusion at the Mayo Clinic (Rochester, Minn., USA) and found malignancy as an important cause of pericardial effusion, whereas tuberculosis was rare[5]. Likewise, the frequency of specific causes of pericardial effusion reported from Spain, America, and France is different from our study[9-11]. The most frequent cause of pericardial effusion was malignancy in these studies. Further, in our study, malignancy (53.8%) was found be the most common cause of cardiac tamponade whereas one-third of cases with tamponade were attributed to malignant causes in an earlier study from the Indian sub-continent, with tuberculosis being the leading aetiology[12].

In about 14.4% of the patients with pericardial effusion, no identifiable aetiology could be ascertained. Idiopathic and

immunological diseases as a group constituted the third major cause of pericardial effusion. All these cases were of mild-to-moderate effusion without tamponade.

In our study, no death or major complication due to pericardiocentesis was encountered, and the rate of minor complications was also rare. Pericardiectomy was performed in two patients. Pericardiectomy remains an important management modality for patients where there is effusive constrictive or constrictive disease, highly symptomatic chronic relapsing pericarditis, or recurrence of effusion despite pericardiocentesis with extended catheter drainage[5]. The overall in-hospital outcome of patients with pericardial effusion was favourable except for malignant effusions.

From the present study, a trend of rise in pericardial effusions associated with malignancies as compared to tuberculosis, can be noted. This change may be due to either an increase in the incidence of malignancies in this region alongwith the availability of better diagnostic tools for their diagnosis, or better control measures and management of tuberculosis with a comparatively low incidence of HIV in this region.

Conclusions

This study retrospectively reviewed clinical characteristics and management of cases of pericardial effusion over the last five-years presenting in a single hospital. Although tuberculosis is still the major cause, malignant pericardial effusions are on the rise. Tuberculous pericardial effusion can be treated effectively by pharmacological therapy in the majority of these patients, whereas percutaneous catheter drainage and pericardiectomy are often needed for malignant pericardial effusions.

Limitations of the study

This is a retrospective study, and over half of all patients included were referred from primary hospitals, and had already received antibiotics. This may preclude positive blood or fluid cultures, and make elucidation of exact aetiologies of pericardial effusions difficult. In our series, we saw no case with HIV infection. Our study analysed the clinical characteristics and aetiological profiles of patients with pericardial effusion in a single, multi-speciality tertiary medical centre, which may not be extrapolated to general hospitals. Nevertheless, despite these limitations, our data still represents an observation of major importance to patients and healthcare providers.

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ORIGINAL ARTICLE

JIACM 2008; 9(2) : 100-2

Clinical and Aetiological Profile of Ring-enhancing Lesions on CT Brain

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Abstract

Background: *The aetiological spectrum of ring-enhancing lesions appears to be different in India as compared to Western literature.*

Methods: *75 patients with single or multiple ring-enhancing lesions on CT brain were included in the study.*

Results: *There was a male preponderance in the study (59%). Seizure was the commonest presentation (68%) as compared to headache (29%). Secondarily, generalised seizure was the commonest type. Majority of the lesions were single (91%) with the parietal lobe being the commonest site of occurrence (45.2%). The commonest aetiology was neurocysticercosis (52%) followed by tuberculoma (20%).*

Conclusions: *This study shows the dominance of small solitary enhancing lesions as an entity distinct to South India with neurocysticercosis being the commonest cause. The low sensitivity of immunodiagnostic tests in our context is due to this lack of multiplicity of lesions.*

Introduction

The advent of computed tomography has had a great impact on neurology, primarily because it solves a fundamental limitation of radiography, namely superimposition of imaged structures.

Contrast uptake in the form of "ring-enhancement" on CT brain has been found in diverse conditions with damage to the blood brain barrier.

A ring-enhancing lesion in brain imaging is a common feature in the Indian subcontinent. The size, shape, wall thickness of ring-enhancing lesions, the extent of surrounding oedema, and importantly clinical history and age of the patient taken into consideration may help to distinguish the condition.

The aetiological spectrum seems to be different from that described in Western literature, with infections like neurocysticercoses and tuberculomas likely to be significant causes of ring-enhancing lesions. With the advent of HIV/AIDS, toxoplasmosis, fungal infections like cryptococcosis/histoplasmosis are also increasingly associated with ring-enhancement.

"Ring-enhancement" can be seen in primary brain tumours, metastases, brain abscesses, granulomas, resolving haematomas, and infarcts. Uncommon conditions include thrombosed aneurysms and tumours such as primary CNS lymphomas.

Progress in immunodiagnostic methods and stereotaxic technology has facilitated definitive diagnosis of the lesions.

Materials and methods

Sources of data

Patients attending OPD and in-patients of medicine department and other specialities at our hospital. The study period was between April 2003 and Oct 2004. Patients of both sexes above the age of 12 years with contrast CT brain film showing single or multiple ring-enhancing lesions were included in the study. Patients with homogeneous nodular enhancements, streaky/patchy enhancement without definite rim pattern, and children below the age of 12 years were excluded from the study. In all patients, a detailed history was recorded and clinical examination was carried-out. All patients underwent routine haematological, biochemical, and serological tests including HIV, VDRL, Chest X-ray and a Mantoux test. Serial transaxial CT scans of the cranium were obtained at 5 mm interval through posterior fossa and at 10 mm interval through the rest of the cranium. Non-ionic contrast was used.

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All CT scans were interpreted in consultation with a radiologist and/or neurologist. Selected cases required interpretation by a neuroradiologist, and if inconclusive, MRI was done. MRI was done if the patient had neurological deficits unexplained by CT scan lesions or when the morphology of ring-enhancing lesion was not clear on CT scan.

Routine CSF tests including cell count, cell type, Gram stain, AFB stain, culture and sensitivity, protein and sugar estimation were done. Special stains like India Ink were done for fungal detection and fungal cultures. Analysis for neurocysticercal antigens was done using Cysticheck kits (ELISA technique). In indicated cases, a stereotaxic biopsy of the ring-enhancing lesion was done or open biopsy when resection was indicated in NIMHANS/ neurosurgery department of our hospital. A Nihon Kohden 1100/A/J/K/G machine was used to record all EEG's.

Results

75 cases of ring-enhancing lesions were studied. 59% of the cases were males and 41% were females. There was a definite male predominance in the study. Maximum number of ring-enhancing lesions were observed in the 21 – 30 years age group. As far as the clinical presentation was considered, seizure was the most common presentation seen in 68% of the cases. Headache was the primary complaint in 29% of the cases. Other presenting complaints included vomiting in 10.6% of the cases, fever in 9.3%, limb weakness in 8%, facial palsy in 5.3%, and altered sensorium in 6.6%. Visual complaints were the presentation in 2.6% alongwith giddiness in a similar proportion of cases. Asymptomatic/unrelated complaints made up the remaining 4%.

When the type of seizures were considered, 65% of the patients presented with a secondarily generalised seizure, 18% had a primary generalised seizure, 12% had a complex partial seizure, and 5% presented with a simple partial seizure. When clinical findings in these patients were considered, subcutaneous nodules were not identified in any of the patients implying the paucity of disseminated neurocysticercosis in our study population. Ongoing seizures in the form of *status epilepticus* or *epilepsia partialis continua* could be observed in 2.6% of the patients. Pyramidal signs were seen in 10.6% of the cases more associated with vascular lesions or large subcortical lesions. Papilloedema was seen in 4% of the cases. As majority of the lesions were supratentorial, cerebellar signs were elicited only in 1.3% of the cases. Associated systemic findings were seen in 2.6% of the cases. When distribution of the lesions was considered, right-sided lesions were seen in 53% of the cases, left-sided lesions in 39%, and bilateral lesions were seen in 8% of the cases. 91% of the lesions were single. Majority of these lesions were less than 20 mm in size. Parietal lobe was the commonest site in 45.2% of the cases. Frontal lobe lesions constituted 32.9%, and occipital lobe lesions were seen in 15%. Temporal lobe lesions were the least forming 6.9% of cases. When aetiology of ring-enhancing lesions was considered, 52% of the cases were neurocysticercosis. Another major aetiology was tuberculoma in 20% of the cases. Brain tumours constituted 8% and brain abscesses made up 6.6% of the cases. Vascular lesions and metastases were found in equal proportion of cases (5.3%) each). Toxoplasmosis was seen in 1.3% of the cases, and the cause of the ring-enhancing lesion remained uncertain in 1 patient.

Discussion

Ring-enhancing lesions are a common problem seen world-wide in all age groups. In this study, ring-enhancing lesions were seen maximum in the 21 – 30 year age group. Wadia *et al*[5] reported that 26.1% of Indian patients with focal seizures have enhancing ring or disc lesions in the CT scan. In another study by Wadia *et al*[4] it was found that among 150 patients with simple partial epilepsy, significant CT abnormalities were found in 68%.Forsgren *et al*[6] in a prospective study of epileptic seizures in adults found that two-thirds of the patients had partial seizures, and in 80% of whom the seizures became secondarily generalised. 16% had generalised seizures without focal onset.

In a series by Ramirez- Lassepas *et al*[7] it was found that 45% presented with generalised seizures, 40% with focal, and 15% with complex partial seizures. CT scan identified structural lesions in 37% of these patients. In the group with non-focal findings, 15% had structural lesions on CT scan. A feature of ring-enhancing lesions in our study which differs from North Indian studies is regarding the multiplicity of lesions. This study shows the dominance of

small solitary enhancing lesions as an entity distinct to South India. This is in accordance to the studies done in Vellore and in NIMHANS. It is this lack of multiplicity of lesions that is cited as the reason for low sensitivity of immunodiagnostic tests in our context . Unlike in Western literature, infective causes were the dominant cause of ring-enhancing lesions in our study.

In a prospective study of 98 adults by Sempere *et al*[3], CT scan disclosed structural lesions in 33 cases. Among those whose CT scans were normal, MRI revealed lesions in 22.2%.

Dam *et al*[1] studied 221 patients with epilepsy and found that among the structural lesions responsible, brain tumours were the cause in 16% followed by cerebrovascular infarctions in 14%.

Daras *et al*[2], in his study of 155 patients from a hospital population who developed seizures after the age of 20, abnormality in CT scan was noted in 62.6% of patients. The occurrence of abnormal CT correlated with patients presenting with partial seizures.

Stereotaxic biopsy is a definitive diagnostic tool which was done in 6 cases in our study. Indications for this included refractory seizures, or progression of lesions in-spite of anti-cysticercal and anti-tuberculous treatment.

Conclusion

In conclusion, there was a male preponderance in the study with seizures being the most common clinical presentation. Partial or secondarily generalised seizures were noted in 35% with only 17% having abnormal EEG findings. Neurocysticercosis was found to be the commonest cause for ring-enhancing lesions across all age groups. Majority of patients with ring-enhancing lesions did not have significant clinical findings on examination.

Immunodiagnostic methods available are not sensitive for the diagnosis of infective causes of ring-enhancing lesions. With the availability of neuroimaging studies like MRI, patients who have structural lesions refractory to medical treatment may be subjected to procedures like stereotactic biopsy for better diagnosis and treatment.

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ORIGINAL ARTICLE

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Evaluation of Levels of p24 Antigen in HIV/AIDS Cases and Correlation with CD4 T Cell Counts

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Abstract

CD4 T cell count and p24 antigen concentration were determined in blood collected from 149 HIV infected patients. HIV infection status was confirmed as per the National HIV testing policy. p24 antigen quantification was done by heat-mediated immune complex dissociation and tyramide signal amplification-boosted ELISA, which has a diagnostic sensitivity similar to that of polymerase chain reaction (PCR). CD4 cells were estimated on FACSCount. Correlation of CD4 T cells and levels of p24 antigen revealed p24 antigen level to be a significant predictor of CD4 T cell decline. CD4 T cell counts at baseline showed that the superiority of p24 measurement was more pronounced at lower levels of CD 4 cells (< 200 cells/µl). p24 antigen level may be of interest as a simple and inexpensive predictive marker of disease progression. p24 antigen level correlated well with that of CD4 lymphocyte count (< 50 CD4 cells r = -0.626, p = < 0.001 and 50 - 200 CD4 cells, r = -0.531, p = 0.016). The lowest level of p24 antigen measurable was 1,905 fg/ml in a patient with CD4 cell count of 222 cells/µl. p24 antigen could be estimated even in patients on ART with stably suppressed viraemia. The level of p24 antigen correlated well with number of CD4 T cells.

Key words: p24 antigen, CD4 T cells, CD8 T cells and HIV.

Introduction

Viral load measurement has become an integral part – and almost indispensable – in the management of patients infected with the human immunodeficiency virus (HIV). This parameter is used to predict progression of HIV disease, assess response to anti-retroviral treatment (ART), and to predict drug failure. However, the viral load assay is not cost-effective for the countries with limited resources like India. The p24 antigen is a major internal structural protein of the human immunodeficiency virus. HIV appears in serum at high level during the primary HIV infection and in the stages of AIDS and advanced AIDS[1-3]. p24 antigen is an excellent marker of HIV expression, replication level, and disease activity, that can be used in the same fields of application as HIV plasma RNA is used[4-6].

In fact, p24 antigen may emerge as an important, and relatively cheaper marker comparable to viral load, which can be used in place of viral load and be of value in the resource-poor countries.

Recently it was shown that heating of plasma or serum sample caused irreversible dissociation of immune complexes leading to improved detection of p24 antigen in HIV infected European individuals. Presence of p24 antigen-antibody complexes lowers the sensitivity for detection of p24 antigen test[7]. This problem has been observed to be particularly prominent in HIV infected African individuals[8]. p24 antigen quantification involving heat-mediated immune complex dissociation and tyramide signal amplification-boosted ELISA gave diagnostic sensitivity similar to that of the RNA quantification by commercial polymerase chain reaction (PCR) kit[9]. The signal amplification boosted HIV-1 protein 24 (p24) antigen level in heat denatured plasma was comparable with HIV-1 RNA level in predicting CD4 lymphocyte decline and survival among persons with the advanced HIV disease[10] and was an effective tool for monitoring response to anti-retroviral therapy. The predictive power of heat denatured p24 antigen level is reported to be comparable with that of CD4 lymphocyte count and/or HIV 1 RNA level, given the low cost [11], the test could be of particular benefit in countries with the highest burden of HIV infection and limited resources.

Hence, a cross sectional study was undertaken to evaluate the role of p24 antigen quantification in HIV infected individuals and to find out whether there is any correlation between CD4 T lymphocyte count and p24 antigen level by performing p24 antigen assay using the heat denatured plasma samples.

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Materials and methods

Subject population

Two-hundred and thirty-three persons with various risk groups referred from various hospitals in Delhi during the period 2002 – 2004 were included in the study. Blood samples were collected and HIV diagnosis was confirmed by detection of HIV antibodies as per NACO guidelines. Out of these, 149 samples were confirmed HIV positive by Western blot assay. These HIV positive individuals on uniform anti-retroviral therapy (first line regimen as recommended by NACO) were divided into three groups: 1) with peripheral CD4 count < 50; 2) 50 – 200 cell/µl; and 3) with CD4 count above 200 cells/µl.

Seventeen (n = 17) samples giving discordant serological results on HIV testing were included for p24 antigen assay. In addition to that, 67 HIV serologically negative samples from cases suffering from infections like hepatitis, tuberculosis, malaria, and leishmaniasis (n = 67) were also included in the study.

CD4/CD8 T lymphocytes enumeration was done by flow cytometry. In brief, a standard flow cytometry method with lysed whole blood and a panel of two colour combinations of fluorescein isothiocyanate and phycoerythrin conjugated monoclonal antibody reagents obtained from a single manufacturer (Becton-Dickinson, San Jose, California) were used to determine the expression of each antigen or antigen combination following the instructions of the manufacturer[12]. Data acquisition was performed on configured FACS Count. p24 antigen level was estimated by ELISA method (according to the manufacturer's protocol). The kits were obtained from Perkin Elmer Life Sciences, Wallac Oy, Finland Turkey. Briefly, the immune disruption of plasma samples was done by using the 1: 6 sample dilution on a dissociation buffer followed by boiling for 5 minutes at 100° C. Samples were cooled and transferred to micro plate wells that are coated with a highly specific mouse monoclonal antibody to capture both free HIV-1 p24 and that which has been released upon disruption of immune complexes in the plasma samples. The captured antigen is complexed with biotinylated polyclonal antibodies to HIV 1 p24 antigen followed by streptavidin +HRP conjugate step. Signal is detected after incubation with OPD which produces a yellow colour that is directly proportional to the amount of HIV-1 p24 antigen captured. Absorbance was analysed on ELISA reader at 492 nm wavelength.

Correlation between CD4 T cells and p24 antigen level could be done in 75 cases.

Statistical analysis: Proportions were analysed by Spearman's correlation.

Results

A total of 233 samples were included in the study. 52.5% were males and 47.5% were females. Mean age of patients studied was 35 ± 1. Evaluation of performance characteristics in terms of sensitivity and detection limit of p24 viral antigen was done in comparison to CD4 T cell counts.

Out of 17 discordant samples, two samples were found to be positive by p24 antigen detection system with an antigen level of 12,080.0 fg/ml and 24,550 fg/ml, respectively.

Out of 149 Western blot confirmed serologically positive cases of HIV, p24 antigen was detected in 143 cases. Sensitivity was found to be 96% and specificity was found to be 97.1%. Lower limit for p24 antigen detected was 1,905 fg/ml in a patient with CD4 T cell count of 222 cells/µl and highest limit of p24 antigen detected was 16,62,000 fg/ml in a patient with CD4 cell count of 194 cells/µl. In the HIV positive group with CD4 T cell count of < 50 correlation between CD4T cells and p24 antigen level was found to be −0.626 and p value was found to be < 0.001 (Fig. 1). Whereas, in the group with CD4 T cell count ranging between 50 – 200 cells/µl the correlation with p24 antigen levels was found to be −0.531 and p values 0.016 (Fig. 2). Correlation of CD4 T cell values ranging > 200 and p24 antigen levels was found to be 0.141 There was no significant correlation between CD 4 T cell counts and p24 antigen levels at counts ranging > 200 cells/µl (Fig. 3).

Table I gives the mean and standard deviations of CD4 T cells and p24 antigen levels in the three HIV positive groups with variable ranges of CD4 T cells.

Table II gives the correlation between the mean CD4 T cell values and the mean p24 antigen levels in the three groups studied.

Table I: The mean of amount of p24 antigen detected at various levels of CD4 cells.

	N	Mean	Standard deviation ±
CD4 cells < 50/mm	25	± 24.24	± 12.98
p24 antigen detected	25	± 86,789.48 fg/ml	± 1,56,574.35 fg/ml
CD4 50 – 200 cells/mm	20	± 141.40	± 32.96
p24 antigen detected	20	± 4,05,565.45 fg/ml	± 8,93,038.16 fg/ml
CD4 > 200 cells/mm	25	± 321.88	± 104.85
p24 antigen detected	25	± 9,619.16 fg/ml	± 17,646.19 fg/ml
Total	75		

Table II: Correlation coefficient.

CD4 cells < 50/mm and p24 antigen level (Figure 1)	*Correlation = –0.626*	p – value < 0. 001
CD4 cells 50 – 200/mm and p24 antigen level (Figure 2)	*Correlation = –0.531*	p – value = .016
CD4 cells > 200/mm and p24 antigen level (Figure 3)	*Correlation = +0.141*	p – value = .500

There is negative and statistically significant correlation between CD4 T cell counts for both < 50 and 50 – 200 cells/mm and p24 antigen level. There was no correlation between CD4 T cell counts > 200 and p24 antigen level.

Discussion

We found a single step procedure for immuno-complex dissociation that does not require chemical reagents easy to perform and feasible. The test can easily be performed by laboratories undertaking ELISA tests for HIV diagnosis.

In an HIV infected individual there is an initial peak of viral replication which is followed by a period during which little virus and/or p24 antigen is present in plasma (clinical latency stage). It has been reported that p24 antigen level was a significant predictor of CD4 T cell count and was superior or equivalent to plasma viral RNA level.

CD4 count at baseline showed that the superiority of p24 – antigen measurement was more pronounced at lower levels of CD4 cells (< 200 cells/µl)[7] as shown by a negative correlation between the two parameters. In our study we also found as expected that the p24 antigen level decreases with increase in CD4 lymphocyte count .

Low levels of p24 antigen may not always be due to immune complex formation but may reflect an effective host immune response which is initially successful in restricting/ controlling the viral replication. There is an inverse relationship between p24 antigen and the CD4 lymphocyte count particularly when the CD4 counts range from < 50 cells to < 200 cells/ul of blood. Increase in free antigen level usually occurs, only when there is a decline in p24 antibody and a drop in the count of CD4 T lymphocytes[13] either early during infection, stage of AIDS and/or in cases of failure of ART.

Viral protein like p24 antigen could be at least as good a marker of HIV disease activity as plasma viral load, provided that it is measured with assays having sufficient sensitivity and accuracy. The assay used has been found to have a sensitivity of 96% and specificity of 97.1%. The p24 antigen assay is inferior to RT-PCR in detecting HIV infection. The p24 antigen detection assay used in the present study has been reported to have sensitivity and specificity similar to RT-PCR for detecting infection in early and late stages of HIV infection when the HIV viral load is expected to be high.

The results of the study show that the p24 antigen quantification may be suitable for monitoring anti-retroviral treatment in both adults and children, particularly in resource-poor countries like India. p24 antigen was measurable even in patients with stably suppressed viraemia, and its concentration correlated negatively with less than 200 CD4 T cells concentration, and positively with the concentrations of activated CD8 T cell subsets.

