study has demonstrated the efficacy of short, daily dialysis in controlling serum phosphorus levels. Alternatively, slow nocturnal haemodialysis (NH) entails a duration of 6 to 8 hours, and a frequency of six to seven nights per week. During a 4-year observational study that compared patients receiving NH, conventional intermittent haemodialysis, and short, daily haemodialysis, only NH showed a significant reduction in the serum phosphorus levels and eliminated the need for phosphate binders[40,41,42]. Some patients actually required phosphorus supplementation during the study. NH has also been associated with improved solute clearance, quality of life, BP control, and reduction in medication requirements[43]. However, obstacles to its use on a larger scale include unfamiliarity with home haemodialysis as well as issues with cost of equipment and non-reusable materials.

Conclusion

Although both calcium and non-calcium phosphate binders are in clinical use, there is no consensus on their relative utility as a primary mode of therapy against hyperphosphataemia of CKD. Newer dialysis techniques like nocturnal haemodialysis, intermittent haemodiafiltration, and short, daily haemodialysis have demonstrated improved phosphorus control and are gaining importance in therapy. While we strive for a better phosphorus control to bring down the mortality in patients of CKD, the search for an ideal phosphate binder continues.

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POSTGRADUATE CLINIC

JIACM 2008; 9(4) : 298-301

Extramedullary Plasmacytoma – A Rare Presentation

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Abstract

A plasmacytoma is a discrete, solitary mass of neoplastic monoclonal plasma cells in either bone or soft-tissue (extramedullary). Extramedullary plasmacytoma progresses to multiple myeloma in 11 – 30% of patients at 10 years. The median age of the patient is 55 years. This median age is 10 years younger for patients with multiple myeloma. However, a multiple myeloma patient developing plasmacytoma of urinary bladder while on treatment for multiple myeloma is very rare and puzzling.

Case

65-year-old woman with history of hypertension and borderline diabetes presented with 5 months history of generalised bodyache, progressive weakness, and back pain. The baseline reports were:

Haematology: Hb – 10.3 g/dl, WBC – 5,950/mm^3, N 46%, L 39%, M 10%, platelets – 94%.

Biochemistry: Beta-2 microglobulin – 16.71 mg/l, FBS – 113 mg/dl, urea – 33 mg/dl, creatinine – 2.5 mg/dl, uric acid – 16.1 mg/dl, albumin – 2.6 g/dl, globulin – 9.6 g/dl, LFT – normal, LDH – 285 U/l, calcium – 12.3 mg/dl, serum phosphorous – 4.6 mg/dl. Sodium 134 mmol/l, potassium – 2.4 mmol/l, magnesium – 1.49 mg/dl.

Routine urine examination: Presence of glucose and excess pus cells.

Serum electrophoresis: Electrophoretic pattern – abnormal; monoclonal band present, located in the gamma region. Concentration of M band – 6.0 gm/dl. Serum immunoglobulins – IgA – 36.2 mg/dl (N = 82 – 453), IgM – 41.2 mg/dl (N = 46 – 304), IgG – 7,280.0 mg/dl (N = 751 – 1,560). Immunofixation – IgG lambda type.

Bone marrow aspiration report: All elements are reduced markedly, clusters of binucleate plasma cells are seen, many of which show prominent nucleoli, rouleaux formation. Plasma cells were 35% of the myelogram.

Bone marrow biopsy: Hypercellular marrow showing mature and immature plasma cells. Tumour cells are positive for CD 138 and show lambda light chain restriction.

Skeletal survey: Lytic lesion in left humerus and multiple lesions in the skull. USG of abdomen did not reveal any abnormality.

Treatment

Patient was put on a 28-day schedule of thalidomide 100 mg once daily, dexamethasone 40 mg/d x 4 days, and aspirin 75 mg OD for 3 months alongwith monthly injections of zoledronic acid. After 3 months of treatment it was found that concentration of M band had come down to 2.0 gm/dl and IgG 2,070 mg/dl. Therefore, the patient was put on another 3 cycles of thalidomide and dexamethasone. 3 months later when the patient was re-evaluated, it was found that M band concentration and IgG were increasing. The patient was now prescribed melphalan 10 mg once daily D1-D5, wysolone 70 mg OD D1-D7; cycle to be repeated every 4 weeks. 6 weeks later, the patient developed haematuria. USG revealed a projectile growth from the bladder wall. Cystoscopy showed the bladder growth to be involving the trigone. The initial impression was that of urothelial cancer. However, the biopsy report demonstrated plasma cell deposits in urothelium. She was further diagnosed as a case of multiple myeloma with plasmacytoma of the urinary bladder.

Patient was treated with 10 fractions of radiotherapy (RT) which led to partial control of haematuria. She was then given lenalidomide 25 mg daily on a trial basis. 2 months since then, the patient is clinically better. Weakness, bodyache, and the bone pain has substantially decreased and haematuria has completely stopped.

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Discussion

A plasmacytoma is a discrete, solitary mass of neoplastic monoclonal plasma cells in either bone or soft-tissue (extramedullary). To simplify, solitary plasmacytomas can be divided into 2 groups according to location:

- Plasmacytoma of the skeletal system (SBP)
- Soft-tissue (extramedullary) plasmacytoma (SEP)

Our discussion will be restricted to extramedullary plasmacytoma.

Diagnostic criteria for soft-tissue plasmacytoma[1] :

- Tissue biopsy showing monoclonal plasma cell histology
- Bone marrow plasma cell infiltration not exceeding 5% of all nucleated cells
- Absence of osteolytic bone lesions or other tissue involvement (no evidence of myeloma)
- Absence of hypercalcaemia or renal failure
- Low serum M protein concentration, if present.

Pathophysiology

A plasmacytoma can arise in any part of the body. SBP arises from the plasma cells located in the bone marrow, while SEP is thought to arise from plasma cells located in mucosal surfaces[2]. Both represent a different group of neoplasms in terms of location, tumour progression, and overall survival rate[3,4]. Interleukin 6 is still considered the principal growth factor in the progression of plasma cell disorders[5].

SEP represents approximately 3% of all plasma cell neoplasms. SEP progresses to multiple myeloma in 11 – 30% of patients at 10 years. The overall survival rate at 10 years is 70%. Three-fourths of SEP cases involve males[1,2,6-8]. The median age of patients with SEP is 55 years. This median age is 10 years younger for patients with multiple myeloma[6-8].

Signs and symptoms

Symptoms from SEP are associated with the site of the tumour, tumour size, and compression and/or involvement of the surrounding structures. SEP of urinary bladder presents with haematuria, dysuria, and nagging lower abdominal pain. Although SEP can occur at any site, 80 – 90% of tumours develop in the head and neck area, especially in the aerodigestive tract. Approximately 80% of cases involve the paranasal sinuses, pharynx, nasal cavity, or gums and oral mucosa[1,2,5,6,8]. A mass (plasmacytoma) in these areas is the most common finding, with compression or invasion of the surrounding structures. Patients with tumours involving the base of the skull may present with cranial nerve palsies. Case reports of involvement of the central nervous system, orbit, gastrointestinal tract, liver, spleen, pancreas, lung, breast, skin, testis, parotid gland, mediastinum, and thyroid gland (associated with goitre and Hashimoto's thyroiditis) exist[5,6]. In 30 – 40% of cases, local lymph nodes are involved at presentation or upon relapse[7].

Other differential diagnoses of SEP[1] are:

– Reactive plasmacytosis

– Poorly-differentiated neoplasms

– Immunoblastic lymphoma

– Marginal zone B-cell lymphoma

– Plasma cell granuloma

Laboratory studies

Protein electrophoresis shows a monoclonal component in 14 – 25% of cases[1,5,8]. In a series of 46 patients by Galieni and colleagues[1], all patients had normal uninvolved immunoglobulins. Peripheral blood cell count, renal function, and calcium are within the reference range.

Imaging studies

Solitary extramedullary plasmacytoma:

- Radiographic assessment shows local bone destruction in most patients with nasal cavity or maxillary sinus involvement[8].
- Computed tomography scan, MRI, and complete endoscopic examination of the aerodigestive and gastrointestinal tracts are required to determine the exact extent of the tumour and its potential for resectability[6].

Histologic findings

- SEP: Biopsy of the soft-tissue lesion shows infiltration by monoclonal plasma cells.
- In SEP, the soft-tissue lesion commonly exhibits submucosal growth, requiring deep biopsy, open biopsy, or complete excision depending on tumour location[6].
- Histologically, SEP may be classified as low, intermediate, or high-grade[9].
- Bone marrow biopsy shows less than 5% plasma cells without evidence of clonality[1].

Staging: Wiltshaw[2] classified soft-tissue plasmacytoma into 3 clinical stages:

- Stage I – Limited to an extramedullary site
- Stage II – Involvement of regional lymph nodes
- Stage III – Multiple metastasis (although it is no longer a solitary plasmacytoma).