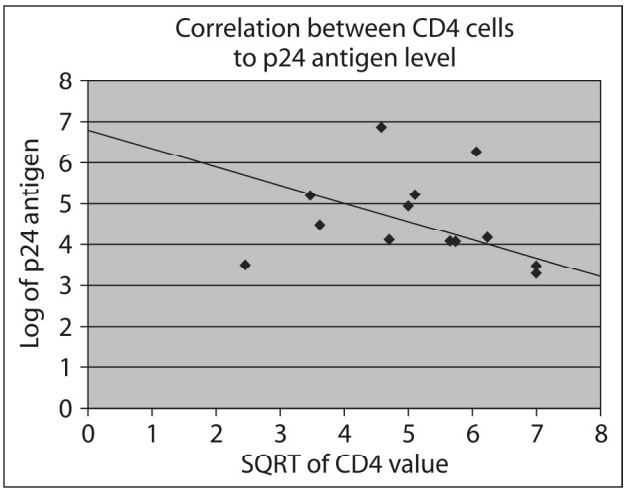

Fig. 1:

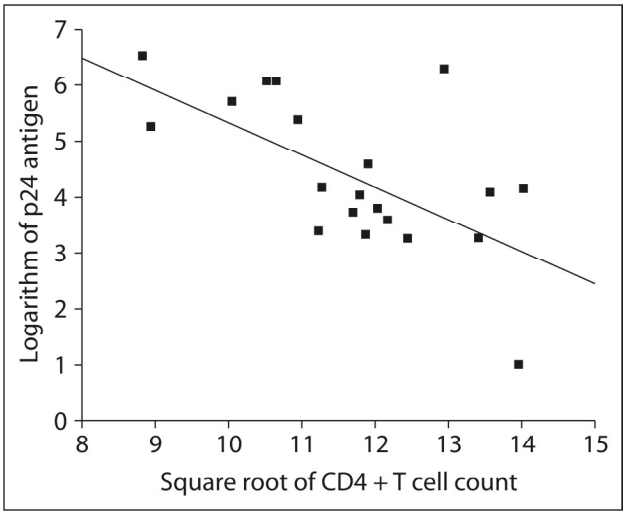

Fig. 2: *Correlation between CD4 cell count 50 – 200 cells/mm and p24 antigen level.*

Since the half-life of virus particles is only a few hours[14], if not minutes[15], a large part of trapped virus will be degraded and viral RNA will be digested. In agreement with this, the viral RNA load in the acute seroconversion phase is high in lymphoid tissues, but low in plasma. So p24 antigen marker is extensively used for diagnostic purpose in the early infection phase rather than as an indicator of the viral load.

p24 antigen concentrations are similarly high in patients exhibiting 100, 200 or 300 CD4 T cells/µl. While patients with 50 CD4 cells/µl or below exhibit slightly lower antigen concentrations[16]. Our study agrees with the above findings, i.e., p24 antigen with CD4 T cell count < 50 correlation

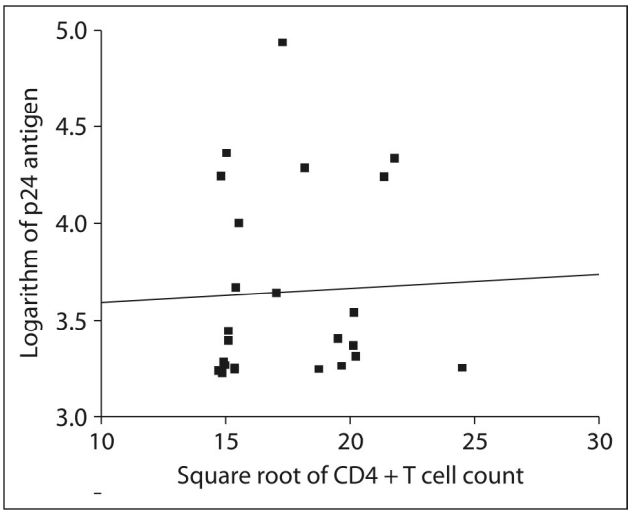

Fig. 3: *Correlation between CD4 cell count < 200 cells/mm and p24 antigen level.*

was found to be –0. 626, and in patients with CD4 cell counts ranging between 50 – 200 cells/µl the correlation was found to be 0.531.

It is likely that the destruction of the follicular dendritic cell network, which is typically present in advanced HIV disease, leads to a decreased retention and destruction of HIV particles, and more virus reaches the peripheral blood[17]. A reduced virus production in the final stage, as suggested by the decreasing concentrations of p24 antigen in plasma would be in keeping with the total destruction of the CD4 T cells. Inverse correlation shows that total p24 antigen increases when the host immune response is depressed.

The level of heat denatured p24 antigen thus predicted subsequent clinical progression in early stage of HIV infection, and closely correlated with CD4 T lmphocyte counts[18]. p24 antigen may be detectable transiently during primary HIV infection and again after years of HIV infection with clinical or laboratory evidence of immunodeficiency[19]. Free antigen may be detected during the period before sero-conversion and during the late symptomatic phase of HIV disease. We have observed that the level of p24 Ag by ICD assay is likely to be high when the CD4 lymphocyte level is low.

The ability of heat denatured p24 antigen level to predict HIV disease progression among adults with various risk groups and the use of the test to resolve the result of serologically discordant samples has not been assessed.

Conclusion

Heat dissociated (HD) p24 antigen is a sensitive, specific, and quantitative marker for HIV in adults. These properties together with the other advantages of ELISA such as simplicity and assay speed, the possibility of automatisation and effectively low cost render testing for HD-Ag an attractive alternative to the technically demanding and expensive PCR and expensive viral load assay. The systematic use of HD-Ag contributes to earlier diagnosis, identification of, and to better knowledge of quantitative viral aspects in the pathogenesis of AIDS. Appearance of ICD p24 Ag in an asymptomatic patient may occur because of a diminution in effectiveness of the immune response and may signify progression to the symptomatic phase of the disease[20].

Additional studies in a larger number of adults are important to further delineate the prognostic value of p24 assays. Evaluation of ICD p24 antigen level assay vis-à-vis viral load estimation will further emphasise the status of this assay for use in monitoring response to ART.

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REVIEW ARTICLE

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Role of Statins in Heart Failure

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Abstract

The prognosis of heart failure (HF) remains grim even after improvement of heart failure treatment with combination of angiotensin-converting enzyme inhibitors, diuretics, beta-blockers and digitalis. Half of all patients with a diagnosis of heart failure could die within 4 years, and of those in severe heart failure, 50% could die within 1 year. In view of this bleak scenario, any new addition of drugs to the existing therapeutic armamentarium for treatment of heart failure is always welcome. Statins have been shown to lower morbidity and mortality in coronary artery disease and other atherosclerotic vascular diseases. Analyses of these trials have shown statin therapy reduces the risk of developing heart failure. Statins have therapeutic properties that are of potential benefit to patients with heart failure of both ischaemic and non-ischaemic aetiologies, irrespective of lipid levels. Some concern has been raised regarding the potential adverse effects of statins in heart failure. Low blood cholesterol levels are associated with poor outcomes in advanced heart failure. However, current observational data strongly support the use of statins in appropriate patients. Ongoing trials like CORONA and GISSI-HF are expected to provide more robust evidence for the therapeutic role of statins in the treatment of heart failure.

Key words: Statins, Heart failure, Pleiotropic effects.

Introduction

Although mortality from coronary artery disease is declining, the incidence and health burden due to heart failure are rising. In the United State of America alone, approximately 5 million persons have heart failure (HF) and 550,000 new cases are diagnosed annually; HF is the most common cause of hospitalisation among persons aged ≥ 65 years and health care costs for HF exceed $20 billion annually[1]. Unfortunately, no data exists regarding the incidence of HF in India. Patients with HF having severely reduced left ventricular function and severe symptoms are at particular risk with mortality rates approaching 30% per year[2]. Current therapy for patients with chronic heart failure includes angiotensin converting enzyme inhibitors, β-adrenergic receptor blockers, diuretics, and digitalis. However, despite aggressive medical therapy, HF is a major cause of morbidity and mortality worldwide. Half of all patients with diagnosis of HF could die within 4 years, and those in severe HF, 80% could die within 1 year[3].

The 3-hydroxy-3 methylglutaryl coenzyme A reductase inhibitors (statins) are among the most frequently prescribed medications in clinical practice used for treating hypercholesterolaemia and coronary artery disease (CAD). However, clinical trials for primary and secondary prevention of CAD have routinely excluded patients with HF. Despite the frequent intersection of CAD with HF, the relationship of statin therapy to outcomes in HF is not well established[2]. Additionally, many patients with HF do not have significant CAD, and the appropriateness of therapy with statins is unclear. In the present article, we shall review the evidence for and against the use of these agents in patients with HF and whether they are indicated at all in patients with non-ischaemic HF.

Role of statins in ischaemic heart failure

Statins are of proven clinical benefit in patients with CAD, at least in those who do not have HF[4]. Consequently, the greatest potential benefit of studies in HF is probably in those patients with CAD. It is highly likely that the proportion assumed to have CAD is actually an underestimate, as patients with HF thought not to have CAD are often found to have CAD, if invasive investigation is undertaken[5].

Current evidences

Fundamental to the proposition that statins may reduce the progression of HF is the belief that acute coronary events (which statins reduce) contribute to this progression. There is good evidence that this is, indeed, the case.

In the Studies Of Left Ventricular Dysfunction (SOLVD), interim myocardial infarction (MI) and unstable angina (UA) increased the risk of death and hospitalisation for HF[6]. MI

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had a particularly powerful effect, more than doubling the one-year risk of HF hospitalisation from 8.6% to 20.5% (relative risk: 2.1, 95% confidence interval: 1.6 – 2.6).

A similar insight can be gained from the Scandinavian Simvastatin survival study[4]. In the placebo group of 4S, 52% of patients developing HF had a preceding, post-randomisation, MI (i.e., in many, if not most, patients a recurrent infarction). Of those not developing heart failure, the proportion having interim infarction was only 16%.

Limitation of present data

However, recognised MIs are uncommon in HF trials[7]. This may be because infarction is more commonly fatal in patients with HF, and death is then classified as sudden death rather than due to MI[8]. It is also possible however, that CAD becomes burnt out as HF worsens. Thus, new coronary events are uncommon, and progression of disease occurs in other ways. Review of data from HF trials and registers also suggests that angina may be more common in milder HF and less so in patients with more advanced HF[9]. Overall, therefore, it is likely that acute coronary events are probably a more important mechanism of progression in patients with lesser degrees of HF and LV systolic dysfunction.

Even in such patients, there is evidence that statins retain their efficacy in preventing acute ischaemic events. In the Cholesterol And Reduction of Events (CARE) study, 706 patients with a LV ejection fraction (EF) of > 0.25 and < 0.40 were randomised[10]. Pravastatin was equally effective in reducing coronary events in these patients as in patients with an EF of > 0.40 (Fig. 1).

Ongoing definitive trials of statins in heart failure

Several large-scale trials are currently underway to examine the efficacy of statins on clinical outcomes in HF patients. The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) is currently enrolling 4,950 patients with ischaemic cardiomyopathy and symptomatic HF (NYHA functional class III or IV) and an EF of 40% or less or NYHA functional Class II and IV of 35% or less.[34] The primary objective of this study is to examine the effect of rosuvastatin (10 mg daily) versus placebo on the composite end-point of cardiovascular death, non-fatal MI or non-fatal stroke.

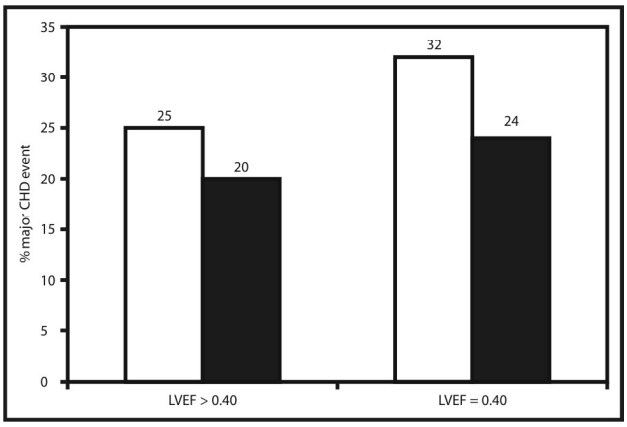

Fig. 1: *Effect of pravastatin on coronary events in patients with coronary artery diseases and a left ventricular ejection fraction (LVEF) of > 0.40 enrolled in the Cholesterol and Recurrent events trial[10]. CHD = coronary heart disease. White bar = placebo, Dotted bar = pravastatin.*

GISSI – HF is another ongoing project which is a placebo controlled multicentre clinical trial[35]. This trial is evaluating the effects of N-3 polyunsaturated fatty acids (PUFAs) and rosuvastatin in patients with symptomatic HF (NYHA functional Class II – IV) of both ischaemic and non-ischaemic origin. Approximately 7,000 patients will be randomised to n – 3 PUFAs (1 g daily) or placebo and to rosuvastatin (10 mg daily) or placebo, with co-primary end-points consisting of, first all cause mortality, and second all cause mortality or cardiovascular hospitalisations. Both trials are expected to be completed within the next few years and should provide strong evidence for the therapeutic role of statins in the treatment of HF.

Evidences for role of statins in ischaemic heart failure

Lowering cholesterol levels with statins results in significant reduction in mortality and cardiovascular end-points in comparison with placebo in patients with relatively preserved left ventricular function and both normal and high levels of plasma cholesterol and proven CAD[4]. Retrospective, non-randomised subset analyses suggest a possible benefit of statins in HF patients.

Retrospective studies

In the 4S study, the mortality rate in patients developing HF was 25.5% in the simvastatin group compared with 31.9%

in the placebo group[4]. Among those who developed HF, simvastatin conferred a 6.1% absolute risk reduction for mortality, compared with 2.6% absolute risk reduction in patients without HF.

Similar results were noted in a retrospective analysis of Losartan Heart Failure Survival Study (ELITE II)[11]. In this study 3,152 HF patients were randomly assigned to either losartan or captopril. While only 11% of the study cohort were on statin therapy, those individuals receiving statin had a significantly lower all cause mortality (10.6%) compared with those not taking statin (17.6%).

These results were validated by a study of 551 patients with advanced systolic HF of various aetiologies referred to the cardiomyopathy clinic for HF management and transplant evaluation[12]. Patients had a mean EF of 25%, and nearly half had CAD. Forty-five per cent of patients in the study cohort received statins. As expected, patients on statins were more likely to have known CAD, or known atherosclerotic risk factors including hypertension, diabetes, and a history of tobacco use. The blood cholesterol levels were nearly similar in all the patients, irrespective of statin use. After adjustments for age, gender, presence of CAD, cholesterol levels, diabetes, medication use, haemoglobin, creatinine, and New York Heart Association (NYHA) functional class, statin use was associated with a 14% absolute risk reduction in mortality or necessity for urgent heart transplantation at one year. Although reduction in mortality associated with statin use was substantial, the findings should be cautiously interpreted in light of the retrospective and non-randomised nature of the study.

Prospective studies

Mozaffarian *et al* have prospectively evaluated the relationship between statin use and clinical outcomes in patients with HF[13]. Using data from Prospective Randomised Amlodipine Survival Evaluation (PRAISE) trial, they examined the effects of statin on overall mortality in 1,153 patients with advanced systolic HF and NYHA Class III B or IV symptoms. The PRAISE trial was a randomised study of amlodipine versus placebo in HF patients. Approximately 12% patients received a statin during the study period. Over a mean follow-up of 1.3 years, statin use was associated with a 62% reduced incidence of death. The association persisted even after adjustment for differences in clinical characteristics and serum cholesterol levels among statin and non-statin treated groups and after propensity score analysis.

Observational studies

Ray *et al* have done largest observational study of statin use in HF[14]. They carried out a population based retrospective cohort study of 28,828 patients, aged 66 – 85 years, who survived at least 90 days following hospitalisation for HF. Using administrative data from the province of Ontario, Canada, the authors reported that, during the 7 years study period, patients who were newly dispensed statins (n = 1140) had a statistically significant 28% reduction in the incidence of death, MI, or stroke (13.6 per 1,000 person years) compared with patients who were not dispensed statins (n = 27692; 21.8 per 1,000 person years). The benefit from statins in the study was mostly related to reduction in all cause mortality. Several important limitations of this study should be considered. Confounding the results are higher rates of previous angina, acute MI, or revascularisation procedures, and greater co-morbid conditions, including hypertension, dyslipidaemia, and diabetes, among those patients prescribed statins at discharge. Consequently, these individuals were more likely to be prescribed ACE inhibitor, angiotensin II receptor antagonists, aldosterone antagonists, and aspirin – all of which are known to improve outcomes in HF patient.

Evidences for role of statins in non-ischaemic heart failure

While CAD is a common cause of HF, the question arises whether patients with non-ischaemic HF can benefit from statins. Very little is known about the benefit of statins in this group of patients.

Node *et al* have examined the effects of short-term statin therapy in patients with non-ischaemic, symptomatic HF[15]. Sixty-three patients with NYHA class II-III HF were randomised to simvastatin (10 mg/day) or placebo. After 14 weeks, the statin group had lower NYHA functional classification (2.04 vs. 2.32, $P < 0.01$) and significantly lower plasma concentration of tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), and brain natriuretic peptide (BNP)

compared with the control group. In addition, statin treated patients had improved EF at 14 weeks (34% to 41%, P < 0.05) compared with baseline. This effect was not seen in the placebo group. These results do provide initial evidence for the beneficial effects of statin therapy in patients with non-ischaemic HF.

Role of statins in diastolic heart failure (DHF)

In a hypothesis-generating preliminary study, Fukuta *et al* examined 137 consecutive HF patients with an EF of at least 50% who were being evaluated at an academic medical centre[16]. During a follow-up of 21 ± 12 months, 20 deaths were observed. Treatment with an ACE-inhibitor or receptor blocker, β-blocker, or calcium blocker had no significant effect on survival. In contrast, treatment with statin was associated with a substantial improvement in survival (relative risk of death [95% CI] 0.22 [0.07 to 0.64]; p = 0.006). After adjustments for differences in baseline clinical variables between groups (hypertension, diabetes, CAD, and serum creatinine), statin therapy was associated with lower mortality (adjusted relative risk of death [95% CI] 0.20 [0.06 to 0.62]; P = 0.005). The authors concluded that statin therapy may be associated with improved survival in patients with heart failure. The study was not a definitively large, multicentre, double-blind, randomised, placebo-controlled clinical study, but rather a hypothesis-generating preliminary study. However, the authors used a state-of-the-art analytic method (propensity matching) in an effort to correct for the bias inherent in the non-randomised treatment assignment.

Mechanisms of beneficial effects of statins in heart failure

The beneficial effects of statin therapy can be divided into those effects that relate to its lipid-lowering effects (lipid-dependent), and those effects that may be independent of its lipid-lowering effects (lipid-independent; Table I).

HF is a complex syndrome characterised by haemodynamic, metabolic, and neurohormonal alterations including elevation of inflammatory markers, endothelial dysfunction, and neurohormonal imbalance with increased levels of catecholamines, cytokines, renin, angiotensin, and aldosterone[17].

Table I: Pleiotropic effects of statins

Lipid-dependent

- Decrease vascular atherosclerosis
- Decrease myocardial infarction
- Decrease cerebral vascular accident
- Decrease peripheral vascular disease

Lipid-independent

- Decrease LV mass
  - Inhibit angiotensin I-mediated cardiomyocyte hypertrophy
  - After intercellular signaling molecules that affect growth regulation
    - Decrease extracellular signal-related kinase (ERK½) activity
    - Decrease ERK, phosphorylation
    - Decrease RAS membrane targeting and activation
  - Antihypertensive
- Decrease LV fibrosis
  - Decrease inflammation (decreased C-reactive protein, interleukin-6)
  - Decrease immune activation
  - Alter matrix metalloproteinase activity
  - Decrease oxidative stress, decrease oxygen free radicals
- Increase arterial compliance
  - Decrease vascular atherosclerosis
  - Improve endothelial function
  - Decrease endothelin synthesis
  - Increase nitric oxide

Decrease morbidity and mortality in patients with diabetes and renal insufficiency

Decrease thrombosis

Antithrombotic effects and statins

The potential efficacy of statin in patients with ischaemic HF is related to its antithrombotic effects. Autopsy data reveal that a large percentage of mortality in patients with impaired left ventricular function results from acute coronary syndrome precipitated by atherosclerotic plaque rupture[19]. The benefits of statin-induced alteration in lipid profiles have been shown in a variety of population resulting in reduced incidence of vascular disease, vascular events (e.g., myocardial infarction and cerebrovascular accident), and cardiovascular morbidity and mortality, which result

from vascular disease[4, 19]. Whether these lipid-dependent benefits can be realised in patients with chronic HF remains an open question because in most published studies, patients with HF were excluded. However, recent studies have thrown light on this aspect and have demonstrated that addition of statin does indeed reduce morbidity and mortality in patients with HF[12].

Cardiac hypertrophy and statins

The efficacy of statins is mostly due to plaque stabilisation. Statins also significantly preserve viable myocardium resulting in improved ventricular function[20]. In animal models of LV hypertrophy, statins have been shown to reduce LV mass and fibrosis[21]. This lipid-independent effect may result from statin-induced reduction of blood pressure, alterations in myocardial growth regulatory signal transduction pathways, changes in inflammatory and immune-mediated systems or increased arterial compliance[22].

Inflammation, oxidative stress, and statins

Inflammatory mediators play an important role in the development and progression of HF. These mediators or cytokines, are generally pharmacologically active proteins that are secreted by various cell types in response to a variety of stimuli. Among the cytokines, TNF-α plays an important role in the progression of HF. TNF-α has been implicated in the development of LV dysfunction, increased cardiac myocyte apoptosis, and the development of anorexia and cachexia, among other effects[23]. Other cytokines, such as IL-6, are involved in myocyte hypertrophy, myocardial dysfunction, and muscle wasting. Higher levels of IL-6, as well as the inflammatory marker C-reactive protein (CRP), are associated with a poor prognosis in HF patients.

Statins have important anti-inflammatory effects. They down-regulate CRP and inflammatory cytokines, which are activated in HF of any aetiology[24]. Recent data have shown a significant reduction in serum levels of hs CRP as well as TNF-α R II and IL-6 in patients with HF treated with statins[25]. In addition, statin treatment was associated with an increase in superoxide dismutase (SOD) activity, suggesting that statins also have anti-oxidant activity in this patient population. These anti-inflammatory and antioxidant effects of statins may account for the beneficial effects of statins in patients with HF.

Endothelial function and statins

The overall effects of statins on endothelial functions merit special attention. Recent research has provided insights into the profound effects of statin on endothelial cell function. The induction of nitric oxide gene transcription, which yields an increased production of the vasodilating molecule nitric oxide, is one among a number of mechanisms contributing to an improvement in endothelial function[26]. Statins also down-regulate the production of reactive oxygen species, which are known to inhibit nitric oxide activity[27].