Medical care

- Based on the documented radiation sensitivity of plasma cell tumours, the accepted treatment is radiotherapy.
- When a lesion can be completely resected, surgery provides the same results as radiotherapy.
- Combined therapy (surgery and radiotherapy) is an accepted treatment depending on the resectability of the lesion. In fact, combination treatment may provide the best results[6].
- The optimal dose for local control is 40 – 50 Gy (depending on tumour size) delivered over 4 – 6 weeks[6-8].
- Because of the high rate of lymph node involvement, these areas should be included in the radiation field[7].
- Adjuvant radiotherapy should be recommended to patients with positive surgical margins.
- Chemotherapy may be considered for patients with refractory or relapsed disease. Regimens used for multiple myeloma can be considered[10].
- Adjuvant chemotherapy may be considered for patients with tumours larger than 5 cm, as well as those with high-grade histology.

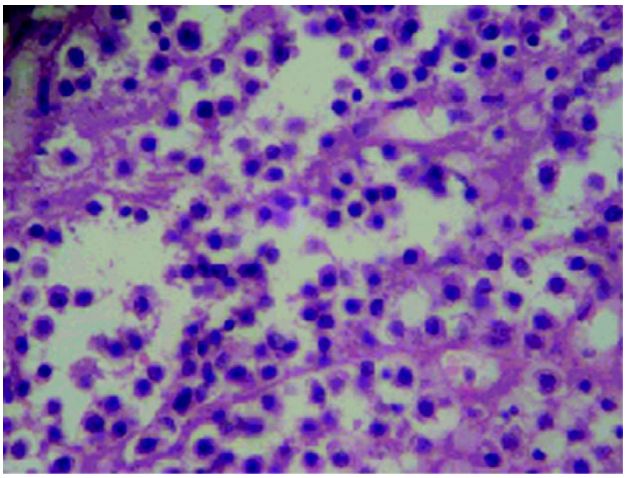

Fig. 1: *Plasma cells in biopsy specimen from urinary bladder.*

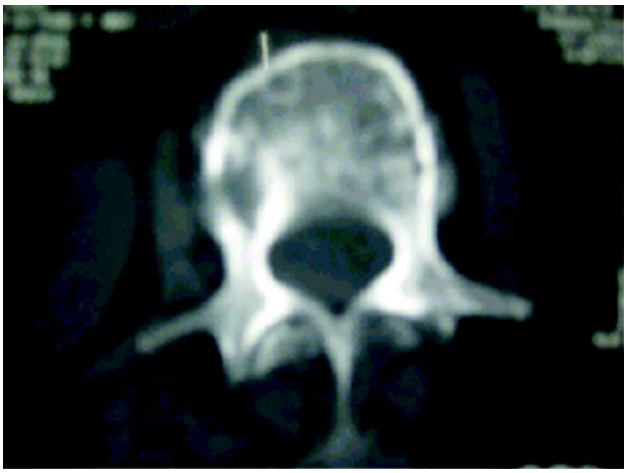

Fig. 2: *Lytic lesion in the vertebra.*

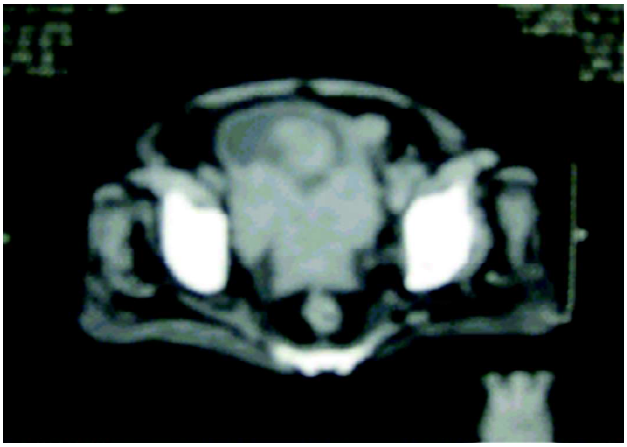

Fig. 3: *Tumour of the urinary bladder.*

Prognosis: The 10-year overall survival rate is 70%[10]. The rate of progression to multiple myeloma is lower than in solitary bone plasmacytoma, ranging from 11 – 30% at 10 years[7].

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CASE REPORT

JIACM 2008; 9(4): 302-5

Limb Girdle Muscular Dystrophy

*Gouranga Santra**

Abstract

Limbgirdle muscular dystrophy includes a large number of rare disorders. It manifests with progressive weakness of pelvic and shoulder girdle muscles. It is usually autosomal recessive in inheritance, but autosomal dominant or sporadic cases may also occur. It occurs both in males and females. Here I am reporting a sporadic case of limb girdle muscular dystrophy in an adult female with predominant shoulder girdle involvement. She had contracture of shoulder girdle muscles and evidence of distal muscular atrophy (e.g., thenar muscles). Gowers' sign was positive. She had history of recurrent foetal losses. She had normal creatinine phosphokinase levels. Distal muscular atrophy, contracture of shoulder girdle muscles, and positive Gowers' sign are seldom seen in limb girdle muscular dystrophy.

Key words: Proximal muscle weakness, Contracture, Distal muscular atrophy, Gowers' sign.

Introduction

The muscular dystrophies are hereditary disorders associated with progressive weakness and atrophy of muscles. Measurement of serum creatine phosphokinase (CPK), muscle biopsy, and recordings of electromyography (EMG) establish the diagnosis of muscular dystrophies.

Case report

A 22-year-old tribal female born of non-consanguineous marriage from sub-Himalayan belt of Darjeeling district presented with difficulty in raising arms above head and difficulty in getting-up from the floor and climbing stairs for the last 7 years. She had disproportionately more weakness in the upper limbs than the lower limbs. She could walk unsupported to a small distance (~ 100 meters), and then she would feel fatigued. She had no history of handgrip weakness, slipping of chappals, falls, etc. The disease remained static for the last 5 years, after initial two years of deterioration. Her household and recreational activities were hampered to a great extent. The patient was experiencing some improvement in performance of daily activities after the stage of initial deterioration (could be due to gradual learning to cope with the problem). There was no history of diurnal variation or any episodic pattern of weakness. She had no history of muscle pain, tenderness, and flexor spasm. She had no history of altered sensorium, headache, vomiting, visual disturbance, dysarthria, nasal intonation, vertigo, or any sensory symptoms. She had no history of difficulty in chewing or swallowing. She had no history of palpitation, chest pain, cough or expectoration, wheezing, shortness of breath, or syncope. She had no history of fever, arthralgia, arthritis, jaundice, or skin rash. Her bladder and bowel functions were normal. She did not have diabetes mellitus or thyroid disorder. Her intelligence was normal. She had no history of contact with tuberculosis, and no history of exposure to STDs. Her birth history was non-contributory and developmental milestones were normal. There was no family history of a similar disease. Her menstrual history was normal, but she had history of 2 foetal losses. She had no history of steroid or statin drug intake.

On examination, the patient was conscious and cooperative. She had mild pallor but did not have cyanosis, jaundice, clubbing, koilonychia, lymphadenopathy, neck vein engorgement, and thyroid enlargement. Her blood pressure, pulse and respiration were normal. Her build/stature was average. On neurological examination, her higher mental function including speech and language was normal. Cranium and spine examination was normal. She had gross atrophy of shoulder girdle muscles including supraspinatus, infraspinatus, trapezius, rhomboides, and paraspinal muscles; and also mild atrophy of medial side of thigh muscles. Pseudo hypertrophy of deltoids, calves, extensor digitorum brevis or lateral quadriceps' were absent. She had atrophy of bilateral thenar muscles. Power of proximal muscles of upper limbs was 2/5 on both sides, but 4/5 in both lower

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limbs. Power was preserved in the distal muscles. Fasciculation was absent. She had contracture of the shoulder girdle muscles. There was no involvement of extraocular, pharyngeal, neck flexors, and facial muscles. Head drop, winging of scapula, and foot drop were absent. There was no sensory loss. Deep tendon jerks were diminished in the lower limbs. In the upper limbs, jerks were absent. Plantar responses were flexor on both sides. Gowers' sign was positive. She had a broad-based waddling gait and lumbar lordosis. She had no intention tremor, nystagmus, or dysdiadochokinesia. No skeletal deformity was present. Rest of the systemic examination was normal.