Tousoulis *et al* carried out a prospective, randomised, placebo controlled study on the effects of four weeks of treatment with atorvastatin (10 mg/day) in patients with chronic HF[28]. Atorvastatin treatment affected the coagulation and fibrinolytic system in that it decreased the plasma concentrations of antithrombin III, protein C, coagulation factor V, tissue plasminogen activator, and plasminogen activator inhibitor type-I. Statins interfere with coagulation factors independently of where the production site is located.

Neuroendocrine activation and statins

Statins also normalise sympathetic outflow and autonomic function[17]. Strey *et al* report that treatment with statin versus placebo is associated with lower concentrations of all measured cardioendocrine hormones, although the difference is significant only for atrial natriuretic peptide (ANP)[29]. Given the problems with cardioendocrine hormone measurement and the small patient population (n = 23) examined, the data are only suggestive of statin derived benefits for the HF typical neurohormonal imbalance. It is uncertain whether the stabilisation of neurohormonal imbalance is secondary to improvement in endothelial dysfunction, or to other statin effects having the potential to delay HF progression. Such effects include the induction of neoangiogenesis, the down-regulation of angiotensin II type 1 receptors, the restoration of autonomic dysfunction, and the inhibition of pro-inflammatory cytokines[9]. However, endothelium-ameliorating and other cardioprotective statin effects probably act synergistically.

Potential drawbacks to statin therapy in heart failure

1 Cholesterol hypothesis

So far it has been argued that the cholesterol lowering and other actions of statins are beneficial in HF patients. However, one should not lose site of the studies that report a survival disadvantage in HF patients with low serum cholesterol levels[30, 31]. Rauchhaus *et al* reported that, in patients with either ischaemic or non-ischaemic cardiomyopathy, low

serum total cholesterol (≤ 201 mg/dl) predicted increased mortality at 12 months independently of other risk factors[31]. This inverse relationship between cholesterol level and mortality has been corroborated by Mozaffarian *et al*[2]. They further observed that, in patients with severe HF, the highest mortality was noted in the group of patients with the lowest quartile of cholesterol (< 172 mg/dl).

2 Ubiquinone hypothesis

The adverse effects of statins may be due to increased blood endotoxin levels and decreased levels of the antioxidant ubiquinone, both of which may contribute to HF progression[17]. It has been postulated that higher levels of total cholesterol may be beneficial in HF due to the ability of cholesterol-rich lipoproteins to bind and neutralise the effects of bacterial lipopolysaccharide. Lipopolysaccharide is translocated across the gut wall in patients with advanced HF and is an important stimulus of pro-inflammatory cytokine production[32]. Ubiquinone, or coenzyme Q10, is a lipid soluble micronutrient that acts as a coenzyme in mitrochondrial oxidative phosphorylation and is believed to be an important endogenous antioxidant. Statin therapy has been shown to be associated with a dose related decrease in serum ubiquinone levels, which may in turn have an adverse effect in HF patients[33].

3 Endotoxin hypothesis

Lipoprotein in plasma can bind and detoxify endotoxins such as lipopolysaccharide entering the circulation via the gut. In the setting of HF, endotoxin may be an important mediator of HF disease progression via activation of pro-inflammatory cytokines such as tumour necrosis factor- alpha. It is, therefore, argued that lipid-lowering with statin therapy may enhance endotoxaemia by reducing plasma levels of lipoproteins. This may, in turn, result in further elevation of plasma levels of pro-inflammatory cytokines, levels of which are strongly linked to adverse prognosis in HF. In support of this hypothesis, plasma levels of lipopolysaccharide have been shown to be elevated in patients with HF, although the impact of statin therapy on this parameter has not been examined in this setting.

In spite of the findings from these small observational studies, and the theoretical concern that reducing plasma lipoproteins too much may be deleterious in HF, it remains unclear whether low cholesterol levels are directly responsible for the increased risk observed or whether they are merely markers of disease severity, poor nutritional status, hepatic dysfunction, or other surrogates of worse prognosis. Table II shows the potential disadvantages of statin therapy in heart failure.

Table II: Potential disadvantages of statin therapy in heart failure.

1.	Higher mortality rate with low serum cholesterol levels.
2.	Decrease in blood levels of ubiquinone, an antioxidant.
3.	Increase in blood levels of endotoxin resulting in elevation of pro-inflammatory cytokines.

Summary and conclusion

Statin therapy lowers morbidity and mortality in coronary artery disease and other atherosclerotic vascular disease, as evidenced by multiple large scale clinical trials. Additional analyses of these trials have shown that use of statins also reduces the risk of developing HF. A reduction in cardiovascular events with statins have been demonstrated irrespective of baseline low-density lipoprotein (LDL) cholesterol. Yet, the impact of statin therapy on HF has not been well studied. So far, the major clinical trials of statin therapy have tended to exclude patients with symptomatic severe HF.

Statins have therapeutic properties which are of potential benefits to patients with HF of ischaemic and non-ischaemic aetiologies, irrespective of lipid levels. Statins improve endothelial function, inhibit inflammatory cytokines, potentiate nitric oxide synthesis, restore impaired autonomic function, and reverse pathologic myocardial remodelling.

Current observational data strongly support the use of statins in patients with both ischaemic and non-ischaemic HF. A recent randomised clinical trial has demonstrated significant mortality benefit with statin therapy in patients with diastolic HF. These data strongly support the use of statins in appropriate HF patients. Reinforcement regarding the statin use may well come after the results of CORONA and GISSI-HF trial are published.

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REVIEW ARTICLE

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Erythropoietin Response to Anaemia in Type 2 Diabetic Nephropathy

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Abstract

Anaemia is a common complication of chronic kidney disease (CKD). It is often more severe and occurs at an earlier stage in patients with diabetic nephropathy than in patients with CKD of other causes. This anaemia is associated with inadequate erythropoietin response. Early erythropoietin-deficiency anaemia occurs in both type 1 and type 2 diabetes, although the prevalence may be higher in type 1 diabetes. However, numerically most patients with erythropoietin-deficiency anaemia have type 2 diabetes as it is a much more common disease. In addition, erythropoietin-deficiency anaemia is associated with the presence of autonomic neuropathy in patients with diabetes. Small studies have suggested that recombinant human erythropoietin (rhEPO; epoetin) treatment is effective in correcting erythropoietin-deficiency anaemia in patients with diabetes. Additionally, rhEPO therapy improves quality of life and well-being in these patients. Studies also suggest that treatment with rhEPO to restore a normal haematocrit ameliorates orthostatic hypotension. Given the high cardiovascular risk in patients with diabetic nephropathy, it is important to determine in prospective clinical trials whether early anaemia correction can also improve cardiovascular outcomes.

Erythropoietin (EPO), a 30.4 - kDa glycoprotein, is produced mainly by the peritubular fibroblasts of the renal cortex in adult life[1]. The actions of EPO include stimulation of erythroid progenitor cells and differentiation of normoblasts to increase the red cell mass in response to tissue hypoxia precipitated by anaemia, haemorrhage, or altitude[1-3]. Diabetes is the most prevalent cause of renal failure. Over the next 10 years, the number of patients with diabetes and end-stage renal disease is expected to double, causing a significant increase in the burden of care for this patient population[4]. Although the prognosis with diabetic nephropathy has improved since early reports[5, 6], there remains an excess mortality of 70 - 100 times that of an otherwise matched population[7]. Patients presenting with diabetic nephropathy commonly have a greater degree of anaemia for their degree of renal impairment than those presenting with other causes of renal failure, and anaemia develops earlier in these patients than in those with renal impairment from other causes[8, 9]. Recent studies have identified anaemia as a risk factor for the need for renal replacement therapy in diabetes[10]; in addition, a lower Hb is significantly associated with a more rapid decline in the glomerular filtration rate (GFR)[11]. Furthermore, treating anaemia early in renal failure has been demonstrated to slow the rate of decline of renal function[12].

Upto now it was considered that a renal anaemia appears only with severe renal insufficiency, i.e., creatinine-clearance < 30 ml/min. However, more recent studies have shown that the haemoglobin concentration starts to decline at a creatinine-clearance of < 60 ml/min[13]. Patients with diabetes in particular seem to have a higher risk of developing anaemia when kidney function is impaired[8,14]. While the initially published studies only reported on small collectives without a precise definition of the stage of the renal insufficiency, the DiaNe project recently conducted a broad screening of the prevalence of anaemia in Germany and its relationship to kidney function in undialysed diabetics.

Prevalence of Anaemia in Diabetic Nephropathy - The DiaNe Project

120,034 patients with known diabetes were screened for the presence of renal insufficiency, defined as a serum creatinine > 1.3 mg/dl. Three thousand, three hundred and seven patients were identified (2,069 men, average age 67.7 years and 1,438 women, average age 71.2 years). Haemoglobin concentration was determined and creatinine-clearance was calculated as per the Cockgroft-Gault procedure. According to World Health Organisation (WHO) criteria, anaemia was diagnosed among men with

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a haemoglobin level of < 13 g/dl, and among women with a level of < 12 g/dl. A therapy-obligatory anaemia was defined gender-independently as a haemoglobin level of < 11 g/dl.

In both sexes the average haemoglobin levels decreased with decreasing kidney function (coefficient of correlation according to Pearson 0.305; $p < 0.01$). According to WHO criteria, 44% of the women and 40% of the men with renal insufficiency revealed anaemia. A severe anaemia, i.e., haemoglobin values < 11 g/dl, was determined in 26% (female), and 17% (male) of the patients.

Figure 1 shows gender-specificity of the prevalence of anaemia according to the stage of renal insufficiency. Already, at a creatinine-clearance of 60 – 89 ml/min, 35% of the women and 25% of the men showed anaemia. The prevalence of a therapy-obligatory anaemia (haemoglobin < 11 g/dl) in these patients already lay at 18% (female) and 11% (male). With increasing renal insufficiency, the anaemia rate increased as expected. With pre-terminal renal insufficiency, about 65% of the female and 83% of the male patients showed anaemia according to WHO criteria; the corresponding prevalence of therapy-obligatory anaemia was 41% and 43%, respectively.

Figure 2 shows the prevalence of anaemia among diabetics of the DiaNe collective compared with a population study from the US (National Health and Nutrition Examination Survey – NHANES III). It shows that anaemia occurs 6 – 10 times more frequently in diabetic patients than in the average population at slight restriction of renal function. When comparing this with patients suffering from renal insufficiency of a non-diabetic origin, a similar result is apparent (Figure 3). The prevalence of anaemia at a serum creatinine level below 3 mg/dl was approximately 2-10-fold higher amongst the diabetics of the DiaNe collective than in patients with a non-diabetic nephropathy[15].

The DiaNe project therefore confirms the initial findings[8,14] that among diabetic patients with renal dysfunction, anaemia occurs earlier than in non-diabetic patients. Similar findings were recently published from 800 diabetic patients with and without nephropathy by Thomas *et al*[9] in an Australian study. In comparison with NHANES III, these authors found a 3-5-fold higher anaemia prevalence in the creatinine clearance range of 90 – 30 ml/min. With more severe impairment of renal function, no difference could be found in comparison with non-diabetics with severe renal insufficiency in the DiaNe collective. This corresponds to the findings of the Predialysis Survey of Anaemia Management (PRESAM), which also found no difference in the anaemia prevalence amongst pre-terminal kidney-insufficient patients with and without diabetes[16].

Anaemia also has a negative impact on patient survival, and is considered to be an important cardiovascular risk factor associated with renal disease. Understanding the pathogenesis of anaemia associated with diabetes and

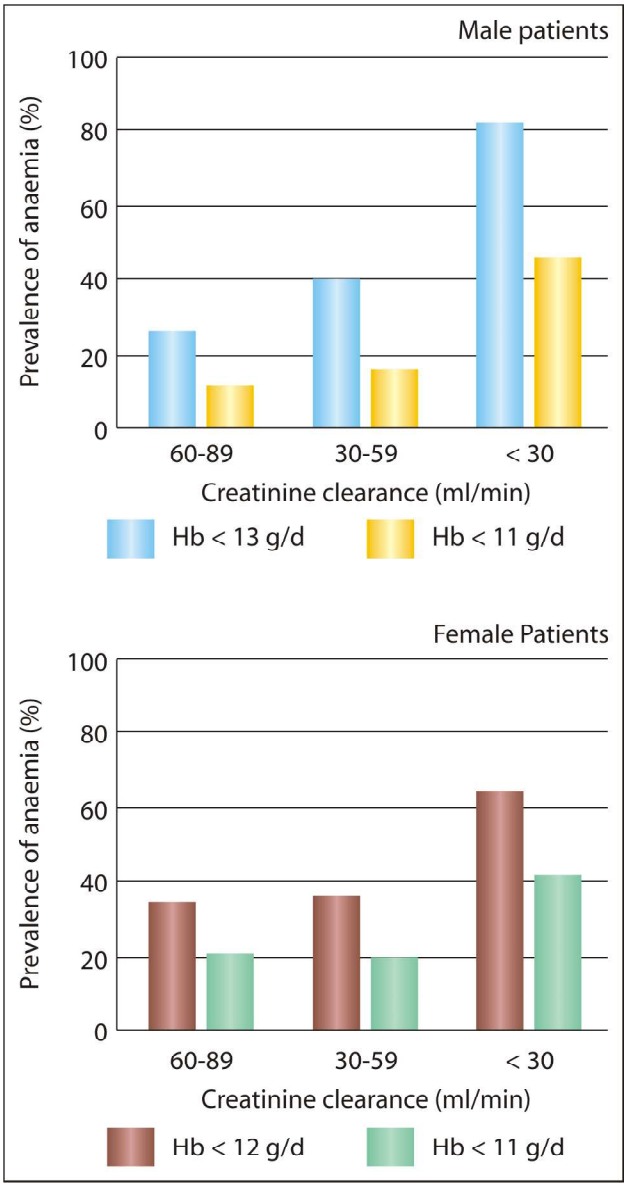

Fig. 1: *Prevalence of anaemia according to various definitions in relation to renal function among male and female diabetic patients.*

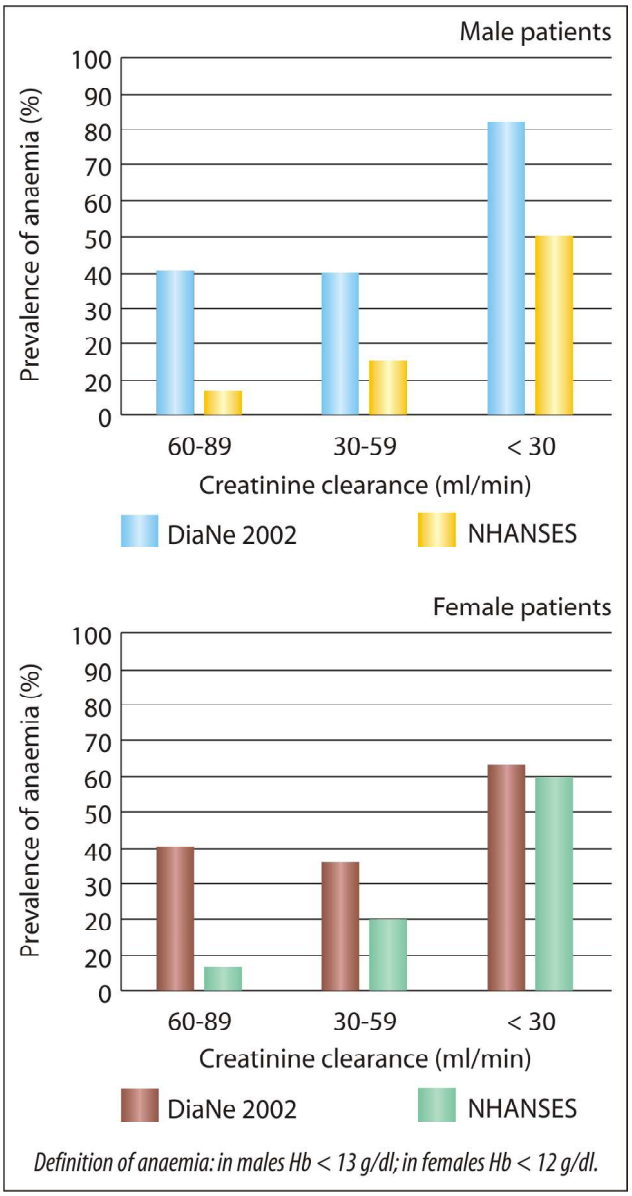

Fig. 2: *Prevalence of anaemia in male and female diabetic patients among the DiaNe collective compared with a population study US National Health and Nutrition Examination Survey III.*

nephropathy may therefore lead to opportunities for developing interventions to optimise outcomes in these patients. Many factors have been suggested as the reason for the earlier onset of anaemia in patients with diabetes, including severe symptomatic autonomic neuropathy, causing efferent sympathetic denervation of the kidney and loss of appropriate erythropoietin (Epo) production; damage to the renal interstitium; systemic inflammation; and inhibition of Epo release.

An association between the sympathetic nervous system and erythropoiesis has been postulated for several years

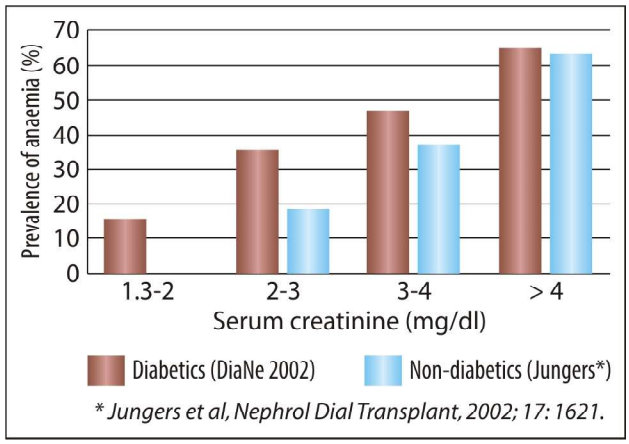

Fig. 3: *Prevalence of anaemia (Hb < 11 g/dl) among diabetic and non-diabetic patients with renal insufficiency.*

and examined in a few animal studies. Takaku and colleagues[17] showed in 1961 that the reticulocyte response to acute blood-letting was greatly diminished in rats when their kidneys were functionally denervated[18]. Intravenous administration of the β-adrenergic receptor agonist salbutamol increased plasma concentrations of erythropoietin-like factor in rabbits, measured with a bioassay in polycythaemic rats[19]. Conversely, β-blockers were shown to blunt the erythropoietin response to hypoxia[20, 21]. The conclusion derived from these and other studies was that sympathetic stimulation, acting through β_2-adrenoreceptors, positively modulates erythropoiesis through increased erythropoietin production. The physiologic significance of these findings and their relevance to humans, however, has not previously been studied. In caring for patients with severe autonomic failure, it has been realised that anaemia was not an uncommon occurrence.

Diabetes mellitus is the most common cause of end-stage renal disease (ESRD) in the Western world[22] and is, therefore, the most common cause of renal anaemia. However, many patients with diabetic kidney disease do not survive to ESRD. In these patients, anaemia is also a common complication and develops earlier than in patients with renal impairment from other causes[8, 23–25]. The prominent damage to the cells and vascular architecture of the renal interstitium, systemic inflammation, autonomic neuropathy and the induction of inhibitors of erythropoietin release have all been suggested as contributing to anaemia in diabetic nephropathy[23]. Like many pathophysiological changes of diabetic nephropathy, anaemia may be apparent before demonstrable change in

renal function[8, 23-25]. A normochromic, normocytic anaemia can also be observed in patients without overt renal disease[24].

A number of explanations have been proposed for the failure of adequate EPO production in diabetic renal failure which accounts for the anaemia with EPO deficiency observed in diabetic patients. Renal damage may lead to an inability to sustain the required increased EPO levels due to limited renal mass, damage of the fibroblast, or inadequate extrarenal supply of EPO[8]. However, as the diabetic patients have a normal EPO response to hypoxia[26] it seems unlikely that the EPO-producing fibroblasts are destroyed by the tubulo-interstitial damage of early diabetic nephropathy[27]. The renal fibroblasts seem to be able to produce EPO appropriately in response to hypoxia. This increased EPO production in diabetic patients may be from the liver, which is known to produce around 10% of the total production in adults.

Alternative explanations for the low EPO levels associated with anaemia might include that cytokines such as IL-1 (α or β) and tumour necrosis factor (α or β)[28] which are thought to inhibit both EPO action and EPO production, cause anaemia of chronic disease and end-stage renal failure. It seems possible that cytokine involvement may contribute to the anaemia of early diabetic nephropathy but these inhibitors can be overcome by hypoxia stimulation[26]. A reduced oxygen affinity of haemoglobin, a decreased sensitivity of the renal oxygen sensor, or an increased EPO metabolism and malnutrition inhibitors of erythropoiesis may also contribute to the anaemia in diabetic subjects with nephropathy.

It seems likely that the anaemia sensing (rather than secretory) mechanisms are dysfunctional in the anaemia of diabetes. Although the mechanism of this remains to be established, it is conceivable that thickening of the endothelial basement membrane and changes in regional blood flow mediated through up-regulation of the local renin-angiotensin system may contribute to the anaemia. It has also been suggested that autonomic degeneration as a result of diabetes may diminish erythropoietin release. Because autonomic neuropathy is closely correlated with renal injury, it is difficult to assess its independent influence. However, denervated kidneys used for transplantation appear to release erythropoietin normally[29].

One of the most potent causes of sub-optimal response to EPO in such patients can be chronic and overt inflammation[30] which is associated with an increased production of cytokines, such as TNF-α, IL-1 or IF-γ[31], which might suppress EPO action or EPO production. Despite the above-mentioned innumerable mechanisms, the pathogenesis for deficient EPO response in diabetic subjects with renal disease remains unclear.

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Oncological Emergencies

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Introduction

In the scenario of emergency medicine, 'oncological emergencies' are gradually occupying an important position. This is true with the increasing number of cancer patients detected both globally as well as in developing countries like India. Oncological emergencies are defined as acute and potentially life-threatening events that are directly or indirectly related to the underlying malignancy or as a sequelae of its treatment.

These emergencies may in majority be classified as:

A. Direct involvement of vital organs by the neoplasm, e.g., cardiac tamponade, superior vena cava syndrome, raised intra-cranial pressure, spinal cord compression,

B. Metabolic emergencies, e.g., tumour lysis syndrome, hypercalcaemia, hyperuricaemia, hyponatraemia,

C. Bone marrow failure leading to cytopenias, neutropenia, thrombocytopenia,

D. Surgical emergencies, e.g., bowel perforation, intestinal obstruction, etc.

It will be pertinent to discuss in this article the medical emergencies in brief, that can be taken care of by practitioners and physicians in primary care and emergency care settings and keep apart the other emergencies which need specific surgical interventions.

A. Direct involvement of vital organs by the neoplasm

Cardiac tamponade

While 10 - 15% of patients dying of cancer are found to have pericardial involvement at autopsy, only a small proportion develop clinical tamponade during lifetime. Breast cancer, lung cancer, and lymphoid malignancies are the commonest causes of malignant pericardial effusion and tamponade[1]. Dyspnoea is the commonest symptom; others include cough, chest pain, orthopnoea, and generalised weakness. Impaired right-heart filling may lead to symptoms of right-heart failure such as peripheral oedema, hypotension, and elevated jugular venous pressure. Treatment is by pericardiocentesis, creating pericardial window or pericardial sclerosis using any one of the cytotoxic drugs like bleomycin, doxycycline, thiotepa, cisplatin, and other agents like 32p colloid[2].

Superior vena cava syndrome (SVCS)

Malignancy causes the majority of cases of SVC obstruction. Amongst these, in adults, lung cancers together with non-Hodgkin's Lymphoma constitute almost 90%. Small cell variety is the commonest histologic type of lung cancer causing Superior vena cava syndrome followed by squamous cell carcinoma[3]. Mediastinal germ cell tumours, thymomas, and sarcomas are some of the other causes of SVCS. Amongst metastatic diseases, metastatic breast cancer is the commonest. Two-thirds of the primary tumours causing SVC compression in childhood are caused by lymphomas. SVC syndrome occurs when extrinsic compression or intrinsic obstruction of the SVC impedes venous return from the head and upper part of body. Patients with SVC syndrome commonly complain of dyspnoea, swelling of face, neck, and upper extremities, chest pain, and headache[4]. Dilated neck veins are usually present on the face, arm, neck, and supraclavicular regions, and visible collaterals develop over the chest. Histological or cytological diagnosis is essential, as specific treatment may be influenced by tumour type. CT scan of the chest can provide information about patency of SVC and adjacent structures, including the presence or absence of compressive mass lesions and thrombus in the SVC. Radiotherapy has been the treatment of choice for SVC syndrome[5, 6]. However, patients with chemo-responsive tumours such as germ cell tumours, small cell lung cancers, and lymphomas should be treated with chemotherapy first, followed by radiation if necessary. Thrombolysis and SVC stenting may also be useful in selected cases[7, 8].

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Spinal cord compression

In an estimated 1% of cancer patients, spinal cord compression develops in the course of their disease[9]. Metastatic breast, lung, and prostate cancers account for the majority of malignant cord compression[10]. Any patient with cancer who develops severe back pain with root distribution should be considered at risk of spinal cord compression and urgently investigated[11]. Weakness of the legs (and arms if the lesion is high in the spine), retention, dribbling, incontinence of urine or faeces, and constipation may occur; and these late symptoms herald poor prognosis and limited reversibility.

Plain X-ray may demonstrate destruction and/or collapse of a vertebra or loss of a pedicle. However, in 15 – 20% of cases, plain films show no abnormality. In this context, MRI has largely superceded CT and myelography, and is presently the investigation of choice. It will not only demonstrate the site and extent of the lesion, but also presence of multiple sites of the lesion in vertebrae and spinal cord. It is particularly useful in case of cauda equina syndrome.

The speed of management of spinal cord compression is most important. Dexamethasone 16 – 20 mg should be given immediately to relieve peritumoral oedema. Surgery for local decompression and radiotherapy may be helpful in selected patients depending on the pathological variety of tumour[12]. Chemotherapy has hardly any role in the management of acute spinal cord compression[13].

Although radiation therapy is the treatment of choice in our clinical practice, radio-resistance and post-radiation recurrence of neoplasms create problems in therapeutic decision making. The accepted indications for surgery are limited and include: a) unknown diagnosis, b) spinal instability or compression by bone, c) radio-resistance, d) total permissible dose of spinal radiation already been given. Contraindications to surgery are multiple level disease, complete paraplegia, advancing age with poor general health, and absolutely terminal disease. Since body of the vertebra is the most common site that is affected, lateral approach to decompress the anterior spinal cord shows a better result[14]. Laminectomy is reserved for the posterior spinal cord compressive lesions. Radiotherapy in addition to surgery has not demonstrated any survival benefit[15].

Raised intra-cranial pressure (RICP)

RICP is characterised in its early stages by headache and vomiting, often worse in the morning, followed by drowsiness and neurological deterioration. Clinical signs suggesting RICP include bradycardia, systemic hypertension and papilloedema. Amongst neoplastic tumours leading to RICP, approximately 50% are due to metastasis, and the remainder are primary brain tumours of which gliomas are the commonest.

Early management involves high dose steroids like dexamethasone, 16 – 32 mg daily, iv mannitol (100 ml 20% solution over 1 – 2 hrs). Thereafter, steroids should continue combined with palliative whole brain radiotherapy. Some patients may benefit from surgical resection (if solitary space occupying lesion)[16].

B. Metabolic emergencies

Tumour lysis syndrome (TLS)

TLS refers to metabolic consequences resulting from the sudden release of potassium, phosphate, and purine metabolites from tumour cells undergoing cell death and is classically associated with acute lymphocytic lymphoma or Burkitt's lymphoma which are tumours having rapid growth rate and high tumour burden, as well as they respond rapidly to cytotoxic chemotherapy[17, 18].

The presenting symptoms may range from arrhythmias, changes in mental status and renal failure to sudden death from hyperkalaemic cardiac arrest. Patients in extreme situations may present with stupor. Two main metabolic consequences of TLS are renal failure and hyperkalaemia. The presence of an elevated serum uric acid, phosphorous and LDH on presentation suggest the presence of large tumour bulk, rapid cell turnover and possible index of suspicion for smouldering tumour lysis, which may be exacerbated after treatment. Increasing potassium and worsening renal failure in a patient at risk suggest the onset of TLS. Because the rate of progression may be unpredictable, the blood biochemistry (electrolytes, creatinine, phosphorous, calcium, and LDH) should be checked in patients at risk of TLS every 8 – 12 hours during the first 2 to 3 days of treatment.

The best management is prevention of TLS[19]. Patients at

high risk need to be identified, (e.g., those with high-grade or bulky lymphoid malignancies like ALL and Burkitt's lymphoma) but chronic lymphocytic leukaemia and small cell lung cancers also may be at risk. The laboratory abnormalities that signify increased risk for TLS include elevated LDH and uric acid and pre-existing renal failure. All patients should get isotonic fluid to achieve brisk diuresis before and during the first 2 to 3 days of chemotherapy. Frusemide may be given to maintain urine output and also may increase excretion of potassium. The urine pH should be greater than 7 to maintain uric acid and phosphorous in their ionized soluble form and prevent crystal deposition in renal tubules. Urine may be kept alkaline by adding sodium bicarbonate. Allopurinol should be given PO or IV at 600 mg/day, starting 24 to 48 hours before chemotherapy. Uricase is another agent that is being tried in acute tumour lysis syndrome[20, 21]. In desperate cases, dialysis may be required for volume overload, hyperuricaemia, or hyperkalaemia. Renal failure caused by TLS is usually reversible.

Hypercalcaemia

Hypercalcaemia is usually a marker of advanced malignancy. Malignant hypercalcaemia develops in patients with (a) extensive skeletal metastases, (e.g., breast cancer, lung cancer, prostate cancer or multiple myeloma), (b) paraneoplastlc secretion of parathyroid hormone-related peptide (PTH-rp), e.g., in squamous cell carcinoma of the lung, cervix, or upper aerodigestive tract, (c) excessive 1,25 – OH vitamin D production, (e.g., non-Hodgkin's lymphoma).

Malignant hypercalcaemia complicates 5 – 10% of all cancers. It is especially associated with breast cancers, myeloma, and squamous cell carcinoma of lung, and is also associated with malignant lymphomas. However, it may occur in association with almost all tumour types[22]. The normal range for serum calcium is 8.6 to 10.3 mg/dl (2.15 to 2.65 mmol/L). About half of the circulating calcium is bound by albumin and the remaining unbound ionised calcium (normal range, 4.5 to 5.1 mg/dl) is responsible for the biologic effects.

The symptoms of hypercalcaemia may develop insidiously and are often difficult to distinguish from the co-existing conditions; conversely, patients may be first seen in acute crisis. They may present with some renal impairment, dehydration, azotaemia, polyuria, and polydipsia. Abdominal symptoms like anorexia, nausea, constipation, and alteration of mental status (e.g., confusion and obtundation) may be present. In the absence of prompt recognition and treatment, hypercalcaemia can progress to renal failure, coma, and death.

Management revolves around the underlying disease condition. Patients are often dehydrated and require normal saline (usually 2 to 3 litres) and then maintenance of IV fluids till oral intake is sufficient. Potassium and magnesium are replenished if required. Hypophosphataemia is common but should not be repleted unless symptomatic, because an increase in calcium x phosphorous product to 70 or more can cause precipitation of calcium salts in kidneys and soft tissues. IV bisphosphonates have become the mainstay of treatment in malignancy-associated hypercalcaemia. These include pamidronate (dose 90 mg) infused over a 2 to 4 hour period or zoledronic acid (4 mg) IV infusion over 15 minutes[23]. These need to be repeated every 3 to 4 weeks for recurrent hypercalcaemia[24]. Oral bisphosphonates are not as effective and are not recommended in the setting of such emergency situations. Calcitonin IM or SC (6 to 8 units/kg) can decrease serum calcium within 2 to 4 hours of administration. Corticosteroids in a dose of 60 mg/day orally may be effective in controlling hypercalcaemia, either used alone or in combination with bisphosphonates in patients with haematologic malignancies such as myeloma or lymphoma. Plicamycin is also effective, but it's use should be reserved only for refractory hypercalcaemia.

Bone marrow suppression

Bone marrow suppression may be caused by either infiltration of marrow by malignant cells or more commonly iatrogenic. The major dose-limiting toxicity of cancer therapy is bone marrow suppression, thereby compromising the potential for cure in many patients with chemo and radio-sensitive malignancies. Manipulation of myelosuppression kinetics with the use of haemopoietic growth factors is a new and exciting development in cancer treatment, and with the advent of stem cell technology, the dose intensity of cancer chemotherapy is being taken to previously unheard limits. Since RBCs survive for 120 days, platelets about 5 days, and neutrophils

approximately 1 – 2 days, early problems relate mainly to neutropenia and thrombocytopenia, and later on anaemia develops[25].

Fever in the neutropenic cancer patient poses a great problem because if left untreated, sepsis may be rapidly fatal. Febrile neutropenia is defined as single oral temperature of 38.3° C or 38.0° C over 1 hour with < 500 neutrophils/mm^3 or < 1,000 neutrophils/mm^3 with a predicted decline to 500/mm^3 over the next 48 hrs.

The absence of granulocytes, disruption of mucociliary barriers, and shifts in inherent microbial flora that accompany severe illness alongwith antimicrobial usage predispose the neutropenic cancer patients to infection. The signs and symptoms of infection are often absent or muted in the presence of neutropenia, but fever remains an early, although non-specific sign. The initial evaluation should focus on determining the potential sites and causative organisms of infection and on assessing the patient's risk of developing an infection-related complication. A site-specific history and physical examination should be performed promptly, cultures should be obtained and empiric antibiotics started soon at the time of presentation. Primary sites of infection are the alimentary tract (i.e., mouth, pharynx, oesophagus, intestine, and rectum), sinuses, lungs, genito-urinary tract, and skin. Neutropenic enterocolitis is a life-threatening condition caused by mixed aerobic and anaerobic Gram-negative bacilli (including *Pseudomonas*) and *Clostridium* species.

Risk assessment should be performed as part of the initial evaluation. High risk factors are mentioned in Table I.

Table I: High risk factors in neutropenic patients.

- inpatient status at time of development of fever,
- significant medical comorbidity or clinical instability,
- serum creatinine > 2.0 mg/dl,
- liver functions > 3 times normal,
- uncontrolled/progressive cancer,
- pneumonia or other complex infections at clinical presentation,
- anticipated prolonged severe neutropenia,
- the Multinational Association for Supportive Care in Cancer risk index (MASCC) score of less than 21.

Using the MASCC-risk score: Using the visual analogue score, estimate the patient's burden of illness at the time of initial clinical evaluation. No signs and symptoms or mild signs and symptoms are scored as 5 points, moderate signs or symptoms are scored as 3 points. There are no points for severe signs and symptoms or if patient is moribund[26]. Factors that determine choice of initial therapy are enumerated in Table II.

Table II: Factors that determine choice of initial antimicrobial therapy.

- Infection risk assessment
- Potential infecting organisms
- Site of infection
- Local or institutional antibiotic susceptibility patterns
- Organ dysfunction/drug allergy
- Broad spectrum of activity
- Previous antibiotic therapy

The first approach is intravenous monotherapy with either a carbapenem (imipenem-cilastatin), meropenem, an extended-spectrum anti-pseudomonal cephalosporin (ceftazidime or cefepime). There is some evidence that piperacillin/tazobactam may be effective monotherapy, but the level of evidence to date is insufficient to warrant a category 1 recommendation [NCCN (National Comprehensive Cancer Network) Guidelines]; however, there is enough clinical experience to recommend it. If piperacillin/tazobactam is used for initial intravenous monotherapy, it may interfere with galactomannan assay (required for the diagnosis of invasive aspergillosis). Recent studies suggest that certain Gram-negative organisms are developing resistance to cefepime and ceftazidime, highlighting the need to know local susceptibility patterns before prescribing monotherapy. The second approach is intravenous dual therapy (category 1) with (1) an aminoglycoside plus an anti-pseudomonal penicillin (with or without a beta-lactamase inhibitor) or an extended-spectrum anti-pseudomonal cephalosporin, or (2) ciprofloxacin plus an anti-pseudomonal penicillin. Aminoglycoside use carries the inherent risk of renal and otic toxicity. These toxicities require careful monitoring and necessitate frequent reassessment, but once-daily aminoglycoside dosing may diminish renal toxicity. Once-daily aminoglycoside dosing should be avoided for treating meningitis or endocarditis, although there is a difference of opinion about this recommendation[27-29]. If there is no

remission of fever within 48 hrs consider vancomycin. If still no remission in next 48 hrs then start empirical antifungals.

Vancomycin should not be considered as an empiric routine component of initial therapy for fever and neutropenia because of the risk of emergence of vancomycin-resistant organisms. Initial vancomycin therapy should be considered for serious infections associated with the following clinical situations[30]:

i. Clinically apparent, serious catheter-related infection

ii. substantial mucosal damage and high risk for infection with penicillin-resistant viridans streptococci (especially patients receiving prophylaxis with quinolone antibiotics or trimethoprim/sulphamethoxazole)

iii. blood culture positive for Gram-positive bacterium prior to final identification and susceptibility testing

iv. known colonisation with penicillin/cephalosporin-resistant pneumococci or methicillin-resistant *Staphylococcus aureus*

v. hypotension or septic shock without an identified pathogen.

Vancomycin should be discontinued in 2 – 3 days if a resistant Gram-positive infection is identified and if clinically appropriate (see above).

Lung infiltrates may manifest as pneumonia with focal/nodular lesion or interstitial infiltrates. In the first case, consider additional empiric coverage for atypical pneumonia pathogens (fluoroquinolone, macrolide, or doxycycline) to cover *Mycoplasma* and *Legionella*, antifungal therapy directed toward molds and addition of G-CSF or GM-CSF. For interstitial infiltrates, consider fluoroquinolone, macrolide, or doxycycline to cover *Mycoplasma* and *Legionella*, empiric trimethoprim/sulphamethoxazole, or pentamidine for sulphur allergic patients or patients at high risk for Pneumocystis jirovecii pneumonia and rimantadine, amantadine during influenza season[31].

Fungal infections are very common in neutropenic patients. *Candida albicans* have recently been surpassed by non-albicans species in neutropenic patients which are resistant to fluconazole. With the widespread use of fluconazole in the 1990s as prophylaxis in high-risk patients with acute leukaemia and transplant recipients, empiric antifungal therapy for neutropenic fever principally involved switching from fluconazole to amphotericin B, to broaden the antifungal spectrum to include molds, but at the expense of greater toxicity. The newer lipid formulations of amphotericin B has significantly less toxicity. Voriconazole or echinocandins can also be used in candidaemia with acceptable toxicity. Voriconazole is approved for use in invasive aspergillosis.

The availability of lipid formulations of amphotericin B, newer azoles, and echinocandins have prompted many centres to use these agents prophylactically. Primary antifungal prophylaxis involves fluconazole 400 mg daily or itraconazole 400 mg daily. Secondary prophylaxis in patients with prior aspergillosis includes voriconazole[32, 33]. Duration of antimicrobial therapy depends on clinical course, neutropenia recovery, toxicity, and opinions of infectious disease specialists.

Thrombocytopenia is very common in cancer patients who are receiving cytotoxic chemotherapy. Spontaneous bleeds are unlikely if platelets are > 10,000/cmm. Transfusion is indicated when platelets are < 10,000/cmm, or if there is active bleeding. Preferably HLA-matched platelets should be used to prevent refractoriness after repeated platelet transfusions. Many centres now have facilities for single donor platelet transfusion rather than pooled random donor platelets by using multicomponent cell separator machines.

Many emergencies such as acute blood loss or leukostasis and others could not be included in this article.

Others

Venous thromboembolism

Thromboembolic complications represent one of the most important causes of death for cancer patients. Deep vein thrombosis (DVT), pulmonary embolism, migrant thrombophlebitis, arterial thrombosis, non-bacterial thrombotic endocarditis, and disseminated intravascular coagulation (DIC) are it's different manifestations[34].

Surgical intervention, immobility, chronic obstructive lung disease, cardiac failure, oestrogen-progesterone use, pregnancy, puerperium, and central venous catheters

increase incidence of thrombotic complications in cancer patients. Even though pancreatic adenocarcinoma has classically been associated with a higher risk of DVT, more recent data from the West show that the highest incidence in men is observed in patients with lung, prostate, and colorectal cancer; and in women with breast, ovarian, and lung cancer[35, 36] as these are the commonest cancers in these sub-populations.

Tumour-specific mechanisms revolve around the potential of tumour cells to activate the coagulation cascade in several ways. The tumour cells are able to interact with host blood cells such as platelets, leukocytes, and endothelial cells by releasing inflammatory cytokines – interleukin (IL) 1, tumour necrosis factor (TNF), vascular endothelial growth factor (VEGF), or by direct cell-to-cell interactions. This results in a down-regulation of anticoagulant and an up-regulation of procoagulant properties of these cells, contributing to the general hypercoagulable condition of these subjects[37]. Moreover, cancer cells also produce a number of procoagulant substances, including tissue factor and cancer procoagulant.

Drugs like tamoxifen increase the risk of thromboembolism by 1 - 2%, specially if used in conjunction with chemotherapy (13%)[38].

The use of dalteparin for 6 months was associated with improved survival compared to coumarin anticoagulants in patients with solid tumours who did not have metastatic disease at the time of an acute venous thromboembolic event (CLOT Study)[39].

Haemorrhagic cystitis

Haemorrhagic cystitis though uncommon, if not treated may lead to a mortaliy rate of 75%. Causes are chiefly chemotherapeutic agents like cyclophosphamide or ifosfamide (producing the urotoxin acrolein) and locoregional radiation. Treatment for drug-induced cystitis is sodium-2-mercaptoethane sulphonate (MESNA) and urothelium healing agents for radiation induced cystitis[40].

Priapism

Haematological malignancies like myeloproliferative disorders, secondaries to the corporal body, or malignancy associated hypercoagulable states can cause priapism. Treatment of the underlying cause is the best approach. Corporal shunting may offer some help[41].

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Incidentally Detected Bilateral Adrenal Masses and Scar in the Neck

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A 38-year-old female presented with vague sensation of heaviness in the abdomen. On examination, her BP was 114/70 mmHg and she had an old scar in the neck (Fig. 1). Systemic examination was unremarkable. Ultrasound of abdomen revealed bilateral adrenal masses which were confirmed on CT scan of the abdomen (Fig. 2).

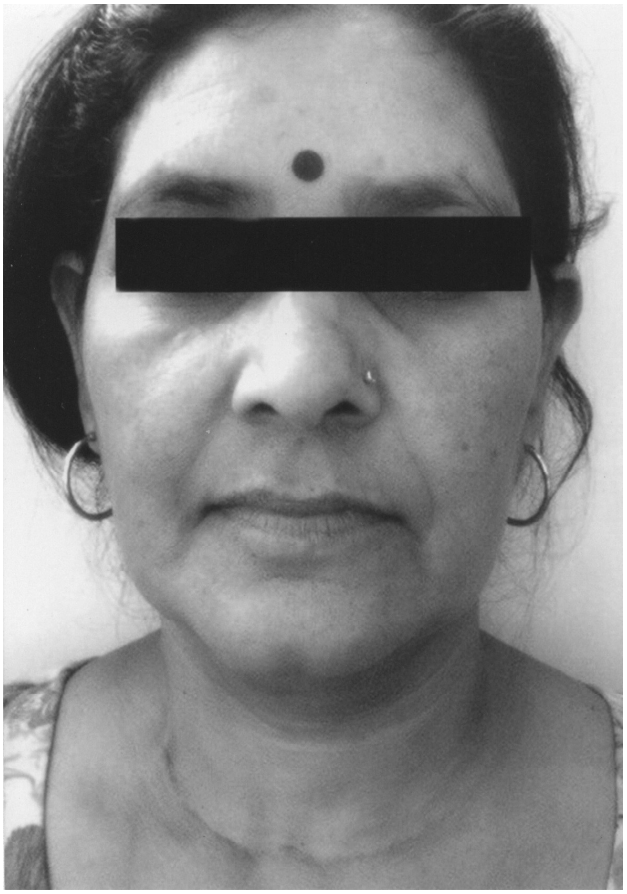

Fig. 1: *Photograph showing an old scar in the neck.*

Q1. What are the causes of bilateral adrenal masses?