Her complete blood count was normal. Blood sugar, urea, creatinine, liver function tests, lipid profile, and serum electrolytes were normal. ANF was negative. HIV I and II were negative. CSF study was normal. Thyroid function test was normal. Her serum CPK was normal. Chest X-ray, ECG, and echocardiography were normal. EMG was done for both quadriceps and deltoid muscles. There was normal insertional activity and absent spontaneous activity in all muscles. Motor unit potentials (MUPs) were small-amplitude, narrow-duration, and polyphasic. Interference was showing early and complete recruitment. Electromyography (EMG) was suggestive of myopathic pattern. Nerve conduction studies were normal, muscle biopsy showed myocyte degeneration, variation in fibre size, necrotic fibres with few

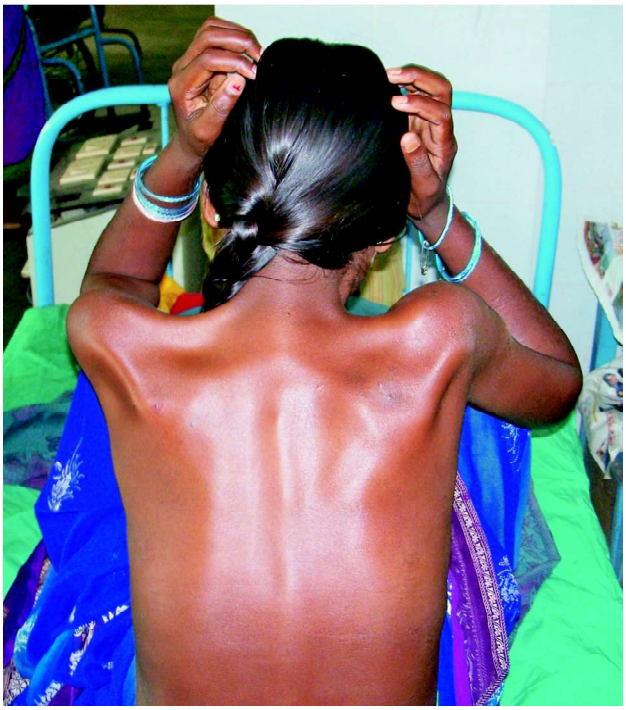

Fig. 1: *Shows gross atrophy of shoulder girdle muscles. The muscles that were predominantly wasted included supraspinatus, infraspinatus, trapezius, rhomboides, and paraspinal muscles.*

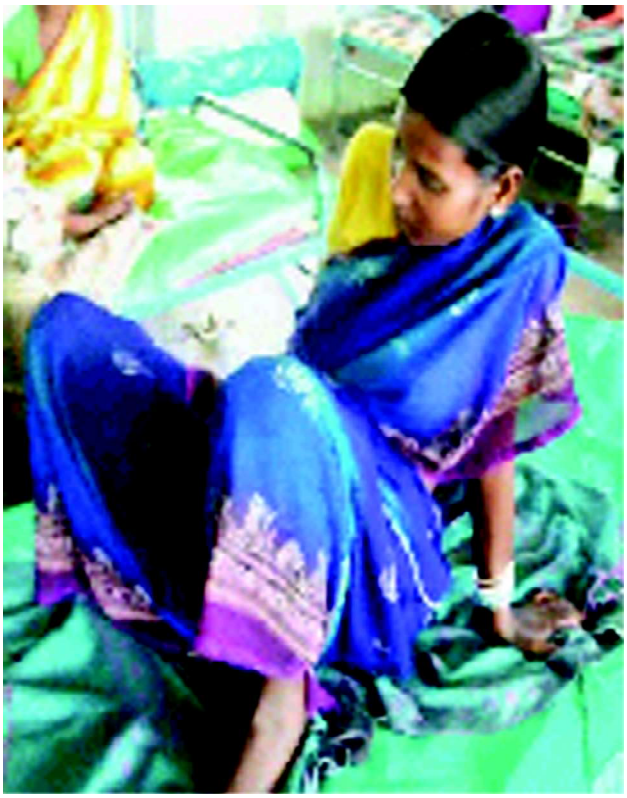

Fig. 2 and 3: *Show Gowers' sign (positive).*

inflammatory cells infiltrates. All this was consistent with the clinical diagnosis of muscular dystrophy. Cytochemistry and DNA analysis were not possible. From history, muscle biopsy, and electromyographic study, she was diagnosed to have limb girdle muscular dystrophy.

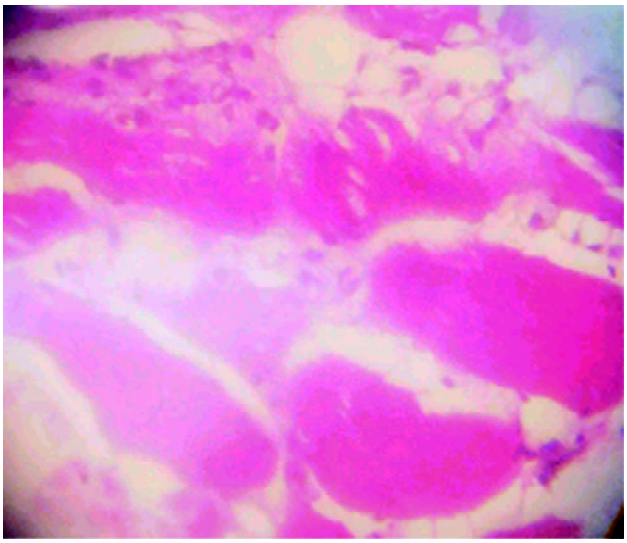

Fig. 4: *Muscle biopsy with haematoxylin and eosin stain showing myocyte degeneration, variation in fibre size, necrotic fibres, few inflammatory cells infiltrates.*

Discussion

The limb girdle muscular dystrophy (LGMD) manifests with progressive weakness of pelvic and shoulder girdle muscles. It is usually autosomal recessive in inheritance but occasionally autosomal dominant or sporadic cases may occur. LGMDs transmitted by autosomal dominant inheritance are designated as LGMD type 1, and those transmitted by autosomal recessive inheritance are designated as LGMD type 2. Subclassification by alphabetical letters characterises distinct genetic forms of LGMD 1 and LGMD 2. At least 7 forms of autosomal dominant (LGMD 1A to LGMD 1G) and 13 forms of autosomal recessive (LGMD 2A to LGMD 2M) variants have been defined. LGMD 2A (calpain-3) is the most common form, representing about 30% of cases. LGMD 2B is the second most common. The autosomal dominant forms tend to be less severe than the autosomal recessive[1]. The disease usually starts in late childhood[2]. Onset may be either in the pelvic or the shoulder girdle. It may remain static for a long period. The distal muscles are affected late in LGMD, if at all. Contractures are unusual. In a study by Meena *et al* of 26 LGMD patients from South India, none of the patients had contractures[3]. Patients may present with frequent falls, difficulty in climbing stairs, and a waddling gait. Pseudohypertrophy may occur in the calves, deltoids, extensor digitorum brevis, and the lateral quadriceps, often associated with early and gross wasting of the medial thigh. Diaphragm may be involved producing respiratory insufficiency. Cardiomyopathy may occur rarely with arrhythmia, heart block, or heart failure[4]. Scoliosis occurs rarely. Intellectual function is unaffected. Serum enzymes are usually elevated but may be normal. Immunohistochemistry and western blotting can now be performed on muscle biopsy to distinguish various LGMDs with known protein deficiencies, including sarcoglycanopathies, calpainopathies, and dysferlinopathies. Molecular genetic studies are required to classify the variants. The CPK elevation in the recessively inherited varieties is significantly higher than the rest of the spectrum of LGMDs, but the level is remarkably less in comparison to other myopathies, e.g., dystrophinopathies, dermatomyositis, polymyositis, hypothyroid myopathy, rhabdomyolysis, and acid maltase deficiency.

Its closed differerential diagnosis is adult variant of spinal muscular atrophy (SMA III, Kugelberg-Welander disease), which can be differentiated by absence of deep tendon jerks, EMG, nerve conduction velocity (NCV) test and muscle biopsy (denervation atrophy). Other differerential diagnoses include polymyositis or dermatomyositis, other muscular dystrophies, e.g., facio-scapulo-humeral, Becker, and Duchenne muscular dystrophy, endocrine and acquired metabolic myopathies (e.g., Cushing's disease, hyperthyroidism, steroid, and statin administration), etc. In polymyositis and dermatomyositis, neck flexor and pharyngeal muscle involvement is common alongwith proximal muscle weakness. Myalgia and muscle tenderness may or may not be present. In facio-scapulo-humeral dystrophy, facial muscles involvement is the early feature and scapular winging is present. Becker and Duchenne muscular dystrophies predominantly involve the lower extremities. Proximal muscle weakness is a common feature of myasthenia but it usually occurs after ocular and pharyngeal involvement, and it has diurnal variation. Other diseases of muscles, e.g., acid maltase deficiency, periodic paralysis, congenital myopathies

(central core, nemaline, myotubular, etc.) should also be kept in mind. In acid maltase deficiency, EMG features are distinctive, including myotonic discharges, trains of fibrillation and positive waves, and complex repetitive discharges. Muscle biopsy shows vacuoles containing glycogen. In congenital myopathies, skeletal deformities are prominent and muscle biopsies are distinctive.

Nerve conduction study results are normal in LGMD. EMG shows early recruitment and the typical small-amplitude, narrow-duration, polyphasic motor-unit potentials that are seen in muscular diseases. Abnormal spontaneous activity in the form of fibrillations and positive sharp waves is not prominent but has been described in a few cases of LGMD. When present, it should raise the clinician's suspicion for an inflammatory myopathy, such as polymyositis.