Answer: Differential diagnosis of bilateral adrenal masses include granulomatous disorders, e.g., tuberculosis, sarcoidosis, fungal infections like histoplasmosis and metastasis from lung, liver and gastrointestinal tract, and rarely non-Hodgkin's lymphoma[1]. Sometimes these bilateral adrenal masses are associated with familial phaeochromocytoma and familial syndromes like MEN2a and 2b. The frequent use of imaging studies, particularly computed tomography (CT) scan has resulted in detection of adrenal incidentalomas in various studies varying from 0.35 – 5%. The majority of incidentalomas are biochemically non-functional and benign. However, in approximately 10% of cases an incidental adrenal mass may be functional[1].

Q2. How do you correlate bilateral adrenal masses with a scar in the neck in this patient?

Answer: The presence of scar in the neck in this lady points towards either old thyroid or parathyroid surgery. She underwent this surgery ten years back and after the surgery she was not under regular follow-up. An ultrasonography of the abdomen was performed for a non-specific pain abdomen ten years later. The possibility of scar in the neck due to previous parathyroid surgery was unlikely in view of lack of symptomatology of primary hyperparathyroidism (bone pains, nephrolithiasis), disease-free interval of 10 years (multiglandular disease being more common) and

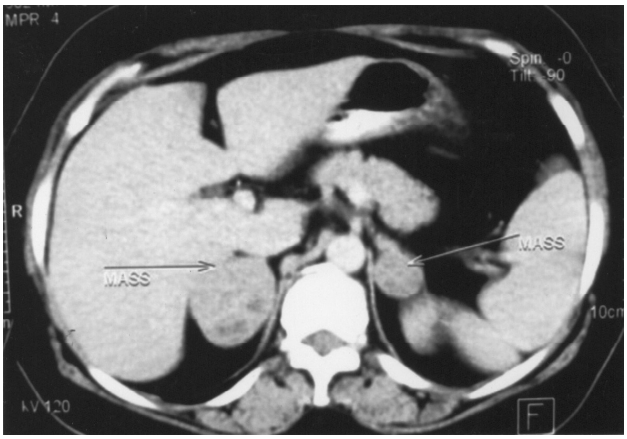

Fig. 2: *Contrast-enhanced CT scan of the abdomen showing bilateral adrenal masses.*

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prevalence of parathyroid disease being lowest (20 – 30%) in patients with MEN2a as compared to MTC (Medullary thyroid Carcinoma) (100%). Therefore, the scar in the neck was due to previous thyroid surgery for MTC and bilateral adrenal masses narrow down the diagnostic possibility to multiple endocrine neoplasia out of various differential diagnoses mentioned above.

Q3. What additional investigation would you like to have to confirm your diagnosis?

Answer: Keeping in view the history of thyroidectomy and presence of bilateral adrenal masses, serum calcium profile, calcitonin, intact parathormone levels and 24-hour urinary metanephrines were advised in this patient. Serum calcium (corrected for albumin), phosphorous and alkaline phosphatase were 9.4 mg/dl, 3.0 mg/dl and 9KA units respectively. Serum 25 (OH) D3 was normal. Serum intact PTH level was 180 pg/ml (N 10 – 69 pg/ml); serum calcitonin 3,720 pg/ml (N < 11.5 pg/ml) and 24-hour urinary metanephrine was 4,031 µg/24 hour (N = 52 – 341 µg/24 hour).

Raised serum calcitonin, elevated intact PTH and increased 24-hour urinary metanephrine were suggestive of residual MTC, evoluting hyperparathyroidism (raised PTH and normal serum calcium and 25 (OH) D_3 levels) and bilateral phaeochromocytoma respectively qualifying for the diagnosis of MEN 2a. She had no family history of medullary thyroid carcinoma, parathyroid adenoma or phaeochromocytoma. RET proto-oncogene mutation could not be performed.

Q4. What are the other features of MEN2a?

Answer: The MEN2a is an autosomal dominant disorder and consists of bilateral and multicentric MTC in 90 – 100%, unilateral or bilateral phaeochromocytoma in half (50%) of the patients, and parathyroid hyperplasia or adenoma in 20 – 30%. All three manifestations do not occur concurrently[2]. However, MTC is the commonest manifesting neoplasia followed by phaeochromocytoma, as happened in our patient after 10 years of first surgery. Biochemically, she had high intact PTH; but parathyroid glands could not be localised even on neck exploration, therefore, she requires close surveillence for ectopic parathyroid later.

Several rare variants of MEN2a include familial MTC (FMTC), MEN2a or FMTC with Hirschprung's disease. All MEN variants are caused by germline mutations in the RET proto-oncogene[2]. The RET gene is near the centromere of chromosome 10 and encodes a plasma membrane basal tyrosine kinase enzyme known as RET. The most common mutation in MEN2 affect, codon 609, 611, 618, 620, 630 and 634 all encoding extracellular cysteine residues[2]. Mutations at codon 634 account for more than 80% of mutations in MEN2. However, in this patient we could not perform proto-oncogene analysis.

Q5. How would you treat this patient?

Answer: Treatment of MEN 2a includes bilateral adrenalectomy followed by complete thyroidectomy with lymph node resection and removal of three-and-a-half parathyroid glands. She underwent simultaneous residual thyroidectomy, parathyroid exploration and one-and-a-half gland adrenalectomy. Residual MTC was extending into anterior mediastinum, was extirpated; however, her parathyroids could not be localised. One-and-a-half gland adrenalectomy was performed because on the right side it was an encapsulated tumour, while the other gland was nodular and adenomatous. Post-operatively, serum calcitonin was normalised and she remained normocalcaemic and eucortisolic.

Since MTC is a multicentric disease, with having metastasis to lymph nodes most of the time when its size is > 1 cm, total thyroidectomy with central lymph node dissection and selective dissection of other regional lymph node chains provides the best chance of a cure[3]. However, in our patient, residual thyroid tissue was removed and serum calcitonin became normal. For hyperparathyroidism, removal of 3½ glands with maintenance of the remaining half gland in the neck is the usual procedure of choice. However, there is always a concern for potential development of permanent hypoparathyroidism which needs to be looked into future follow-up and, if present, needs appropriate management. Laparoscopic adrenalectomy is the procedure of choice for a patient with unilateral phaeochromocytoma[4]. With bilateral abnormalities, bilateral adrenalectomy should be performed by open or laparoscopic approach. In our patient, one-and-a-half adrenalectomy was performed since the other adrenal had an encapsulated adenoma. Adrenal

cortical sparing adrenalectomy is a promising technique for preventing adrenal insufficiency, but there is a limiting long-term experience and increased chance of recurrence[5].

Final diagnosis: Multiple endocrine neoplasia II a.

Keywords: *Medullary thyroid carcinoma, Multiple endocrine neoplasia, Phaeochromocytoma.*

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A Disease Called Alcoholism

Turned to the boss, he stammered 'PLEASE,
I'm overwhelmed by this disease.
I cannot help it that I drink
and if I AM now at the brink
of losing what pays all my bills,
your verdict Sir, will be what kills
and you would carry in your soul
the guilt from taking on the role
to pull the rug from under me
and hang me from the tallest tree.

You know, mylord, I cannot stop,
a kangaroo must always hop,
I have, as you will, doubtless, guess
searched deep within, my heart, no less.

The fault, however, does not rest
with me but hatched inside the nest,
you see my father was too strict
he labelled me a derelict.

My mother nursed me for two moons
next door they raised a pair of goons.
And that, of course, was what soon paved
the road for me to a depraved
andhelter-skelter life of stress,
so, on your sacking, stop the press!

Genetically, I carry genes
that ripened in my early teens.
It's chromosomes from Mum and Dad
and if you ask me, they are bad.

Thus, all in all, I'mNOT to blame.
The world around me takes the shame.
A drink to me is medicine
and not some godforsaken sin.

– Dr. Herbert Nehrlich
(Queensland, Australia)

CASE REPORT

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Two Cases of Paraquat Poisoning from Himachal Pradesh

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Abstract

Paraquat (1, 1'-dimethyl-4, 4'-dipyridylium) is a broad spectrum, contact, liquid herbicide associated with both accidental and intentional ingestion, leading to severe and often fatal toxicity. Despite its free availability in the Indian market for use by agriculturists, it is an uncommon poisoning in India with only a few case reports described from India. We report two cases of fatal paraquat poisoning from a tertiary care hospital in the northern state of Himachal Pradesh, India.

Key words: Paraquat, Poisoning, Herbicide.

Introduction

Paraquat is a quarternary nitrogen herbicide that is sprayed on unwanted weeds and other vegetations before planting crops. It is a fast-acting, non-selective compound, which destroys tissues of green plants on contact and by translocation within the plant. Paraquat exerts its herbicidal activity by inhibiting reduction of NADP to NADPH during photosynthesis. This disruption leads to the formation of superoxide anion, singlet oxygen, as well as hydroxyl and peroxyl radicals. These reactive oxygen species (ROS) interact with the unsaturated lipids of membranes, resulting in the destruction of plant organelles, inevitably leading to cell death. The strong affinity for adsorption to soil particles and organic matter is one of the major advantages in introducing paraquat as a herbicide because it limits its bioavailability to plants and microorganisms. Moreover, paraquat is not mobile in most soils and the portion that does not become associated with soil particles can be decomposed to a non-toxic product by soil bacteria; thus, paraquat does not present a high risk of groundwater contamination. However, paraquat has been demonstrated to be a highly toxic compound for humans and animals and many cases of acute poisoning and death have been reported over the past few decades[1]. It is produced commercially as a brownish concentrated liquid of the dichloride salt in 10 – 30% strength under the trade name of 'Gramoxone' and for horticultural use as brown granules called 'Weedol' at about 5% concentration[2]. Paraquat poisoning has been widely reported worldwide, but only a few case reports are described in literature from India[3-5]. We report two cases of fatal paraquat poisoning from the northern Indian state of Himachal Pradesh, who were admitted in a tertiary care hospital. Both the patients were agriculturists and belonged to a vegetable growing area of the state where 'Gramoxone' is freely available for use in the fields. On extensive literature search no case of paraquat poisoning was found to be reported from this state of India.

Case report

Case No. 1

A forty-year-old male patient was admitted in the medical ward with history of ingestion of 5 ml of paraquat dichloride (Gramoxone – 24% SL) six days back. The patient had vomited immediately after ingestion of paraquat. There was history of yellowishness of sclera for three days. There was no history of oliguria. Clinical examination revealed oral erosions and icterus. Rest of the examination was normal. Investigations showed serum urea as 292 mg/dl and creatinine as 9.8 mg/dl on admission. Total serum bilirubin was 36.9 mg% and conjugated was 24.0 mg%. The transaminases were raised (SGOT – 300 IU and SGPT – 311 IU). The alkaline phosphatase was 426 KAU. The patient was managed conservatively for five days alongwith two sessions of haemodialysis. Thereafter, the patient developed features of adult respiratory distress syndrome and died on ventilatory support. On autopsy, lungs showed bilateral emphysematous bullae with extensive haemorrhagic areas. The brain, heart, liver, and kidneys were congested. Histopathological examination was not done.

Case No. 2

A twenty-one-year-old female patient was admitted in the medical ward with history of ingestion of 20 ml of

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paraquat dichloride (Gramoxone – 24% SL) three days back. History of oliguria was present for last two days. On examination, she had tachycardia and was tachypnoeic. Oral erosions and icterus were present. On nervous system examination, deep tendon reflexes were absent. Rest of the examination was normal. The serum urea was 253 mg/dl, and creatinine was 11.0 mg/dl. Total serum bilirubin was 6.2 mg% and conjugated was 4.2mg%. The transaminases were raised (SGOT – 199 IU and SGPT – 210 IU). The alkaline phosphatase was 207 KAU. Patient was managed conservatively for two days including one session of haemodialysis, and became haemodyanamically unstable with features of adult respiratory distress syndrome and died despite ventilatory support. On autopsy, stomach showed erosions and patchy haemorrhages. Histopathological examination was not done.

Discussion

Acute paraquat self-poisoning is a significant problem in parts of Asia, the Pacific and the Caribbean[6]. The most frequent routes of exposure to paraquat, either accidentally or intentionally, in humans and animals are following ingestion or through direct skin contact. If ingested, paraquat induces a burning sensation of the mouth and throat, followed by gastrointestinal irritation, subsequently resulting in abdominal pain, loss of appetite, nausea, vomiting, and diarrhoea. Direct contact with paraquat solutions or aerosol mists may cause skin burns and dermatitis. Paraquat splashed in the eyes can irritate, burn, and cause corneal damage and scarring of the eyes. Due to its low vapour pressure and the formation of large droplets, inhalation of paraquat spray used in the open environment has not been shown to cause any significant systemic toxicity; however, inhalational exposure to paraquat in confined spaces, such as a greenhouse, is known to be associated with fatal pulmonary disease. Irrespective of its route of administration in mammalian systems, paraquat is rapidly distributed in most tissues, with the highest concentration found in the lungs and kidneys. The compound accumulates slowly in the lungs via an energy-dependent process. Excretion of paraquat, in its unchanged form, is biphasic, owing to lung accumulation and occurs largely in the urine and, to a limited extent, in the bile. Biotransformation of paraquat is, in general, poor in all species studied and the excreted compound is unchanged.

The primary injury caused by paraquat to mammalian systems occurs in the lung, where paraquat is accumulated through a process of active transport in the Clara cells and alveolar type I and II epithelial cells. The paraquat-induced lung injury is morphologically characterised by an early destructive phase, in which the alveolar type I and type II epithelial cells are damaged; and a second proliferative phase defined by alveolitis, pulmonary oedema, and infiltration of inflammatory cells. In addition to the lung, paraquat administration has been shown to injure other major organ systems, but to a lesser extent. Pathological changes have been observed in the liver, kidney, and heart at high doses; but death is usually associated with respiratory insufficiency injury. The mechanisms of paraquat toxicity involve: the generation of the superoxide anion, which can lead to the formation of more toxic reactive oxygen species, such as hydrogen peroxide and hydroxyl radical; and the oxidation of the cellular NADPH, the major source of reducing equivalents for the intracellular reduction of paraquat, which results in the disruption of important NADPH-requiring biochemical processes[1]. Treatment involves removal of ingested paraquat by immediately induced emesis or by gastric lavage in a health care facility. Clay (Fuller's earth) and activated charcoal are effective adsorbents. Administer repeated doses of 60 gm of activated charcoal by gastric tube every two hours for three or four doses. Supplemental oxygen should be withheld unless the pO_2 is less than 70 mmHg because oxygen may contribute to the pulmonary damage which is mediated through lipid peroxidation[7]. Since the principal biochemical mechanism for lung damage is initiated by oxygen free radicals produced by peroxidation, clinicians have tried a number of anti-oxidant treatments in the hope that they might interfere with the process. Unfortunately, none of the studied treatments, including controlled hypoxia, superoxide dismutase, vitamins C and E, N-acetylcysteine, desferrioxamine, and nitrous oxide, has been proven to be effective[1, 6]. However, recent evidence regarding the use of immunosuppressive therapy with glucocorticoids and cyclophosphamide in the management of lung injury in patients with severe paraquat poisoning has been encouraging. Two randomised controlled trials have suggested a definite trend in benefit with immunosuppressive therapy in patients with moderate to severe poisoning[8, 9]. In an Indian study, five patients with

severe and fulminant paraquat poisoning were started on the day of hospital admission on intravenous methylprednisolone 15 mg/kg/day for three consecutive days, intravenous cyclophosphamide 10 mg/kg/day for two consecutive days, followed by intravenous dexamethasone four milligrams thrice a day until recovery or death. Two out of the five patients did survive[5]. In another meta-analytical review evidence of benefit was shown with the use of immunosuppression in all forms of studies, and hence supported the use of immunosuppression in patients with severe paraquat poisoning[10]. A systematic review performed in 2003 did not find good evidence of benefit or harm from immunosuppression, so a large randomised controlled trial is required to affirm the role of immunosuppression in paraquat poisoning[6]. Diquat is another dipyridyl herbicide widely used in agriculture and has early corrosive effect similar to paraquat. Diquat is not selectively concentrated in lung tissue so pulmonary injury is less prominent and no progressive pulmonary fibrosis has been noted. However, toxic effects on central nervous system and kidneys are prominent[11]. Prognosis in paraquat poisoning is largely dependent on the amount of paraquat absorbed. Rapid identification of the symptoms of paraquat toxicity (burns or ulceration at the site of ingestion or injection, acute respiratory distress, and renal failure) can facilitate early treatment intervention to limit absorption. According to our knowledge these are first cases of paraquat poisoning reported from the state of Himachal Pradesh, India. These cases are reported to highlight the high mortality rate associated with Paraquat poisoning in spite of advances in treatment and supportive care.

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CASE REPORT

JIACM 2008; 9(2): 133-5

Acute Severe Poisoning by Barium Carbonate (Rat Poison)

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Abstract

Barium Carbonate, the commonly used rodenticide is a highly toxic substance. Weakness and hypokalaemia are the characteristics signs of barium poisoning. Early and appropriate management can be life-saving. We hereby report a case of a 22-year-old male with acute severe barium carbonate poisoning with life-threatening cardiac complications.

Keywords: Barium Carbonate, Rat poison, Severe hypokalaemia.

Introduction

Barium Carbonate is a highly toxic substance used in the past as a rodenticide and currently in some part of the world as a male depilatory. It is a yellowish white, slightly lustrous lump. The insoluble form of barium, such as barium sulphate, commonly used in radiographic procedures is harmless[1]. However, soluble salts of barium are highly toxic; weakness and hypokalaemia being the characteristics signs of barium poisoning[2].

Case report

A 22-year-old male attempted suicide by ingesting 20 gm of barium carbonate (rat poison) following which he developed multiple episodes of vomiting and excessive secretions in the mouth, and profound weakness. He was brought to our medical casualty four hours after the ingestion of poison. On examination, his general condition was poor with pulse rate of 120/min and regular, blood pressure 90 mmHg systolic, respiratory rate 30/min and JVP was not raised. He had multiple self-inflicted lacerations all over the body. On CVS examination, heart sounds were faint and no murmur was audible. Bilateral diffuse crepitations were present all over the chest. On CNS examination, patient was drowsy, had generalised muscle weakness, power grade II (on Medical Research Council's Grading), plantar bilateral non-elicitable and both pupils showed normal size and normal reaction. ECG done showed T-wave inversion and prominent U waves (Fig. 1).

Nasogastric lavage was done and patient was started on IV fluids. After 2 - 3 hours he suddenly developed respiratory arrest requiring endotracheal intubation. Cardiac monitor showed ventricular fibrillation, which was reverted with DC cardioversion and rhythm was maintained with continuous infusion of amiodarone. Emergency investigations revealed severe hypokalaemia (serum potassium 1.4 mEq/l). Intravenous potassium chloride was given. After correction of hypokalaemia, ECG changes became normal (Fig. 2). Repeated electrolytes and all other routine investigations including urine, haemogram, liver function tests, renal function tests, etc., were within normal limits. The patient's condition improved gradually and he was discharged after seven days.

Discussion

A rodenticide is any product commercially marketed to kill rodents, including mice. The "perfect rodenticide" one that efficiently kills rodents but is not toxic to human or non-rodent pets has yet to be discovered. They have been classified in several ways: Arena and Drew divided them into inorganic compounds including arsenic, thallium, phosphorus, barium carbonate and zinc phosphide and organic compounds including sodium fluroacetate, warfarin, red squill, strychnine, and norbromide.

Barium carbonate is a highly toxic substance used as a rodenticide. Barium is a muscle poison. Most of the toxic effects of barium result from its direct stimulation of all types of muscles, including cardiac muscle, and from its ability to cause a profound reduction in serum potassium together with an increase in intracellular potassium. Barium itself is responsible for membrane depolarisation by causing release of acetylcholine and by competitively

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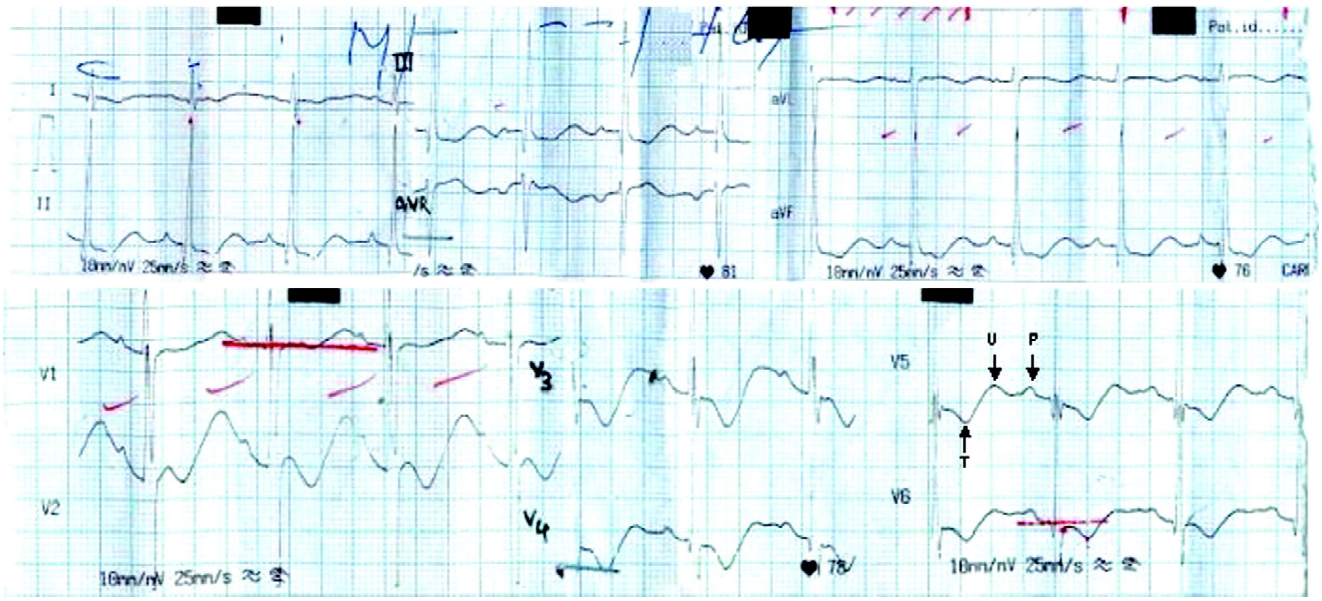

Fig. 1: *ECG showing T wave inversion and prominent U wave due to hypokalaemia.*

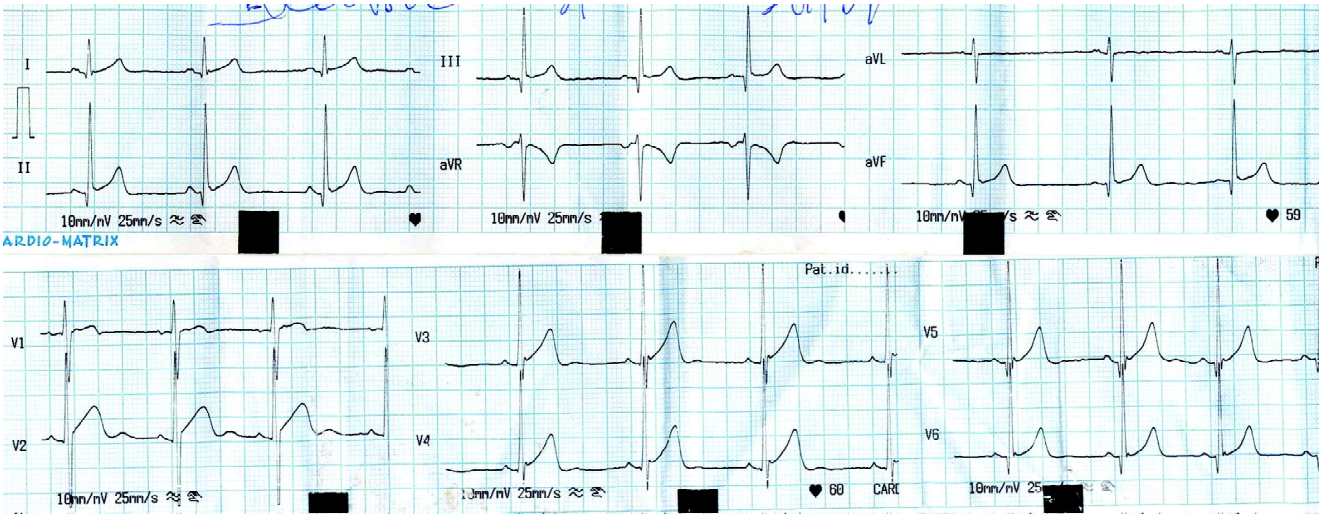

Fig. 2: *ECG showing appearance of normal T wave and disappearance of U wave.*

reducing the permeability of all membranes to potassium with the resultant intensity of neuromuscular blockade correlating directly with plasma barium concentration. Onset of action is about 1 – 8 hours and estimated fatal dose is 20 – 30 mg/kg[1].

The diagnostic presenting signs and symptoms include headache, paraesthesia, peripheral weakness, paralysis, nausea, vomiting, diarrhoea, abdominal pain and sometimes respiratory paralysis and ventricular tachyarrhythmias[3].

Progressive areflexic quadriplegia with intact sensations very closely resembled Guillain-Barre syndrome. Clinically, there may be some common presenting features between barium carbonate poisoning and Guillain-Barre syndrome, namely, ascending quadriplegia, areflexia, absence of sensory impairment and involvement of respiratory muscles. In Guillain-Barre syndrome, weakness may progress rapidly or over several days, reaching a peak at 3 – 4 weeks of onset. Disturbances of autonomic function, such as persistent tachycardia, cardiac arrhythmias and ST-T wave changes on the ECG are common, thus confusing the picture further with barium overdose. Features which may differentiate Guillain-Barre syndrome from barium carbonate poisoning include, a history of respiratory or

gastrointestinal infection (in 50% of cases), cranial nerve involvement, protein cytologic dissociation in the CSF (in second week) and early conduction block in nerve conduction velocity studies (in 90% of cases)[4].

In a patient presenting with areflexic or hyporeflexic quadriparesis with respiratory muscle involvement similar to acute post-infective polyneuropathy a possibility of barium poisoning should be entertained[5].

Barium causes increased automacity of the myocardium and has been used for the treatment of Stokes-Adams attacks. This increased automacity gives rise to various tachyarrhythmias. Ventricular ectopics, ventricular tachycardia, increased Q-Tc interval and sudden cardiac asystole are encountered. Though some of these can be attributed to hypokalaemia. All cases of barium poisoning need continuous cardiac monitoring after hospitalisation[6]. Death results from hypokalaemia, cardiac dysarrhythmia, congestive heart failure and pulmonary toxicity.

Treatment for the ingestion of soluble form of barium includes emesis, if it can be accomplished rapidly outside the hospital, or orogastric lavage with sodium sulphate in the hope of converting the barium carbonate to barium sulphate[1]. Barium sulphate thus formed is precipitated and is not absorbed. Intravenous administration of sodium sulphate has also been used for this purpose, however, this may result in the precipitation of barium in the kidneys and give rise to tubular obstruction or necrosis[6]. Rapid, aggressive potassium replacement intravenously as indicated by frequent serum potassium monitoring is the most important aspect of management[1]. Ventilatory support should be given if there is any indication of respiratory insufficiency due to the involvement of the respiratory muscles[6]. Haemodialysis is also efficacious in the therapy of barium intoxication[7].

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CASE REPORT

JIACM 2008; 9(2): 136-9

Spontaneous Spinal Epidural Haemorrhage: An Unusual Cause of Paraplegia

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Abstract

Spontaneous spinal epidural haemorrhage (SSEH) is a rare but an important cause of compressive myelopathy. A case of a 35-year-old female is being reported, who presented with sudden onset paraplegia after an episode of severe pain in cervico-dorsal spinal region. An emergency MRI was performed within six hours which revealed SSEH at D1 - D2 level. This patient was managed conservatively and the symptoms resolved in three days. On account of rarity of SSEH this case report alongwith review of literature is being documented.

Keywords: Epidural haematoma, Magnetic resonance imaging, Paraplegia.

Introduction

Spontaneous spinal epidural hematoma is an uncommon entity in which the etiology remains unidentified. Trauma is a leading cause of SSEH, whereas the non-traumatic causes of SSEH are anticoagulant therapy, vascular anomalies, hypertension, and spinal surgery[1]. In up to 40% of the cases, no underlying cause can be identified[2].

The clinical presentation can be varied and usually presents with acute spinal cord compression, beginning with backache and radicular pain followed by sensory changes; and finally motor weakness or paraplegia follows[3]. Magnetic Resonance Imaging (MRI) is indispensable for the diagnosis of spinal haematoma[4]. A case report of SSEH alongwith review of literature is being documented below.

Case report

A 35-year-old female patient presented with sudden onset of dorsal pain radiating to the cervical region. This was followed by gradually progressive weakness and paraesthesia with tingling sensation in both lower limbs within a short duration of three hours. The patient also developed urinary symptoms for which she was catheterised. There was no recent history of trauma or use of oral anti-coagulants. Patient had no history of hypertension or spinal surgery in the past. Clinical examination of CNS revealed normal higher functions and cranial nerve functions. Examination of the upper limbs including both sensory and motor examination was normal. On examination of the lower limbs, power was grade 0, reflexes were absent, but plantar reflexes were bilaterally extensor. There was sensory loss (in all modalities) till level of D4 dermatome. There was associated truncal weakness as well. Other systemic examination was normal. Emergency MRI was performed on the same day (within 6 hours). It revealed extra-dural lesion at D1 - D2 level which was isointense to cord on T1W images (Fig. 1) and hyper-intense on T2W images, (Fig. 2). On STIR images, surrounding bony elements appeared normal with no alteration in bone marrow signal intensity. On contrast enhanced (CE) image (Fig. 3) very poor heterogenous enhancement was seen. There was, in addition, a paraspinal mass within the planes between scalene and levator scapulae muscles on the right-side posteriorly at D1 - D2 level, similar in signal intensity to the epidural lesion described previously. FNAC from this paraspinal mass showed skeletal muscle bundles and a few mature fibroadipose tissue fragments in a haemorrhagic background. Haematological profile (including platelet counts) alongwith coagulation profile (clotting time, PTI and PTTK) were found to be within normal limits. Based on the clinical history, haematological investigations (including coagulation profile) and MRI findings, a diagnosis of SSEH was made. Patient was managed conservatively (including nursing care). She showed rapid clinical improvement and completely recovered within three days. Follow-up MRI after one month revealed complete resolution (Fig. 4).

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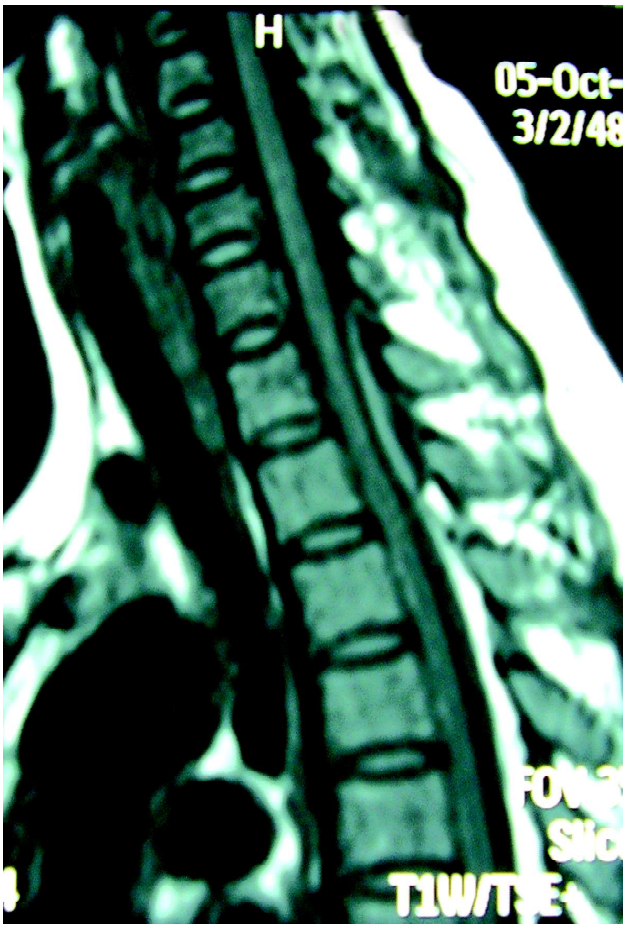

Fig. 1: *Sagittal T1W image revealing a posteriorly located extradural soft tissue lesion isointense to cord at D1-D2 level.*

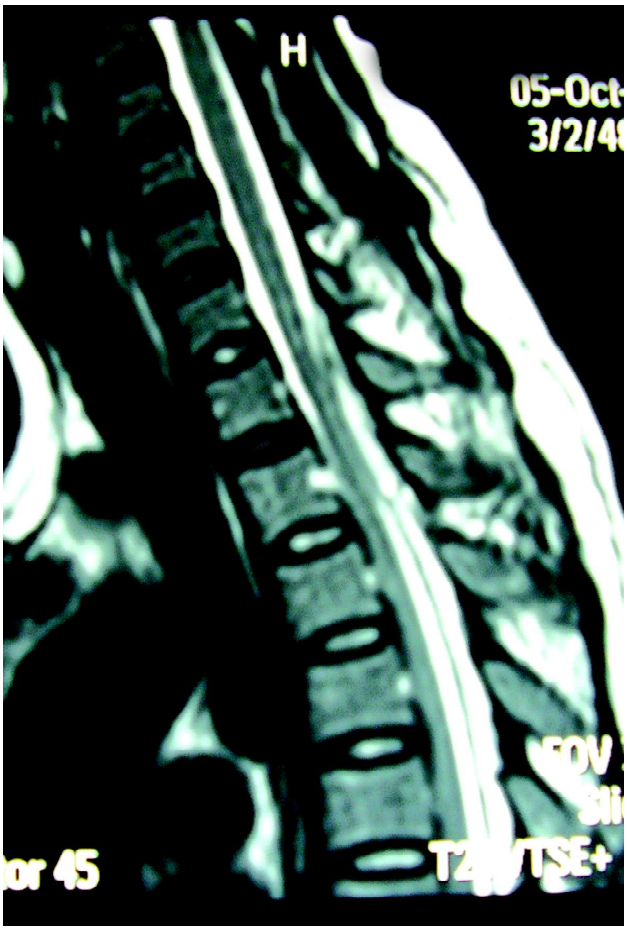

Fig. 2: *Sagittal T2W image reveals that the lesion is hyperintense to cord.*

Discussion

Since the first case report of a spinal epidural hematoma described by Jackson in 1869[3], approximately 600 case reports of spinal epidural hematoma have been reviewed in the international literature. Out of these approximately 515 were operated upon while remaining showed spontaneous recovery on conservative management.

Underlying disease and factors inducing spinal epidural haematoma include: vascular abnormality including congenital anomaly[5] and haemangioma[6], external factors such as trauma or catheterisation for anaesthesia[7], traumatic lumbar punctures[8], pregnancy[9] and drugs including cocaine[10]. However, a substantial number of epidural hematomas with unknown origin have also been reported.

The aetiological mechanism of spinal epidural haematomas still remains controversial. Most authors believe the bleeding of spinal epidural haematomas to be venous in origin[3, 4, 11]. Congestion that precedes rupture of the fragile spinal veins, especially the valveless epidural venous plexus is a potential pathophysiological mechanism. Usually a high intracavitary pressure induced by, for example, pregnancy increases the plexus pressure, that finally brings about rupture. Beatty and Winston, on the other hand, suggested the spinal epidural arteries as the haemorrhage source[11, 12]. Proof of either theory has been difficult, because of lack of angiographic documentation of the lesion as well as inconsistent findings of a cause of surgically removed clot.

Spontaneous spinal epidural haematomas generally occur in adults and in male patients and are most frequently located in lower cervical or cervicothoracic regions[14]. Epidural haemorrhage is frequently located dorsal to the spinal cord because of tight fixation of the dura to the vertebral bodies[4].

The first clinical symptom of acute spinal epidural

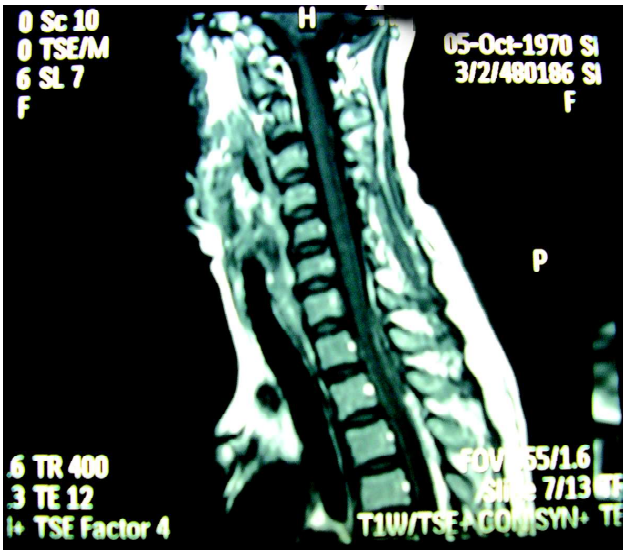

Fig. 3: *Contrast enhanced sagittal T1W image revealing poor heterogenous enhancement.*

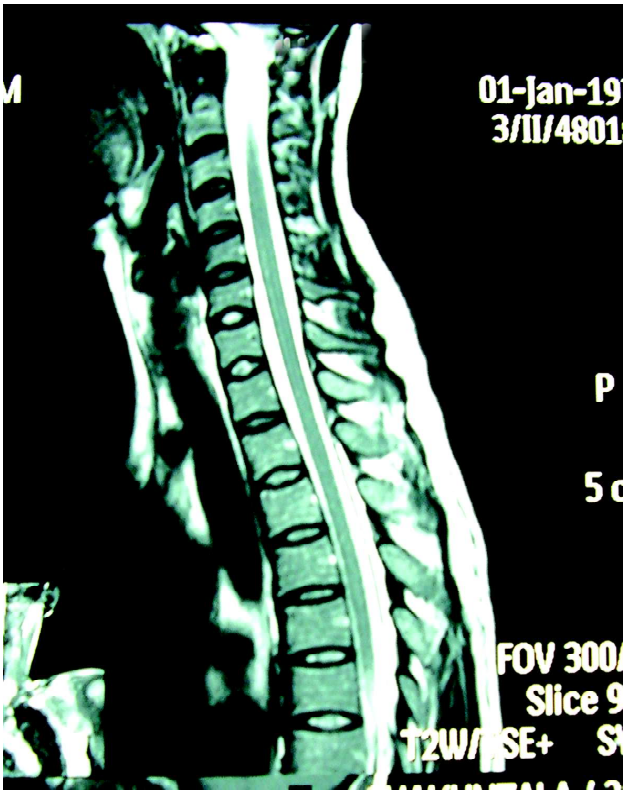

Fig. 4: *Follow-up MRI of the same patient showing complete resolution.*

haematoma is the sudden onset of severe spinal pain. Various degrees of sensory loss due to compression of the spinal cord by the localised bleeding and a rapidly progressive muscle weakness of the legs is followed by complete or partial paraplegia within several hours to days after onset. In some cases, bladder and bowel may be involved[3]. In our case, severe neurological symptoms were observed at 3 hours after onset of symptoms.

MRI is effective in the diagnosis of SSEH because of its sensitivity in depicting soft-tissue lesions and it's ability to survey and cover the full extent of haematoma[1]. The signal intensity of SSEH varies over time. During the acute stage, the haematoma is isointense relative to spinal cord on T1-weighted images and hyperintense relative to spinal cord on T2-weighted images. During the subacute stage, such as 30 hours after symptom onset, the haematoma is usually a heterogenous hyperintensity on both T1- and T2- weighted images. The increased heterogeneity of the haematomas results from degradation products of haemoglobin[15]. Contrast enhancement seen in our patient is similar to the presentation of bleeding diathesis. Chang F *et al* also observed similar enhancement in their two patients and could not determine the cause. They speculated that it might be because of continuous extravasation of contrast medium from the torn epidural venous plexus or an engulfed epidural vascular soft-tissue within the acutely enlarging haematomas[16]. MRI is a less complex procedure than myelo-CT and provides the same information.

The standard therapy of SSEH has been prompt evacuation of the haematoma, resulting in good neurological recovery. In recent years, the number of spinal epidural haematoma cases which improved without surgical decompression has tended to increase. On comparing cases which were treated operatively and which were treated conservatively, on the basis of several factors like age, sex, medical history, position of haematoma, segmental distribution and length of haematoma, diagnostic imaging, neurological condition and outcome, it was found that the mean length of the haematoma was significantly higher in patients treated conservatively as compared to patients treated operatively (5.4 versus 4.2 vertebral segments)[17]. However, the mainstay of treatment remains surgery. The decision for conservative therapy is based on severity of neurological deficit and on the clinical course[17].

The present case was relatively unique in that there was no predisposing cause; also, the initial neurological status was relatively severe but showed rapid improvement on conservative therapy. This may be because the length of

segment in our case was small, i.e, two vertebral lengths.

Conclusion

Spontaneous spinal epidural haematoma is an uncommon disease commencing with back and radicular pain, quadriplegia and rectovesical insufficiency. Early diagnosis and surgical decompression is generally imperative, although an exceptional remission without operation such as was observed in this case may occur. Surgical treatment seems to be unnecessary when the clinical symptoms are not progressive or when early recovery is observed.

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CASE REPORT

JIACM 2008; 9(2): 140-2

Cauda Equina Syndrome in Pregnancy Due to Disc Prolapse

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Abstract

Clinical examination is of paramount importance to diagnose the rare condition of cauda equina syndrome due to disc prolapse during pregnancy. Diagnosis of this treatable condition can easily be missed, because most of the complaints of discogenic cauda equina syndrome are similar to that of normal pregnancy. Delay in treatment of this benign condition can cause irreversible neurological damage. We report here such a case of delayed diagnosis of cauda equina syndrome in pregnancy, its management, and its sequelae.

***Key words:** Disc, Pregnancy, Surgery, Anaesthesia, Imaging.*

Introduction

Cauda equina syndrome due to disc prolapse is very rare and can be missed because it simulates symptoms of normal pregnancy. Reported incidence of symptomatic disc prolapse in pregnancy is one in 10,000 and out of hundred such cases requiring surgery, two may have a cauda equina syndrome[1, 2]. There are only a few case reports of cauda equina syndrome during pregnancy in the English literature and we could not find any report published from India.

Case history

A 30-year-old lady with 20 weeks of gestation was referred to neurosurgery department of our hospital for retention of urine. She presented with complaints of low back pain and pain along the posterior aspect of both thighs for 25 days and retention of urine for 22 days. She also had difficulty in walking for 22 days.