Treatment for LGMD is primarily supportive. Exercise and physical therapy are advised to maintain muscle strength and joint flexibility as much as possible. Aids to daily living will help. Gene therapy may be available in the future. Two small, double-blind trials have suggested that co-enzyme Q10 might be beneficial in this and other dystrophies, but larger trials are needed[5]. Surgical treatment may be required for contractures or scoliosis.

Conclusion

The muscular dystrophies are predominant in males, e.g., X-linked recessive disorders like Duchenne's and Becker muscular dystrophies. LGMD occurs both in males and females. This case which has been reported here as LGMD is uncommon. This is a sporadic case. She had predominant shoulder girdle involvement with uncommon features like contracture of shoulder girdle muscles, positive Gowers' sign, distal muscular atrophies (e.g., thenar muscles), history of recurrent foetal losses, and normal CPK. She had no history of falls. Pseudohypertrophy of deltoids, calves, extensor digitorum brevis, or lateral quadriceps were absent. The disease had long static course after initial deterioration. Distal muscular atrophies, contracture of shoulder girdle muscles, and positive Gowers' sign are seldom seen in LGMD. Reports on LGMDs and their subtypes are very few from India[3,6,7].

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CASE REPORT

JIACM 2008; 9(4) : 306-7

Benign Recurrent Intrahepatic Cholestasis

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Abstract

Benign recurrent intrahepatic cholestasis (BRIC) is a rare cause of cholestatic jaundice in children and young adults. Jaundice persists or recurs throughout life but does not lead to chronic liver disease or cirrhosis. Treatment is mostly symptomatic. Very few cases of BRIC have been reported till date. Here we report the case of a 25-year-old man who had recurrent episodes of jaundice since the age of 12 years.

Key words: BRIC, Cholestasis, Jaundice, Cirrhosis.

Introduction

Benign recurrent intrahepatic cholestasis (BRIC) is a rare disorder characterised by repeated episodes of intense pruritis, profound elevation in serum alkaline phosphatase and bilirubin, with normal or nearly normal values for serum gamma glutamyl transferase. An attack lasts from several weeks to months and resolves spontaneously. Between attacks, the patient remains asymptomatic for months to years. The disorder does not lead to progressive liver injury and is not fatal. There have been isolated case reports of BRIC in Indian and foreign literature[1]. Here we report an interesting case of BRIC in a 25-year-old male.

Case report

A 25-year-old non-alcoholic man presented with history of recurrent yellowish discolouration of sclera for the last 12 years. The patient had his first episode when he was 13-years-old which started with generalised pruritis followed by yellowish discolouration of sclera. This episode lasted for two months. Since then, the patient has had six episodes of jaundice ranging from one to three months occurring after every one to two years. At the time of presentation, this time patient had been asymptomatic for the last eight months. During each episode the patient was admitted and discharged in a stable condition and he used to recover completely. Liver function tests done previously during these episodes showed conjugated alkaline phosphatase levels ranging from 560-840 IU. Serum transminases were normal or slightly raised on all the occasions. Viral markers for hepatitis B and C were negative, and ultrasound abdomen was normal. CT scan of abdomen also showed no abnormality. There was no evidence of Kayser-Fleischer ring, and the patient had normal intelligence.

On examination, the patient had deep icterus but no pallor, pedal oedema, cyanosis, lymph nodes, or signs of vitamin deficiencies. There were no signs of liver cell failure. The liver was palpable in the right hypochondrium two fingers below the costal margin, and the liver span was 13 cm. The spleen was not palpable, and there was no free fluid in the abdomen. The rest of the systemic examination was normal. Investigations revealed haemoglobin of 11.0 gm% with normal total and differential counts, serum bilirubin levels were 28.0 mg% with direct and indirect component being 14.0 mg% each. Serum alkaline phospahtase level was 480 IU. Serum transaminases, prothrombin time, serum proteins, gamma glutamyl transpeptidase were within normal limits. Viral markers for hepatitis B and C were negative, and serum ceruloplasmin levels were within normal limit. Anti-smooth muscle antibodies (anti-SMA), anti-liver kidney microsomal antibodies-1 (anti-LKM-1) and anti-mitochondrial antibody (AMA) were also negative. Ultrasound of liver showed normal echotexture and there was no evidence of intrahepatic or extrahepatic biliary obstruction. Endoscopic retrograde cholangio-pancreatography (ERCP) was normal. Liver biopsy showed cholestasis within hepatocytes with some portal inflammation, while the lobular architecture was preserved. Based on the above findings, a diagnosis of benign recurrent intrahepatic cholestasis was entertained and the patient was treated symptomaticaliy. Thereafter, he showed complete recovery in three weeks.

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Discussion

Benign recurrent intrahepatic cholestasis, a rare cause of cholestatic jaundice, was first described by Summerskill and Walshe[2]. The clinical features include: the onset, usually before the age of 30 years, and recurrent attacks of cholestasis lasting several months[3]. In a large series of patients, the age of presentation varied from 1 to 59 years and duration of icteric phase varied from weeks to months[3]. The cholestasis is preceded by intense pruritis, malaise, lassitude, and occasionally by erythematous rash. Genetic studies have demonstrated that the disorder is the result of a mutation in ATP8B1, a gene that codes for the FIC1 (familial intrahepatic cholestasis) protein. It is believed that this protein plays a role in bile acid secretion, in aminophospholipid transport, and in maintaining fluidity of the cell membrane[5]. The diagnosis is difficult and remains one of exclusion. The biliary tree is patent and no cause for cholestasis can be found. Liver biopsy shows normal architecture with centrilobular cholestasis and Kupffer cell hyperplasia. The disease follows a benign course and there is no progression to cirrhosis[6]. Treatment is purely symptomatic. There have been conflicting reports regarding the use of cholestyramine and ursodeoxycholic acid[7]. While there has been no proven role of corticosteroids, some studies have shown a beneficial role of rifampicin in remission of cholestasis[8]. A single study from Holland also describes the use of nasobiliary drainage via ERCP for long-lasting relief from pruritis and jaundice[9]. Our patient was given ursodeoxycholic acid and he made an uneventful recovery in three weeks.

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CASE REPORT

JIACM 2008; 9(4) : 308-10

"Wellens' Warning" – a Typical ECG Pattern Indicating a Critical, Proximal Lesion in LAD

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A 52-year-old male, smoker, known hypertensive and non-diabetic patient with a history of crescendo angina of recent onset was admitted to our hospital on 14.09.2006. On examination, he revealed a blood pressure of 130/86 mmHg, a pulse rate of 44 bpm, and normal systemic examination, blood investigations and cardiac enzymes. His ECG revealed sinus bradycardia with a heart rate of 43 bpm and ST segment and T wave changes suggestive of anterior wall ischaemia with a characteristic ST-T segment pattern in leads V2 – V4, a typical "Wellens' warning" (Fig. 1). He was treated with intensive medical therapy as a patient of CAD with unstable angina and referred for urgent coronary angiogram and early revascularisation which revealed proximal 90% obstruction in the left anterior descending coronary artery (LAD), and 70% in the left circumflex coronary artery (Fig. 2). The characteristic ST-T segment pattern in leads V2 – V4 disappeared (Fig. 3) after PTCA and stenting to LAD on 26.09.2006 (Fig. 4). After interventional therapy he was asymptomatic, though PTCA with stenting to the left circumflex coronary artery (LCX) was also done on 06.03.2007.

The characteristic ST-T segment pattern in leads V2 – V4 (arrows in Fig. 1) is a classical example of "Wellens' warning" – an ECG pattern occasionally taken lightly. "Wellens' warning" is a typical ECG pattern which indicates a critical, proximal lesion in LAD suggestive of an impending massive anterior infarct. It is characterised by a typical ST-T segment pattern in precordial leads