On the 2nd day of onset of symptoms she was seen by an orthopaedic surgeon for low back pain and watery discharge from vagina who referred the patient to an obstetrician for presumed leaking membrane of pregnancy. The obstetrician on the other hand diagnosed it to be a case of pregnancy related retention and accordingly treated her with catheterisation. But since intermittent, and later indwelling, catheterisation did not relieve her symptoms, she was referred to neurosurgery. Though she complained of constipation, she was having incontinent bowels, as evident from soiling of clothes and inability to control flatus. This was her second pregnancy; the first childbirth was a full-term normal vaginal delivery. She had no history of trauma to her spine. On examination, her vitals were normal. Her higher functions, cranial nerves and upper limb functions were normal. In lower limbs, on the left side, knee extension was grade 4+/5, knee flexion grade 3/5; on the right side, knee extension was grade 5/5, knee flexion grade 3/5. On both the sides, dorsiflexion and plantar flexion of ankles as well as great toes were grade 2/5. She had sensory loss to fine touch and pin prick from L_4 segment downward on the left side, and S_1 downward on the right side. On the left side knee reflex was diminished, while on the right side it was normal. Ankle reflexes were impaired on both the sides; moreover, she had a trophic ulcer on the right peri-anal region (Fig. 1). Her peri-anal reflex was absent and tone of the anal sphincter weak. She was on catheter at the time of

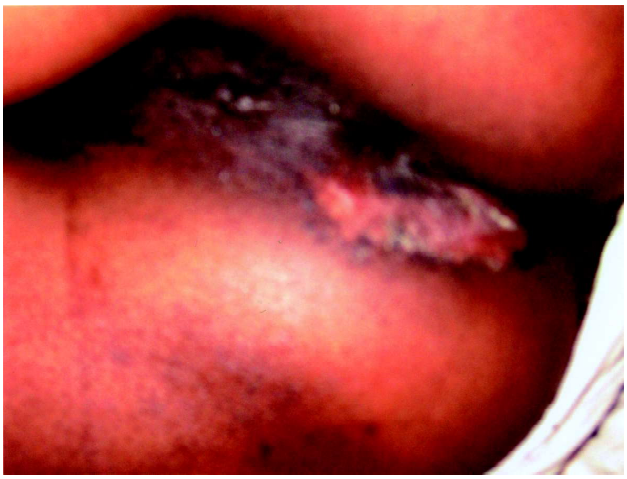

***Fig. 1:** Peri-anal trophic ulcer.*

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examination. Her gestation was of 20-weeks duration. The foetus was in a good condition as assessed by the obstetrician. Blood chemistry and haematological tests did not reveal any abnormality. All the biochemical parameters and haematological test reports were within normal limits. A clinical diagnosis of cauda equina syndrome due to disc disease was made and the patient was subjected to MRI scan of lumbo-sacral spine. MRI scan revealed extruded disc fragment encroaching the total spinal canal at L_5/S_1 level (Fig. 2). She was subjected to conventional laminectomy of L_5 and S_1 with excision of extruded disc fragments of L_5/S_1 disc space under general anaesthesia. Advanced surgical methods were not used as radiological localisation is a contraindication in pregnancy. Surgery was done in prone position. Recovery after surgery was uneventful. The lady gave birth to a healthy, full-term male child vaginally during follow-up. At seven month follow-up post-delivery she does not have pain any more, though weakness still persists in her feet; she is able to walk independently. Her trophic ulcer has healed. She is able to perceive sensations in this previously numb area. But her bladder and bowel remain incontinent till the last follow-up and probably will remain like that for ever.

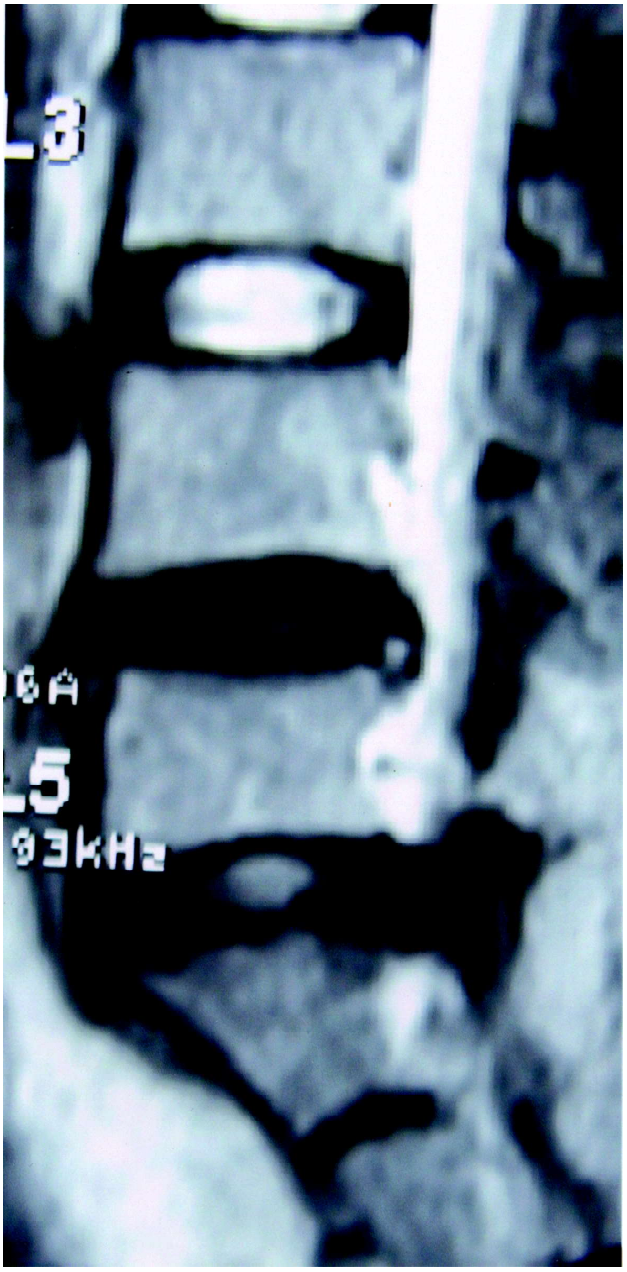

Fig. 2: *MRI scan of lumbo-sacral spine shows total encroachment of spinal canal at L5/S1 level by extruded disc material.*

Discussion

Back pain is reported to occur in more than 50% of pregnant women[3]. Pregnant women may undergo functional changes like increasing weight of uterus and stretching of the surrounding tissue with resultant posture change, dysfunctional changes like separation of pubic bones or stress on sacroiliac joint[3]. Also, muscles of anterior abdominal wall are stretched and due to increased lordosis of lumbar spine, paraspinal muscles are shortened. Relaxin also plays its role on all ligaments making them lax[4]. In spite of all these changes, prolapse of a lumbar disc is not found to be common in pregnant women, though it is associated with backache when present. Weinveb *et al*[5] with the help of MRI, found disc bulges and herniations in 53% of pregnant women as opposed to 54% of a control group non-pregnant, asymptomatic women. Chan *et al*[6] in their research work, reported significant correlation of high signal intensity in the uterine cervix (in MRI) and back pain, but though disc bulge or prolapse was associated with back pain were relatively infrequent. They opined that soft tissue laxity may be a more important cause of back pain in pregnancy than disc prolapse.

Cauda equina syndrome is a surgical emergency[1, 7, 8]. Patients present with asymmetrical paralysis, sensory loss, and areflexia including loss of bladder and bowel control[8]. Cauda equina syndrome due to disc prolapse in pregnancy is very rare. Exact incidence of cauda equina syndrome in pregnancy due to disc disease is not known. Symptoms of

cauda equina syndrome are astonishingly similar to symptoms of pregnancy. Low back pain, pain along the thigh and legs and stress urinary incontinence are common to normal pregnancy.

But objective signs like weakness in lower limbs, sensory loss, trophic ulcers, loss of tendon reflexes and bladder symptoms should alert the physician to look for neurological conditions. In our patient, bladder symptoms were misinterpreted for leaking membrane and then for pregnancy related retention; other symptoms were not recognised properly probably due to rarity of the condition as well as their similarity with normal pregnancy. Delay in treatment in cauda equina syndrome can cause permanent neurological disability[9]. MRI scan, general anaesthesia, prone position during surgery and the surgery itself are safe in pregnancy as is proved in this case[1, 4, 8, 9].

This rare condition of cauda equina syndrome can be suspected and diagnosed during pregnancy only by careful history taking and examination of the patient. On the other hand, the diagnosis of this treatable condition can easily be missed if the physician does not suspect the condition and does not examine the patient carefully. Once suspected, patient should be subjected to MRI scan of spine and surgical treatment without any delay to avoid preventable life-long disability.

This case illustrates the significance of clinical examination in our day-to-day practice.

Acknowledgement

We are thankful to Dr DN Mohapatra, Director, Medical and Health Services, RSP, Rourkela for granting permission to publish this case report.

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CASE REPORT

JIACM 2008; 9(2): 143-5

Myelodysplastic Syndrome with Leucocytosis, Pleural Effusion, and Oedema

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Abstract

Myelodysplastic syndrome usually presents with peripheral leucopenia and myeloid hyperplasia in bone marrow. Monosomy 7 in such cases portends leucopenic crisis with infections. A case of refractory anaemia with myelodysplastic features in bone marrow with excess sideroblasts, monosomy 7, persistent peripheral monocytosis, pleural effusion and peripheral oedema in the absence of infections constituting CMML without splenomegaly is reported.

Keywords: Myelodysplastic syndrome, Persistent monocytosis, Monosomy 7, Pleural effusion, Oedema, CMML, Absence of splenomegaly.

Introduction

Myelodysplastic syndrome (MDS) usually presents with peripheral leucopenia and bone marrow myeloid hyperplasia. Cytogenetic studies are often performed in such cases to prognosticate survival. Monosomy 7 portends poor survival due to infections during leucopenic crisis. Usually a rising leucocyte count in myelodysplastic syndrome raises the suspicion of acute myeloid leukemic transformation. But rarely, peripheral monocytosis in such cases without blast transformation can not only confound the diagnosis but may be associated with serous effusions and peripheral oedema in the absence of infections or CHF and constitutes a diagnosis of chronic myelomonocytic leukaemia (CMML). Since CMML shares considerable cytogenetics, especially monosomy 7 and +8, with myelodysplastic syndrome, the bone marrow picture in these two conditions can be similar and the absence of splenomegaly does not rule out the diagnosis of CMML. Treatment remains supportive in both conditions.

Case report

A 65-year male, a retired paramilitary officer, a known case of well controlled diabetes mellitus and hypertension for 6 years on glipizide and nifedipine retard presented with breathlessness and non-productive cough with mild swelling of legs for 5 - 6 days. There was no history of fever, angina, or oliguria. There was no past history of tuberculosis or CAD. He had never smoked and had alcohol on occasions only. He was recently treated for dimorphic anaemia (on the basis of peripheral smear) with inj B12 and oral iron, with little improvement. On examination he was afebrile, pale and had mild pitting pedal oedema. His BP was 150/90 mmHg and chest revealed rhonchi and end-inspiratory crepts. Abdomen, CVS, and CNS examination was unremarkable. His Hb was 6.8 g/dl, TLC 23,000/cu mm and DLC- polymorphs 50, lymphoctes 30, monocytes 18, eosinophils 2. Platelet count was 2,50,000/cu mm. The peripheral smear showed normocytic normochromic RBCs with 4 nucl RBC/100 WBC showing dyserythropoietic features. There was shift to left with promyelocytes 3%, myeloblasts 2%, monocytes 15%, promonocytes 4% and metamyelocytes 24% with dysgranulopoietic features. Several hypersegmented polymorphs were also seen. Chest x-ray showed prominent right horizontal fissure with clear lung parenchyma. Echo showed normal LV systolic function, no RWMA or pericardial effusion. KFT, LFT, and urine R/E were normal. Blood sugar was140 mg/dl and there was no ketosis. Pyogenic blood culture was sterile and ELISA for HIV was negative. BM aspiration done showed hypercellular marrow with 1:1 M/E ratio (Fig. 1a) with trilineage dysplasia and 12% monocytes. Leukaemia cytochemistry was negative. Iron stains showed 12% ringed sideroblasts (Fig.1b). LAP score was 78 (N: 40 - 140). Iron studies showed transferrin saturation of 34% and s. ferritin

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was 132 µg/dl. A diagnosis of myelodysplastic syndrome with refractory anaemia with excess sideroblasts and non-specific chest infection was made. The symptoms recovered with co-amoxyclav and inhaled bronchodilators for 7 days and Hb rose from 6.8 g/dl to stabilise at 8.0 g/dl. and TLC settled to 8,000/cu mm.

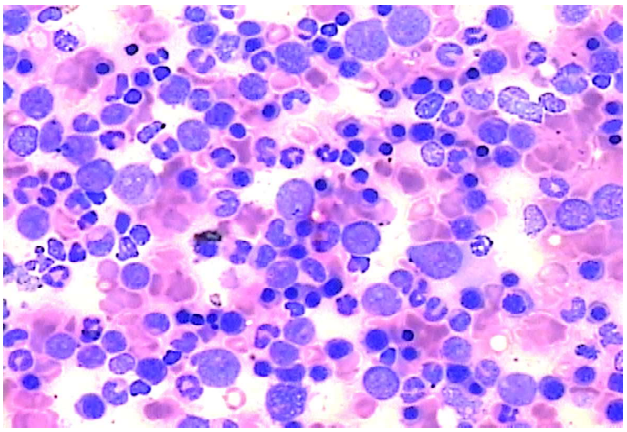

Fig. 1a: *Bone marrow aspirate smear showing hypercellular marrow with 1:1 M/E ratio.*

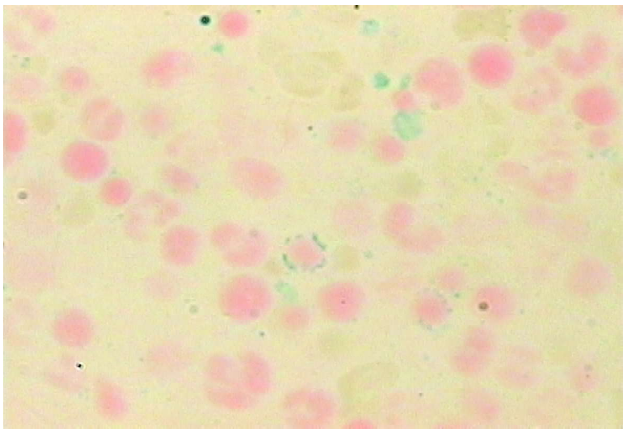

Fig. 1b: *Bone marrow smear showing ringed sideroblaster (12%).*

Cytogenetic study performed on the BM aspirate revealed Monosomy 7 with negative Philadelphia chromosome.

During follow-up with treatment with erythropoietin 2,000 units/week the Hb remained at 9 g/dl and TLC remained at 6,000 – 8,000/cu mm with DLC showing 3 – 4% monocytes. There were no episodes of leucopenic crisis.

Six months later the patient had recurrent episode of non-productive cough, breathlessness, and pedal oedema. There was no splenomegaly. There was reduction of Hb from 9.0 to 6.0 g/dl with leucocytosis of 33,000/cu mm, predominantly mature mononcytes (18%), 2 – 5% myeloblasts and normal platelet count. Chest x-ray showed right pleural effusion with patchy opacity in right mid-zone. CT chest showed nodular opacities in the right mid-zone with significant right pleural effusion (Fig. 2). Bronchoalveolar lavage for AFB and fungal smear as well as bacterial culture was negative. Fungal culture sent was later reported negative. There was no response to prolonged antibiotics for 4 weeks with worsening of pleural effusion, breathlessness and pedal oedema. Repeat LFT, KFT, bld sugar and echo were normal. Repeated ABGs were suggestive of type I respiratory failure. Pleural fluid was exudative (protein 3.1 g/dl) with 1,260 cells/cu mm, 39% mononuclear, 11% polymorphs and large number. of clustered mesothelial cells. Pleural fluid cytology for malignant cells was thrice negative and ADA was 24.8 u/l (n: <30 u/l).

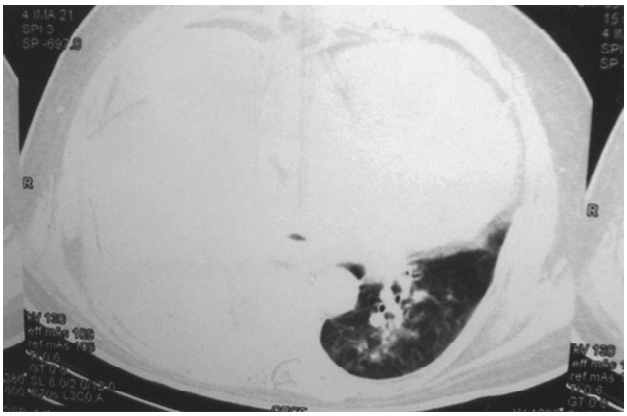

Fig. 2: *CT chest (lung phase) showing pulmonary parenchymal nodules and massive right pleural effusion.*

Over the next 15 days the constellation of pedal oedema, breathlessness, and pleural effusion further worsened necessitating ICD insertion. The leucocyte count increased to 60,000/cu mm with repeated peripheral smears showing monocytes, premonocytes and only 2 – 5% myeloblasts with marginal reduction of platelets to 1,20,000/cu mm (Fig. 3). The patient succumbed inspite of all supportive measures.

Due to persistent monocytosis for more than 3 months in the absence of proven infections and peripheral blasts < 5% with bone marrow blasts < 20%, a diagnosis of CMML type I with infiltration of lung parenchyma and pleura was kept and only supportive measures could be offered.

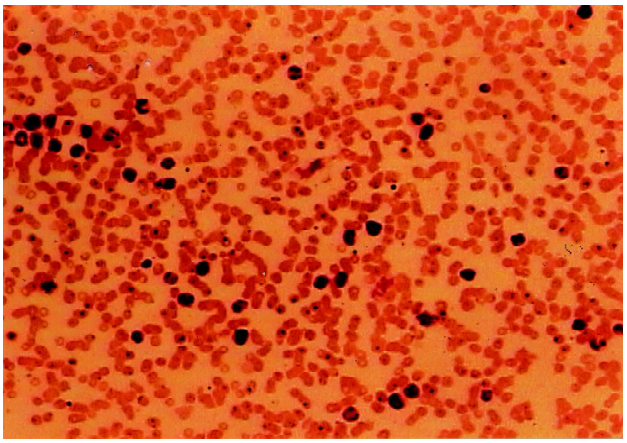

Fig. 3: *Peipheral smear showing leucocytosis with shift to left, monocytosis and marginally reduced platelets.*

Discussion

CMML usually presents with anaemia and splenomegaly in the elderly and may present in association with monosomy 7, Juvenile CMML manifesting with frequent skin involvement or Sweet's syndrome presenting as acute febrile neutropenia in children. Monosomy 7 usually predisposes to frequent infections.

However, since the bone marrow aspirate may resemble that seen in MDS, as in this case, the diagnosis may be confounded[1]. Infiltration of various organs/structures such as gums, CNS, skin and serosal surfaces is rare in monocytic and myelomonocytic leukaemias unlike in acute myeloid leukaemia[2]. The degree of effusions are in direct proportion to high/uncontrolled monocytosis[2], as seen in this case. The monocytic counts have been known to fluctuate over months[2] as noted in this case. Haemorheological manifestations in the form of pulmonary leucocytoclasis are usually seen with counts > 1,00,000/cu mm but in monocytic leukaemias the leucocytoclasis can occur at lower counts of upto 50,000/cu mm only[3] accounting for the respiratory distress seen in this case with counts between 30,000 to 60,000/cu mm. Cases of CMML with > 6,000/cu mm monocytes in peripheral blood and < 5% marrow blasts have median survival of about 52 months, whereas those with 5 – 20% marrow blasts survive for a median time of 15.5 months similar to cases of MDS with RAEB[4]. But a monocytosis alone > 26,000/cu mm correlates with poor survival[5], as seen in this case.

MDS and CMML share considerable cytogenetics wherein 1/3rd cases of CMML share monosomy 7 or +8 cytogenetics as seen in MDS[6]. Splenomegaly, a commonly relied clinical criteria for diagnosis of CMML is seen in 25% cases only[6]. Thus, WHO had revised the diagnostic criteria of MDS and CMML wherein CMML is classified under MDS. MDS which was earlier categorised by peripheral cytopenia now includes monocytosis (unexplained/persistent) as another alternate diagnostic criteria[1]. The revised WHO classification of CMML now is: i) persistent (> 3 months) peripheral monocytosis of > 1,000/cu mm and leucocytosis > 13,000/cu mm with all other causes excluded and peripheral blasts < 5% and BM blasts < 20%; ii) absent Philadelphia chromosome, and iii) clonal cytogenetics (–7, +8). A futher sub-classification includes:

a. CMML-I : with < 5% peripheral blasts and < 10% BM blasts, and

b. CMML-II : 5 – 20% peripheral blasts and 10 – 19% BM blasts or Auer rods with < 20% blasts in peripheral blood or bone marrow.

Conclusion

The presence of monosomy 7 in the case of MDS portends subsequent leucopenic crises, but the presence of unexplained persistent (> 1,000/cu mm) monoctyosis should suggest the diagnosis of CMML even in the absence of splenomegaly. Serous effusions and peripheral oedema can occur rarely in such cases with rising peripheral monocyte count in the absence of chronic infections.

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CASE REPORT

JIACM 2008; 9(2): 146-9

Dengue with ARDS

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Abstract

Dengue fever is a major public health problem in India. Dengue haemorrhagic fever (DHF) is a more serious form of the disease. As dengue infections have become more common, an increasing number of DHF cases are associated with unusual presentations. Pulmonary manifestations are uncommon in this disease, except for pleural effusions. Acute respiratory distress syndrome in dengue haemorrhagic fever is rarely reported in the literature. We report two cases of dengue haemorrhagic fever presenting with acute onset of breathlessness, diagnosed to be due to ARDS. Both cases were treated with ventilatory assistance and recovered completely.

Keywords: Dengue haemorrhagic fever, Unusual presentations, Acute respiratory distress syndrome (ARDS).

Introduction

Dengue fever is the most important arboviral infection in the world, with an estimated 100 million cases per year and 2.5 billion people at risk[1]. Dengue is characterised by four different serotypes (DEN-1, DEN-2, DEN-3, and DEN-4). Infection with any one of these serotypes may present as illness ranging from asymptomatic infection to dengue fever, dengue haemorrhagic fever (DHF), or dengue shock syndrome (DSS). Acute respiratory distress syndrome (ARDS) is a heterogeneous clinical syndrome comprising of respiratory distress, severe hypoxaemia, diffuse radiographic infiltrates, and decreased lung compliance that has a high mortality rate. Dengue haemorrhagic fever presenting with ARDS in adults has not been reported widely, the first case in the literature was reported in 1999[2]. We report two similar cases of dengue haemorrhagic fever presenting with ARDS.

Case - 1

20-year-old girl who was in perfect health previously, was brought with history of high-grade fever for one week. Fever was associated with myalgia and rash. She was admitted to a hospital elsewhere, where she was tested to be dengue IgM positive; platelet counts were documented to be 80,000. She developed breathlessness and was shifted to this hospital for further management.

On examination, the patient was conscious, well oriented, but dyspnoeic at rest with a respiratory rate of 34 per minute, saturation was 85% on O_2 10 litres per minute. She was afebrile at presentation with a heart rate of 140 per minute, BP was 140/80 mmHg. She had petechiae on the lower limbs, examination of the respiratory system revealed decreased breath sounds and extensive crackles bilaterally. Other system examination was normal. ABG showed severe hypoxaemia. She was therefore shifted to the ICU and was intubated.

Laboratory investigations – Hb: 10.6 gm%, TLC: 11,200/cmm, platelets: 1,35,000/cmm; renal parameters were normal; liver function tests showed mild elevation of enzymes;

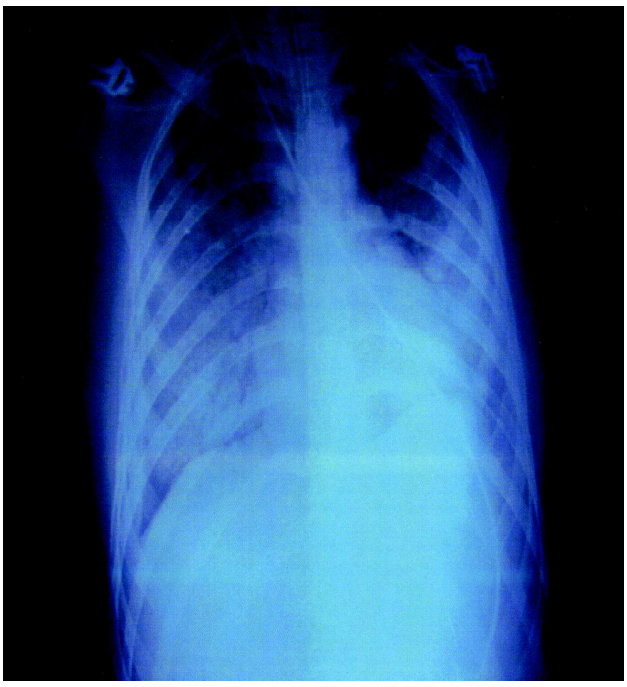

Fig. 1: *CXR showing diffuse radiographic infiltrates bilaterally suggestive of ARDS.*

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PT:INR – 1.3; PTT: test – 35, control – 29; Dengue IgM was positive; antibodies to leptospira, widal, MP were negative. CXR showed bilateral diffuse infiltrates with bilateral mild effusions. Bronchoscopy was performed; BAL showed 450 cells/cu mm, neutrophils 60%, lymphocytes 38%, eosinophils 2%, fair number of macrophages, epithelial cells and RBCs. Bronchoscopy was negative for AFB, fungi, or *Pneumocystis jirovecii* and culture was negative for bacterial pathogens. Three sets of blood cultures, and urine cultures were negative. Echo revealed normal LV function. Ultrasound abdomen revealed free fluid in the abdomen. ANA, DsDNA, ANCA were negative. She was kept on ventilator, supportive treatment, and was extubated after 3 days and subsequently was discharged with stable vitals.

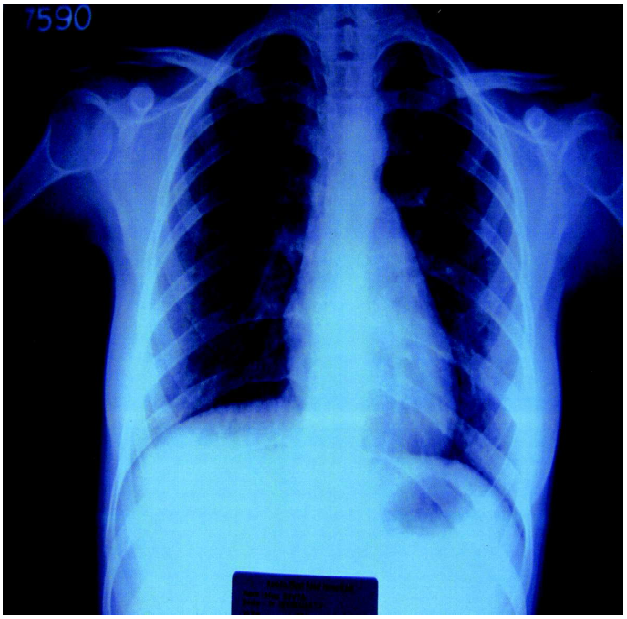

Fig. 2: *Repeat CXR 10 days later.*

Case – 2

48-year-old man was brought to EMR with history of breathlessness since one day. He had high grade fever for a week, which was treated with chloroquin elsewhere. No laboratory tests were done outside. He was a known diabetic not requiring treatment.

On examination, he was restless with respiratory rate of 30 per minute, saturation 85% on room air. Heart rate was 90 per minute, BP was 150/90 mmHg. He had petechiae on lower limbs; examination of respiratory system revealed diminished air entry and crackles bilaterally. CXR showed diffuse infiltrates suggestive of ARDS. ABG showed hypoxaemia. He was shifted to the ICU and was kept on non-invasive ventilation.

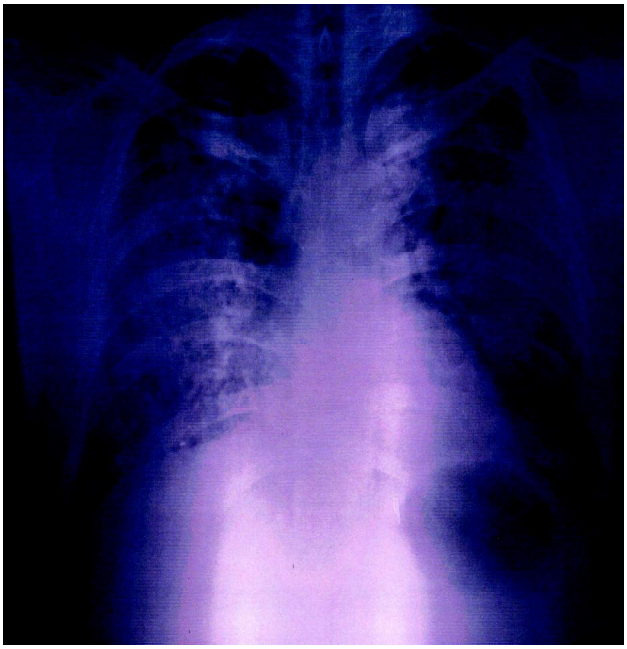

Fig. 3: *CXR shows ARDS.*

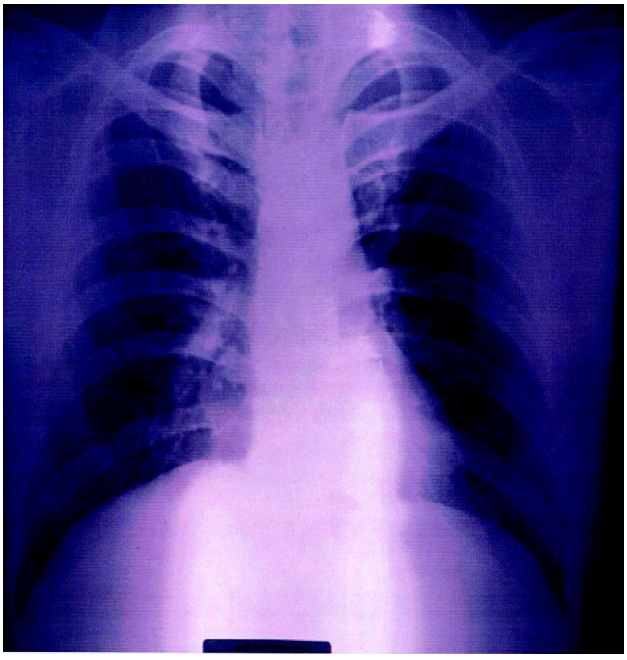

Fig. 4: *CXR normalised after a week.*

Laboratory investigations revealed Hb: 12.9 gm%, PCV: 38, TLC: 11,000/cmm, platelets: 90,000/cmm. Coagulation profile and renal parameters were normal; liver enzymes

were mildly elevated. IgM antibodies to dengue were positive. MP, antibodies to leptospira; widal; blood, sputum and urine cultures were negative. Echo was normal. Ultrasound abdomen showed bilateral mild pleural effusion and ascites.

He was treated with non-invasive ventilation, empirical antibiotics, and supportive treatment. Blood sugar was controlled with insulin. He recovered and was later discharged.

Discussion

Dengue fever is caused by flavivirus, and the principle vector is *Aedes aegypti* mosquito. Infection may be asymptomatic or may lead to dengue fever, or more severe forms – DHF, or DSS. DHF is characterised by high fever, haemorrhagic phenomenon, and often with hepatomegaly and circulatory failure. Mild-to-moderate thrombocytopenia with concurrent haemoconcentration is a distinctive clinical laboratory finding of DHF. The major pathophysiological change that determines the severity of disease in DHF and differentiates it from dengue fever is an acute increase in vascular permeability that leads to leakage of plasma into the extravascular compartment, resulting in haemoconcentration and decreased blood pressure thought to be mediated by histamine and the cytokines[3, 4] and is manifested by an elevated haematocrit, a serous effusion or hypoproteinaemia[5]. Our cases were diagnosed as DHF according to the WHO criterian.

Case definition for dengue haemorrhagic fever: the WHO criteria

The following must all be present:

1. Fever or history of acute fever, lasting 2 – 7 days, occasionally biphasic.
2. Haemorrhagic tendencies, evidenced by at least one of the following:
   - a positive tourniquet test
   - petechiae, ecchymoses or purpura
   - bleeding from the mucosa, gastrointestinal tract, injection sites or other locations
   - haematemesis or malena
3. Thrombocytopenia (100,000 cells per cu mm or less).
4. Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following:
   - a rise in the haematocrit equal to or greater than 20% above average for age, sex and population;
   - a drop in the haematocrit following volume-replacement treatment equal to or greater than 20% of baseline;
   - signs of plasma leakage such as pleural effusion, ascites, and hypoproteinaemia.

Confirmation of diagnosis is by PCR or serology. Treatment mainly is symptomatic.

Acute respiratory distress syndrome is marked by acute hypoxaemic respiratory failure due to pulmonary oedema caused by increased permeability of the alveolar capillary barrier. It is the most serious manifestation of acute lung injury which arises as a complication of a widespread systemic response to acute inflammation or injury. It is precipitated by various conditions that range from direct injury (e.g., aspiration, diffuse infection) to indirect injury (e.g., sepsis, non-thoracic trauma). Many infectious agents have been found to trigger ARDS, ranging from bacteria, viruses, fungi, and parasites. Complete clinical evaluation is needed to diagnose and establish the cause of ARDS. Treatment consists of ventilator and haemodynamic support besides treating the primary aetiological agent. Dengue virus is not a well known cause of ARDS. In our cases, a diagnosis of ARDS was made on the basis of chest X-ray findings and the PaO_2/FiO_2 ratio, in accordance with the American-European consensus conference on ARDS guidelines[6].

Our cases reported here were diagnosed and confirmed to be DHF. They had acute breathlessness and were diagnosed and treated as ARDS. In the absence of any other pathogen/cause identified, we believe that DHF was the cause of ARDS in these patients. We suggest that clinicians in areas where dengue fever is endemic should be made aware of this unusual complication of DHF.

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CASE REPORT

JIACM 2008; 9(2) : 150-2

Arsenic Intoxication Presenting as Peripheral Neuropathy and Dermatological Disorder

TP Singh, Vishal Kumar Gupta***

Abstract

Sub-acute and chronic arsenic poisoning usually involves multisystems. Sub-acute or chronic arsenic intoxication presented as peripheral sensory motor neuropathy, encephalpathy, brownish – black pigmentation of skin, and hyperkeratosis of palms and soles. We report a case of sub-acute arsenic poisoning who presented initially as encephalopathy and later developed peripheral sensory motor neuropathy and skin manifestations. Arsenic poisoning was suspected because many of the other family members also developed similar symptoms simultaneously.

Introduction

Most common cause of arsenic poisoning is suicidal, homicidal, or accidental ingestion of herbicides, insecticides, or rodenticides containing copper acetoarsenale (Paris green) or calcium or lead arsenate. Arsenic is found in significant levels in ground water in various parts of the world[12-14]. A significant level of arsenic is found in drinking water in various regions of India[15], including northern India[9]. Many part of India and Bangladesh are affected by arsenic intoxication due to contamination of ground water with arsenic[13,14]. It is one of the most potent toxins affecting GI system, neurological, renal, hepatic system, and skin[4]. We present a case of arsenic poisoning who developed neurological symptoms, skin manifestations, and peripheral sensory, motor neuropathy.

Case report

A 22-year-old student presented with vomiting, abdominal pain, and fever persisting for 5 days. Two weeks later he developed tingling, numbness, paraesthesia, gradually progressive weakness of all 4 limbs, irrelevant talking, agitation, restlessness, aggressiveness, and blackish discolouration of skin all over the body. All other 7 family members (excluding a breast-fed female infant) also development hyperpigmentation, hyperkeratosis of palms and soles, and tingling, numbness with this patient. The patient and his family members gave a history of water comsumption for drinking and cooking from deep bore well (using a submersible pump) for last two months. Before this they had used water from government supply. No cranial nerve involvement and no bladder-bowel involvement was present. Examination revealed hyperpigmentation of face, arms, legs, upper chest, and abdomen. There was hyperkeratosis of palms and soles. Sensory motor symmetrical predominantly distal, peripheral neuropathy was present with power around 4/5 in all 4 limbs. Subsequently, all the family members were examined and they showed symmetrical distal neuropathy; hyperpigmentation was present in all of them. Electrophysiologically, severe axanopathy was present. The arsenic level was significantly high in urine (24 hr urine arsenic level 1.09 mg, by atomic absorption spectrometry). Water sample of deep bore well was sent for arsenic estimation. Collagen profile, CSF, biochemical tests and haemogram were normal except for presence of anaemia. Treatment for arsenic poisoning for this patient and all his family members was started with oral D-penicillamine. The water source has since been changed from deep bore well to government supply water. After two months follow-up, skin lesion had subsided in this patient as well as all his family members. There was mild relief from symptoms of peripheral neuropathy after two months of treatment, but complete recovery from symptoms of peripheral neuropathy has not yet occurred.

Discussion

Encephalopathy[2], peripheral neuropathy[5], and hyperpigmentation, hyperkeratosis, exfoliative dermatitis, are the features of sub-acute or chronic arsenic intoxication. Peripheral neuropathy[1] which occurs in chronic arsenic

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poisoning may manifest between 1 – 2 weeks after recovery from acute poisoning and is in form of both demyeliniting and distal axonopathy[5]. The symtpoms of encephalopathy (headache, drowsiness, mental confusion, delirium) may also occur as part of chronic intoxication. Encephalopathy is accompanied by weakness and muscular aching, haemolysis, chills and fever. Diffuse scaly desquamation and transverse myelitis may occur.

Arsenic exerts it's toxic effect by reacting with sulphydril radicals of certain enzymes necessary for cellualr metabolism. Inorganic arsenic is readily absorbed (lung and GI), sequestered in liver, spleen and kidneys. Residues persist in skin, hair, and nails for a long time. The diagnosis of arsenic poisoning depends upon the demonstration of increased level of arsenic in hair and urine[3]. Arsenic is deposited in the hair within 2 weeks of exposure and may remain fixed there for long periods. Concentration of > 0.1 mg arsenic per 100 mg hair are indicative of poisoning. Arsenic also remains within bones for long periods and is slowly excreted in the urine and faeces[3]. WHO Guidelines for drinking water published in 1999 suggested that arsenic concentration should be < 0.01 mg/litre (< 10 microgram/lt.) and more than 50 microgram/lt. is associated with manifestations of arsenic toxicity[18].

Excretion of more than 0.1 mg arsenic per litre of urine is considered abnormal (no sea foods should have been consumed for 24 hours before collection of specimen)[6]. Individuals who consume fish on regular basis, as occurs in coastal regions may have slightly or moderately elevated level of arsenic.

The CSF protein level may be raised by 50 – 100 mg/dl with normal cell count. In our case, arsenic poisoning manifested by symptoms of encephalopathy (irritability, aggressiveness, confusion, delirium) peripheral sensory motor neuropathy in form of abnormal sensations (tingling, numbness and decreased sensation), and dermatological manifestations (hyperpigmentation, hyperkeratosis of palm and sole). Skin manifestations in our patient are similar to those described by Saha *et al*[16] in which arsenic in tube-well water is associated with hyperkeratosis and hyperpigmentation. Peripheral neuropathy[1] is the main feature of subacute or chronic organic poisoning and is the predomlnant symptom in our patient as described in literature including Hafeman *et al*[11]. Similar neuropathy due to arsenic toxicity is also described by Chuttani[5]. The possible cause of arsenic poisoning in our patient is arsenic present in deep bore-well water. Symptoms of arsenic intoxication only occured in our patient after start of consumption of water from deep bore-well. Study conducted in Taiwan[17] showed that subjects who drank well water containing arsenic concentration > 50 microgram/lt. have peripheral neuropathy evidence by slow conduction velocity on NCV. Recommended treatment of arsenic poisoning is for acute poisoning. It consists of gastric lavage, vasopressor agents, fluid and electrolyte maintenance, and BAL[7]. Maintenance of renal perfusion and exchange transfusion is required if massive haemoglobiuria occurs as in chronic poisoning. Oral succimer (DMSA, D. penicillamine[8]) vitamin supplement are also required. After change of their water source and treatment with oral D-penicillamine and supportive care, skin lesions resolved but complete recorvery from peripheral neuropathy did not occur. Sensory neuropathy predominates over motor as described by Rehman *et al*[10]. Similar type of neuropathy was detected in our patients.

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CASE REPORT

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A Pictorial CME: Central Nervous System Toxoplasmosis in HIV/AIDS

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Introduction

A 35-year-old male, known to have HIV since 2005, had been doing reasonably well on anti-retroviral therapy, when he presented to the hospital with a history of severe headache and fever of 15 days duration with altered sensorium, all of a sudden. There was no history of seizures. On examination, the patient was afebrile and had essentially stable vital signs. He had GCS (Glasgow Coma Scale) of 6. Signs of meningeal irritation were present with bilateral plantar extensor response. There were no cardiac murmurs and his chest was clear on auscultation. His complete blood counts showed leucocytosis. Biochemical tests for blood sugar, renal, and liver functions were unremarkable. CSF analysis, done after fundus examination, revealed raised levels of protein (245 mg%), and of cells (60% lymphocytes and 40% polymorphs) with normal sugar (45 mg%). CSF for cryptococcus (India ink preparation) and PCR for *M. tuberculosis* were negative, but was strongly positive for toxoplasmosis.

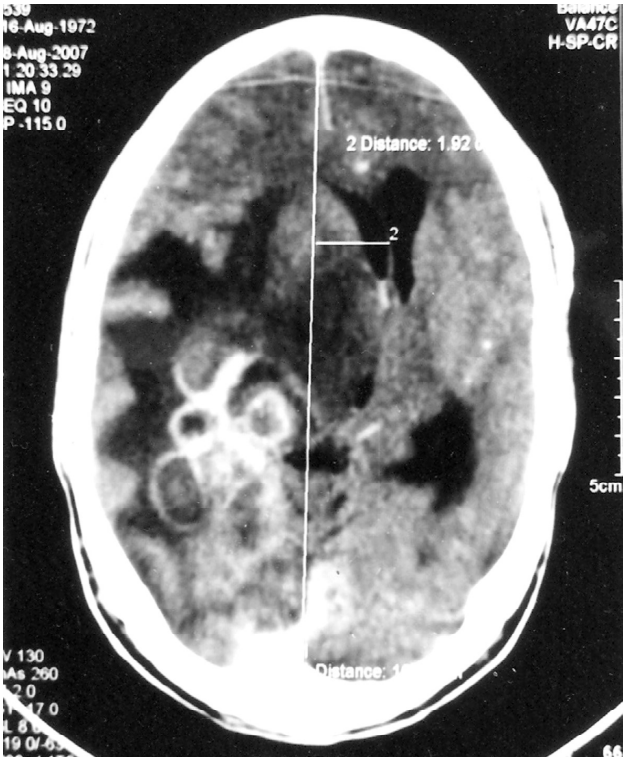

Fig. 1:

His CD4+ count was 91/mL. CT and MRI (brain) revealed typical multiple enhancing lesions with perifocal oedema and mass effect in the grey-white matter interface of the cerebral hemispheres. The patient was started on presumptive treatment for cerebral toxoplasmosis with tab. pyrimethamine 100 mg once daily and tab. sulphadiazine 1 gm 6 hourly.

The patient's condition improved over a period of 4 weeks.

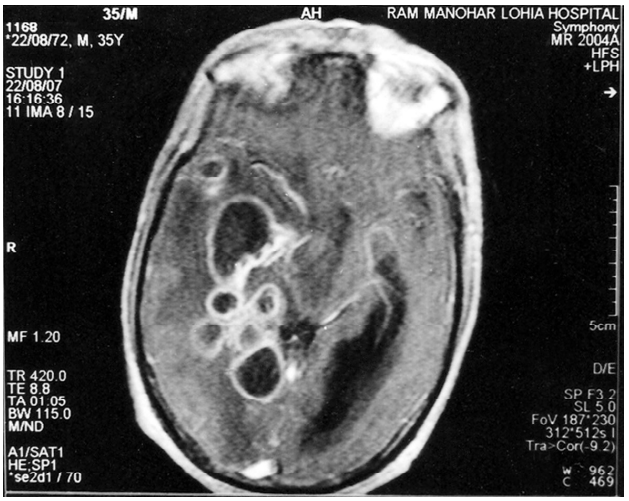

Fig. 2:

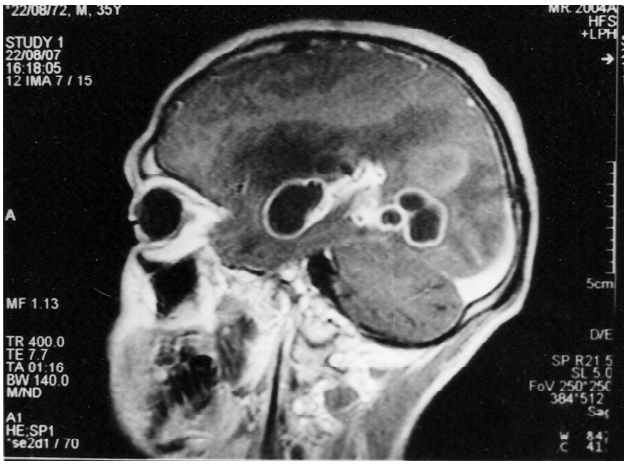

Fig. 3: *Fig. 1, 2, and 3 (CT and MRI Brain) Showing large heterogeneous mass lesions with cystic component involving right temporo-parietal and occipital region with intensive perilesional oedema and midline shift of 1.56 cm.*

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