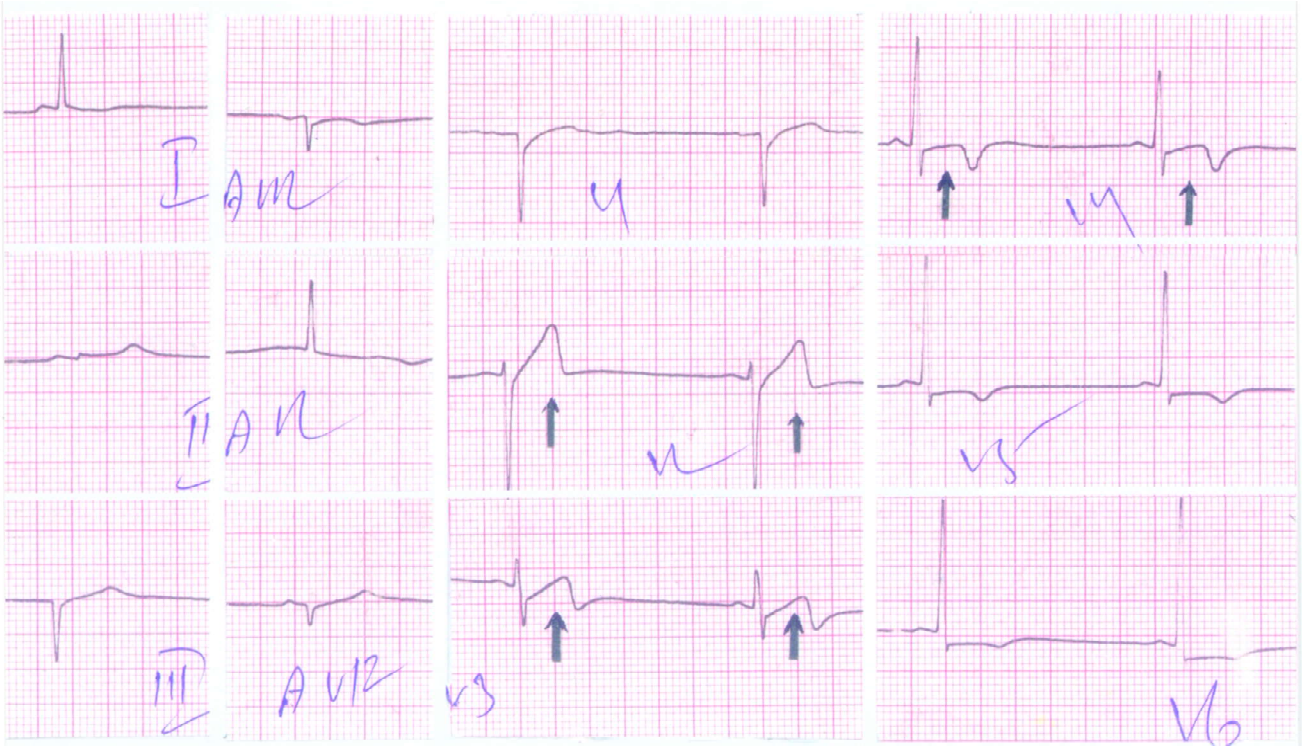

Fig. 1: *ECG showing "Wellens' warning" – a typical ST-T segment pattern in leads $V_2 - V_4$ (arrows) indicating a critical, proximal LAD lesion.*

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from V1 – V6 consisting of an isoelectric or minimally elevated (1 mm) take-off from QRS complex of a concave or straight (convex and subisoelectric common in V4 – V6) ST segment passing into the first part of a negative T wave at an angle of about 60° to 135 ° and symmetrically inverted T wave[1]. The pattern suggests either nontransmural or subendocardial ischaemia in the absence of, or a subendocardial infarction of the anterior wall in the presence of cardiac enzyme rise. The illustrations (Figs. 1-4) emphasise that patients with

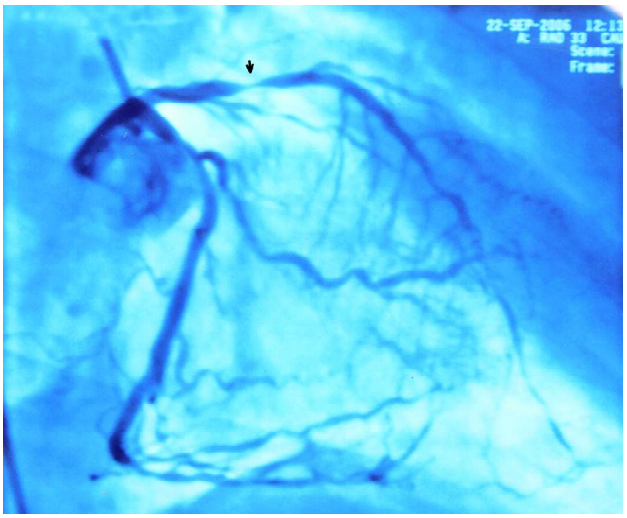

Fig. 2: *Coronary angiogram confirms a critical, proximal obstruction in LAD (arrow) and in LCX.*

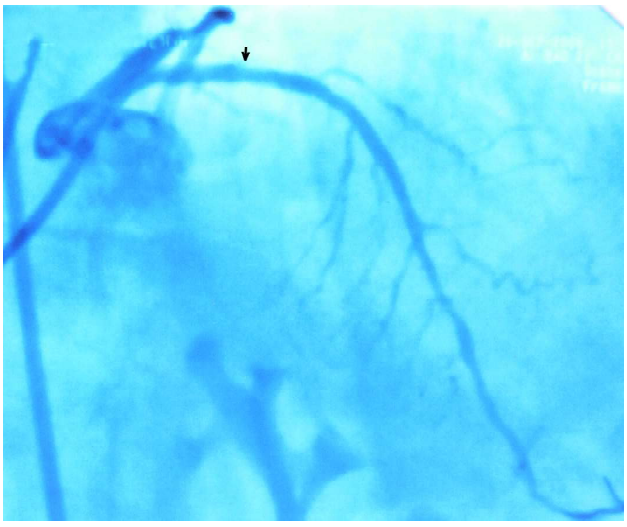

Fig. 4: *Coronary angiogram showing successful result after PTCA and stenting to LAD (arrow).*

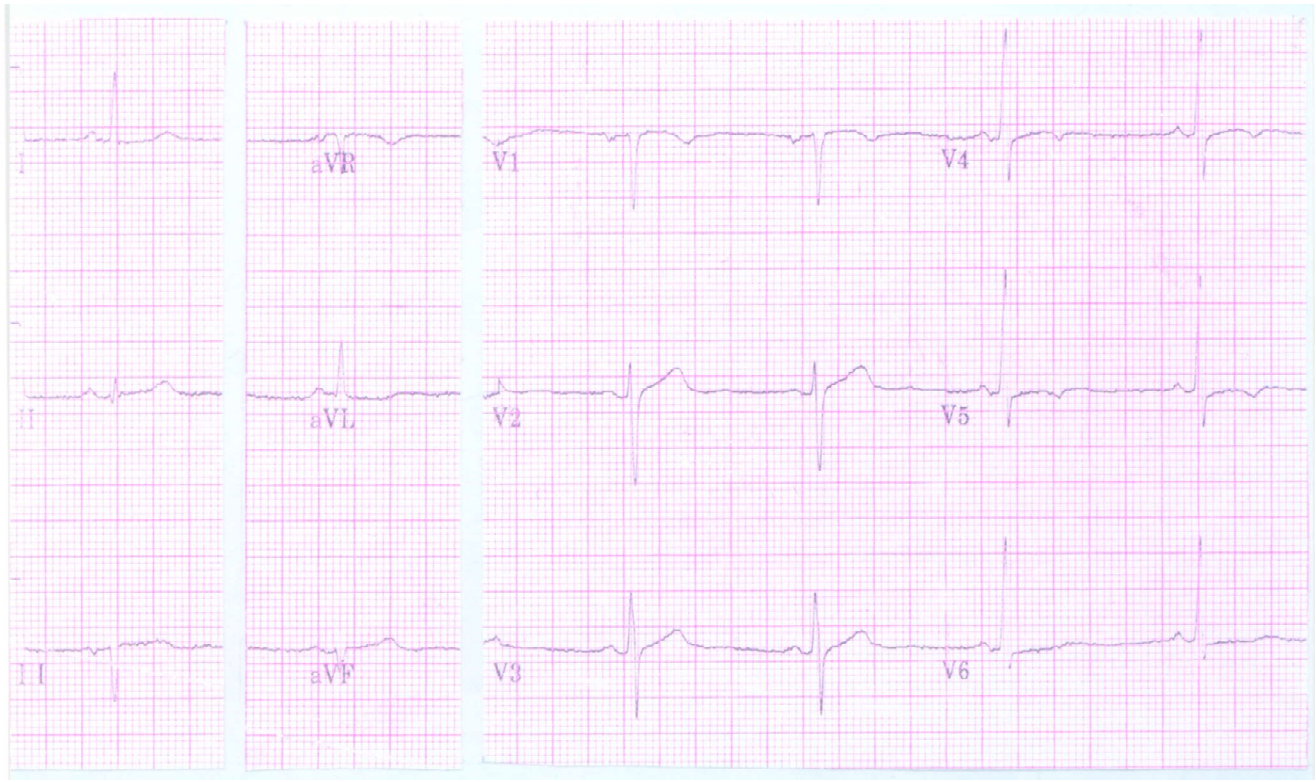

Fig. 3: *ECG showing disappearance of ST-T segment pattern of "Wellens' warning" in leads $V_2 - V_4$ after revascularisation to LAD.*

ischaemic heart disease showing "Wellens' warning" in ECG is an alert to look for a critical, proximal LAD lesion, and such patients should be managed aggressively with early revascularisation to ward-off an impending extensive anterior infarct.

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CASE REPORT

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Recurrent Valproate Responsive Stereotyped Episodes of Generalised Dystonia as an Unusual Manifestation of Moyamoya Disease

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Abstract

Moyamoya disease (MMD) usually manifests with repeated ischaemic episodes in children, and intracranial hemorrhage in adults. Recurrent focal neurological deficits and seizures may occur. Involuntary movements in the form of dystonia, chorea, or athetosis have been reported but are uncommon. We report an unusual case of childhood MMD presenting with recurrent stereotyped episodes of generalised dystonia responsive to valproate, as the predominant manifestation of this disorder.

Key words: Moyamoya disease, Valproate, Involuntary movements, Dystonia.

Introduction

Moyamoya disease (MMD) is a chronic progressive occlusive disease of the cerebral vasculature with a predilection for involving the distal internal carotid arteries and their branches alongwith a concomitant proliferation and enlargement of abnormal collateral vessels in the circle of Willis at the base of the brain[1]. The exact aetiology of MMD is not known. Congenital, hereditary, and some secondary or acquired aetiological factors have however, been implicated in its genesis. The clinical features and severity of the disease varies with age at presentation. Recurrent episodes of cerebral ischaemia or haemorrhage may manifest with focal neurological deficits, seizures, or rarely involuntary movements[2]. We report a unique case of MMD presenting with recurrent stereotyped episodes of generalised dystonia as the predominant manifestation of the disease.

Case history

A 10-year-old boy presented to us with a three-months history of rapidly evolving and progressive dystonic posturing and abnormal movements of all the four limbs and trunk accompanied by facial grimacing, dysphagia, dysarthria, dysphonia, and dribbling of saliva. There was no history of nasal regurgitation, visual loss, motor weakness, sensory deficit or any bladder and bowel disturbance. He was not able to walk or sit unsupported at the time of presentation but his orientation and comprehension were intact. There was no history of accompanying fits, headache, vomiting, or loss of consciousness.

In the past history, there was a history of jaundice with recovery within ten days at the age of two-and-a-half years. At four-years of age he had developed an acute onset right-sided motor weakness accompanied by an abnormal posturing of the upper and lower limbs, and dysarthria which recovered fully within one month of onset, without any specific treatment. Two months later he had one episode of generalised tonic-clonic seizure (GTCS) during sleep. A CT scan of the head done at this stage revealed a small left frontal hypodensity. The patient subsequently received valproate in a dose of 100 mg three times a day, which was stopped after a two-year seizure-free interval.

At six-and-a-half years of age, i.e., two months after stopping valproate, he developed a rapidly evolving generalised dystonia with abnormal posturing and movements of the limbs and trunk besides dysarthria, dysphagia, dysphonia, and drooling of saliva which evolved to its peak over a period of one month. In view of the appearance of these symptoms within two months of stopping valproate, he was again prescribed valproate in a dose of 100 mg three times a day by his treating physician, even though there was no history of a seizure recurrence. The dystonia responded and recovered completely within 15 days of restarting the medication. Valproate was again continued for the next two years, and during this period the patient remained asymptomatic. However, at nine-years of age, and within two months of

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once again on stopping valproate, he developed a fresh episode of generalised dystonia and abnormal movements similar to the preceding episode. He was once again prescribed valproate (600 mg/day). He recovered fully within 15 days and remained asymptomatic for the next one year. However, within one month of stopping valproate for the third time, he once again developed a fresh stereotyped episode of generalised dystonia which evolved over a period of three months. It was with this attack, that the patient reported to us for consultation. Overall, over a period of six years, starting from age four, the patient suffered a single attack of GTCS and four attacks of neurological dysfunction, one episode of hemiparesis with dystonia, and three stereotyped episodes of generalised dystonia with bulbar symptoms. The last three episodes of generalised dystonia had occurred within four to eight weeks of stopping valproate and historically the previous two episodes had responded to valproate, with the patient remaining asymptomatic for long intervals of 1 to 2 years while on therapy. Perinatal history, psychomotor developmental history, and family history was not significant.

On examination at the time of presentation, his vitals were stable. There was no Kayser-Fleischer ring on corneal examination. The rest of the general physical, cardiovascular, respiratory, and abdominal examination was unremarkable. Higher mental functions were normal. He was having severe oromandibular dystonia with facial grimacing, dysarthria, dysphonia, dysphagia, and drooling of saliva. There was generalised dystonia with abnormal posturing and movements of the limbs and trunk. Deep tendon reflexes were difficult to elicit, but the plantar reflexes were bilaterally flexor. Other central and peripheral nervous system examination was unremarkable.

Routine investigations including haemogram, blood sugar, kidney and liver function tests, lipid profile, ASO titre, CRP, electrocardiogram, electroencephalogram, echocardiography, serum ceruloplasmin, slit lamp examination of eye, and X-ray chest were all within normal limits. MRI brain revealed bilateral areas of altered signal intensity in the frontal lobes (left > right), hypointense on T1, and hyperintense on T2 weighted and FLAIR images, besides nonspecific mild cerebal atrophy (Fig 1). Contrast MRI revealed an abnormal leash of blood

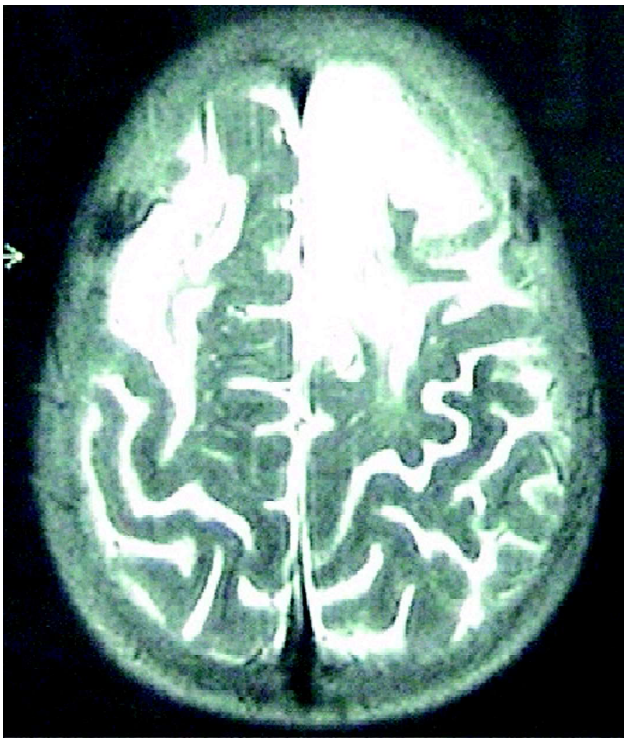

Fig. 1: *T2 weighted axial MRI image showing bilateral frontal hyperintense areas (left > right) suggestive of old infarcts.*

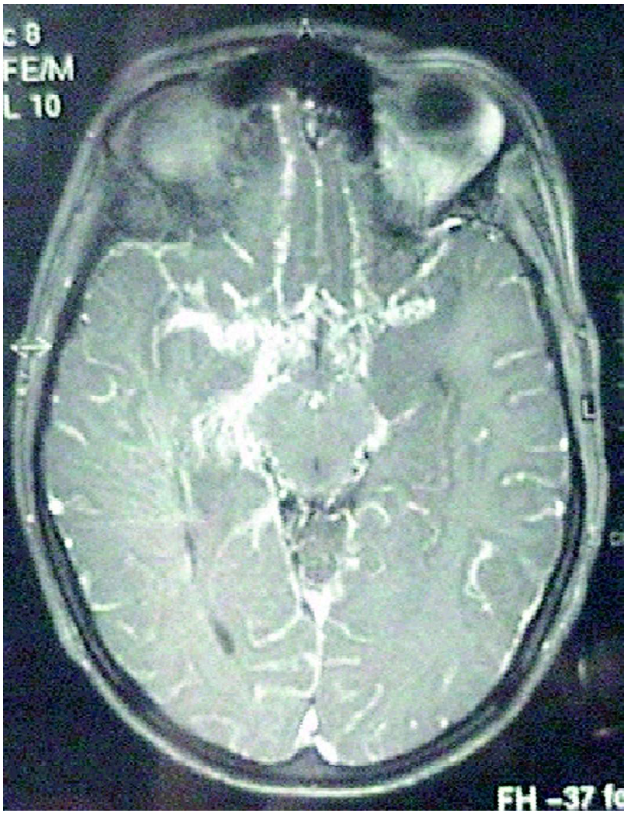

Fig. 2: *Contrast axial MRI image showing an abnormal leash of blood vessels in the circle of Willis at the base of the brain.*

vessels in the region of the circle of Willis at the base of the brain (Fig 2). Magnetic resonance angiography (MRA) reveled occlusion of the supraclinoid portion of the internal carotid arteries on both the sides, with prominent bilateral posterior communicating arteries and multiple small basal telangiectatic collaterals and dilated lenticulostriate and thalamoperforate vessels with relative sparing of the posterior circulation, suggestive of MMD (Fig 3).

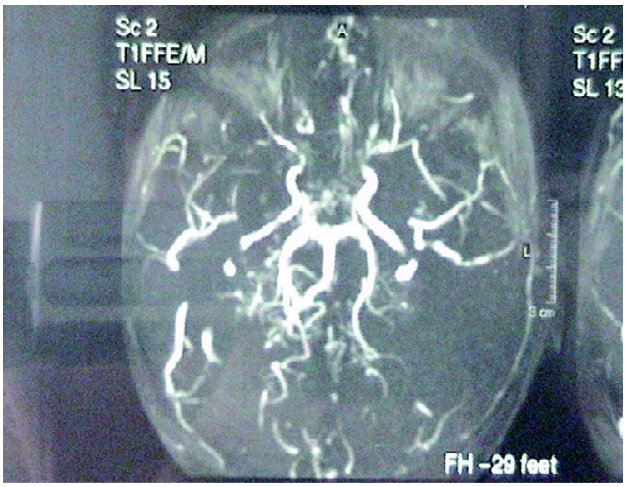

Fig. 3: *MRI showing occlusion of the supraclinoid portion of both the internal carotid arteries.*

A trial of trihexiphenidyl (upto 30 mg per day), for symptomatic control of dystonia, failed to provide any relief. In view of the past history of response to valproate, the drug was restarted in a dose of 200 mg three times a day. A significant improvement in dystonia was noted within two weeks of starting therapy, with near complete recovery by one month. The patient was subsequently referred for neurosurgical intervention.

Discussion

MMD occurs primarily in Asians, but has also been reported from other parts of the world. Japan has the highest prevalence (3.16 per 100,000 population) and incidence (0.35 per 100,000 population) of MMD[3]. Female to male ratio is 1.8:1. The age of onset may range from six months to 67 years, with the highest peak in the first decade, and smaller peaks in the third and fourth decades[3]. Our patient also had onset of symptoms by four years of age.

MMD is a progressive occlusive disease of the cerebral vasculature characterised by bilateral stenosis or occlusion of the distal internal carotid arteries and their main branches due to fibrocellular thickening of the intima. Abnormal vascular collateral networks develop adjacent to the stenotic vessels in the circle of Willis, giving the angiographic appearance of a "puff of smoke" or "Moyamoya" in Japanese. The exact aetiology of MMD is unknown, but it may be familial in around 10 % cases[4]. Autosomal dominant inheritance with reduced penetrance has been reported in a recent Japanese study. Genetically, susceptibility loci have been found on 3p, 6p, 17q, and band 8q23[5].

The symptoms and clinical course of MMD may vary widely from asymptomatic to transient events, to severe neurological deficits. Children and adults may have different clinical manifestations. Intraventricular, subarachnoid, or intracerebral haemorrhage of sudden onset is more common in adults. In childhood MMD, ischaemic strokes predominate. TIAs occur in 40% and infarction in 29%, representing 69% of all the cases, in patients younger than 10 years of age[2]. Recurrent strokes can present as focal neurological deficits in the form of monoparesis, haemiparesis, alternating hemiplegia, aphasia, and sensory deficit. Seizures have been reported in about five per cent cases[6].

There was history of a single GTCS in our case also. Headaches, dizziness, mental retardation, or persistent neurologic deficits may be present. These however, were not observed in our case. Involuntary movements have been described but are rare, especially as an isolated, initial, or the predominant manifestation of MMD. Recurrent generalised dystonia however, was the early and predominant manifestation in our case as already discussed. Transient or persistent hemichorea, hemidystonia, bilateral choreo-athetosis, and recurrent torticollis have been reported as early manifestations of MMD by a few authors only[7-14]. Gonzalez-Alegre P *et al*. reported two patients with paroxysmal dyskinesia as the initial symptom of MMD, one resembling paroxysmal kinesogenic dyskinesia (PKD) and the other paroxysmal non-kinesigenic dyskinesia (PNKD)[10]. Handa *et al* however, observed dyskinesias as an initial manifestation of MMD, in only three per cent of a large series of 1,500 Japanese patients[15].

As the disease occurs as a result of progressive occlusion of the intracranial internal carotid arteries and to a lesser degree the proximal anterior and middle cerebral arteries, occurrence of basal ganglia infarcts leading to involuntary movements can be expected. Sudden onset hemichorea or hemidystonia can be attributed to a basal ganglia infarct. In our case however, the occurrence of recurrent stereotyped attacks of generalised dystonia evolving over a period of days to weeks, in the absence of a frank history of stroke-like events was an unusual feature. Reccurent or chronic striatal hypoperfusion seems to be the possible mechanism. Another unusual observation was, that despite recurrent episodes of generalised dystonia, our patient recovered fully and remained completely asymptomatic for long intervals while on valproate therapy, with relapse of dystonia within a few weeks of stopping valproate on three occasions over a six years period from the onset of the illness. Subacutely evolving or chronic dystonia implies a more widespread, recurrent, or chronic ischaemic insult to the basal ganglia, and could be the possible mechanism accounting for the unusual presentation in our case. However, the complete resolution of dystonia with valproate, in the setting of a chronic insult to the basal ganglia, is unusual and remains an enigma.

Conventional angiography has traditionally been regarded as essential for definitive diagnosis of MMD, but recently MRI and MRA have substituted it as a diagnostic test[16]. In our case, the abnormal leash of blood vessels in the region of the circle of Willis was detected on the contrast MRI film itself, while the characteristic MRA findings confirmed the diagnosis.

The outcome depends on the severity of the case. Patients with static or fixed deficits have the worst prognosis. Mortality rates are around 10% in adults, and 4.3% in children[3]. Death is usually from haemorrhage. Gradual deterioration of cognitive function due to recurrent stroke may be observed in 50 to 60% cases[2]. Our patient however, remained cognitively intact despite recurrent episodes of generalised dystonia.

Treatment-wise, observation and conservative treatment is advocated for mild or transient symptoms, but neurosurgical intervention is required for the more severe cases. Various cerebral revascularisation surgical procedures used in the management of MMD include, superficial temporal artery – middle cerebral artery (STA-MCA) anastomosis, encephalo-duro-arterio-synangiosis (EDAS) and encephalo-duro-arteio-myo-synangiosis (EDAMS) but their efficacy remains controversial[17]. Improved cerebral blood flow and some symptomatic benefit may occur, but data proving sustained or improved long-term outcomes is insufficient. Parmar *et al* have reported good control of disabling chorea in two cases following bypass surgery[13].

Very little literature is available with regards to the medical management of involuntary movements in MMD. Pavlakis *et al* reported improvement with steroid therapy, in 13-year-old boy with disabling chorea due to MMD[18]. None of the available drugs have proved to be particularly effective in the management of dystonia but pharmacotherapy may provide an overall benefit in 30 – 40% cases. Trihexyphenidyl, an anticholinergic agent that blocks acetylcholine receptors in the brain, is the most commonly used medication for children with dystonia. High doses of upto 50 to 100 mg per day may be required for maximal benefit. Other medicines that may have some benefit include diazepam, clonazepam, and GABA-associated drugs like valproate, gabapentin, lamotrigine, carbamazepine, and baclofen – besides other agents like reserpine and tetrabenazine. Injection of botulinum toxin may be used in patients with focal dystonia. Choice of the best regimen however, is usually by trial and error.

In our case, the dystonia failed to improve with trihexiphenidyl but responded to valproate. The response was sustained while valproate was continued, with relapse of dystonia within a few weeks of stopping the drug on several occasions. Valproic acid enhances activity at the inhibitory GABA receptors in the basal ganglia. It also increases the GABA content of the brain by impeding the hydrolysis of two enzyme systems that inactivate GABA, namely, GABA-transaminase, and succinic semialdehyde dehydrogenase, whilst also affecting the sodium channels. It is helpful for movement disorders like myoclonus and there are some case reports of its benefit in chorea and tardive dyskinesia[19]. Brennan *et al*, reported a good response to combined therapy with sodium valproate and baclofen in a case of idiopathic orofacial dystonia (Meige's syndrome)[20]. Even though it is not regarded as the first-

line therapy for dystonia, it may benefit patients with dystonia, as was the case with our patient. However, the dramatic and complete response to valproate remains an unusual feature in our case.

We conclude that MMD should be kept in the differential diagnosis of recurrent involuntary movements (dystonia, chorea, athetosis), especially in children; and valproate therapy may ameliorate moyamoya-associated involuntary movements and dystonia.

Key points

- Moyamoya disease (MMD) is a rare, chronic, progressive, occlusive disease of the cerebral vasculature with recurrent episodes of ischaemia and haemorrhage.
- Recurrent stroke, focal neurological deficits, and seizures are the usual manifestations.
- Involuntary movements in the form of chorea, athetosis or dystonia, are uncommon, but can be the predominant or presenting feature of the disease.
- MMD should be entertained as a differential diagnosis of unexplained, recurrent movement disorders in childhood.
- MRI and MRA can confirm the diagnosis.
- MMD associated dystonia may respond to valproate.

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CASE REPORT

JIACM 2008; 9(4) : 316-8

Bleeding Manifestations and Pancytopenia Secondary to Bone Marrow Infiltration in Tuberculosis

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Abstract

Haematological abnormalities like anaemia, leucopenia, leucocytosis, monocytosis, and thrombocytopenia due to tuberculosis are common, but bleeding as a presenting manifestation due to tuberculosis is rare. We hereby report a 40-year-old female patient admitted with fever, headache, dyspnoea, palpitations, diminution of vision, and bleeding per-vaginum. Examination revealed severe pallor and other findings were within normal limits. Chest radiograph was normal. Peripheral smear revealed pancytopenia and bone marrow aspiration showed cellular marrow with multiple epithelioid granulomas. Mantoux test was positive and erythrocyte sedimentation rate (ESR) was elevated. Patient was put on four-drug antitubercular therapy (RHZE) and showed excellent recovery with improvement in cytopenias and cessation of bleeding within three weeks.

Keywords: Pancytopenia, Epithelioid granuloma.

Introduction

Tuberculosis continues to remain the world's most important and challenging communicable disease. Inspite of recent advances in our understanding of the disease, tuberculosis still remains a major public health problem, particularly in developing countries. Patients with disseminated tuberculosis have varied presentations including pyrexia of unknown origin (PUO), hepatosplenomegaly, lymphadenopathy, and meningitis[1]. Though haematological abnormalities associated with tuberculosis have been well-recognised, the bleeding manifestation as a presenting symptom alongwith bone marrow infiltration is uncommon.

Case report

A 40-year-old female was admitted with complaints of moderate-to-high grade continuous fever for three weeks. She also complained of headache, dyspnoea, and palpitation for the same duration. There was also history of menorrhagia and diminution of vision for 15 days. There was no history of vomiting, cough, expectoration, seizure, rashes, altered sensorium, family history of tuberculosis, drug intake, chemical/radiation exposure, oligomenorrhoea or infertility, and no history of deviant sexual behaviour. Nutritional status of the patient was average. On examination, her general condition was poor, blood pressure 110/70 mm Hg, pulse rate 102/min, regular, and she was severely anaemic. Systemic examination revealed just palpable soft liver; spleen was not palpable, and there was no ascites. Other findings included soft systolic murmur at apex while both respiratory and nervous system were essentially normal. Fundus examination revealed numerous haemorrhages around the disc as well as pre-retinal haemorrhage in the macular region. On the basis of history of fever, severe anaemia, bleeding manifestation and hepatomegaly, a provisional diagnosis of acute leukaemia, aplastic anaemia, or infiltrative bone marrow disorders were entertained and urgent investigations were carried out.

Investigations revealed haemoglobin (Hb)-3.5 g/dl, total leucocyte count (TLC)-2,600/mm^3, differential leucocyte count (DLC)-$P_{55}L_{42}M_3E_0B_0$, platelet count-23,000/mm^3, reticulocyte count 1%, packed cell volume (PCV)-8.5%, mean corpuscular volume (MCV)-94.7 fl, mean corpuscular haemoglobin (MCH)-39.2 pg, mean corpuscular haemoglobin concentration (MCHC)-41.4 g/dl and ESR was 150 mm in the 1st hour. Peripheral blood smear - red cells showed mild hypochromia, moderate anisocytosis with fair number of macrocytes, microcytes, tear drop cells and occasional schistocytes; leucocytes showed shift to left till myelocyte stage; cytoplasm of the neutrophils showed toxic granules, and occasional macropolymorphonuclear cells were seen with hypersegmentation (6 lobes), platelets were reduced in

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numbers (Fig. 1). Liver and kidney function tests, serum electrolytes, blood sugar, and urine examination were all within normal limits. Serum calcium was 10.2 mg/dl. ANA and ELISA for HIV were negative. X-ray chest did not reveal miliary mottling or adenopathy. Abdominal ultrasound showed hepatomegaly and there was no evidence of splenic enlargement, ascites, retroperitoneal lymphadenopathy. Two units of platelet concentrate were transfused to tide over the bleeding crisis. Mantoux test was positive (24 x 36 mm). Bone marrow aspiration was done to look for the cause of pancytopenia and was found to be cellular alongwith megaloblastic maturation in the form of giant metamyelocytes, doughnut neutrophils with some showing hypersegmentation in the myeloid series. Erythroid cells showed megaloblastic maturation with dyserythropoiesis and prominent mitotic figures. Myeloid-erythroid ratio was 4:1. Megakaryocytes were adequate, showing hypersegmentation and hypolobation; plasma cells being mildly raised in number. Multiple epithelioid cell granulomas and binucleate histiocytes were prominently seen (Fig. 2). A diagnosis of disseminated tuberculosis was made and the patient was prescribed four-drug anti-tubercular regimen (RHZE). The patient showed remarkable improvement within 3 weeks in the form of resolution of symptoms (disappearance of fever and cessation of bleeding) and correction of cytopenia. Repeat haemogram showed haemoglobin of 7 g/dl, TLC-7,600/mm^3, DLC-$P_{68}L_{30}E_1M_1$, platelet count-2,40,000/mm^3 and ESR was 76 mm/hr.

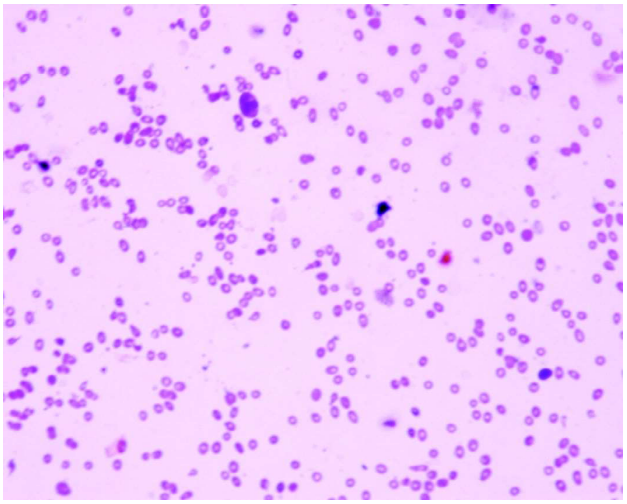

Fig. 1: *Peripheral smear showing pancytopenia (400 x Wright's stain).*

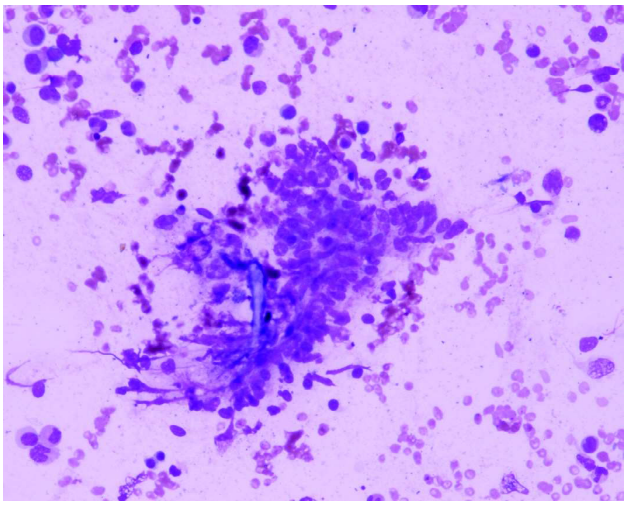

Fig. 2: *Bone marrow showing epithelioid cell granuloma (400 x Wright's stain).*

Discussion

A number of haematological alterations have been described in patients with miliary or disseminated tuberculosis including anaemia, granulocytosis, leucopenia, leucocytosis, thrombocytosis, and monocytosis; but bleeding manifestations and/or pancytopenia as a presenting feature of disseminated tuberculosis is extremely uncommon both in children and adults. To the best of our knowledge, massive vaginal bleeding and serious ocular complications secondary to macular or retinal haemorrhages as seen in this patient had not been described as presenting manifestation in patients with granulomatous involvement of bone marrow.

There are occasional case reports of pancytopenia in disseminated tuberculosis[1] and demonstration of tubercular granuloma on bone marrow examination during investigative work-up for patients with fever of unknown origin[2]. Pancytopenia was seen only in 8% in a series of 38 patients with miliary tuberculosis by Mert *et al*, but there was no episode of significant bleeding, although thrombocytopenia, leucopenia, and anaemia were seen in significant number of patients ranging from 16 – 76%. Granulomas were found in 56% patients' bone marrow tissue specimen, and polymerase chain reaction (PCR) was positive in 47% specimens with granuloma[3]. Our patient had presented without miliary shadows on the chest radiograph.

It has been suggested that subjects with caseating granuloma carry very poor prognosis although early diagnosis and recognition coupled with effective antitubercular therapy have altered the course of such illness[1].

Numerous hypotheses have been put forward to explain the occurrence of pancytopenia in disseminated tuberculosis, such as hypersplenism, histiocytic hyperplasia and phagocytosis, bone marrow infiltration by tubercular granuloma or occasionally maturation arrest[4,5]. Tubercular granuloma can cause pancytopenia by physical replacement of marrow cells or depression through certain interferons and cytotoxins. Newer diagnostic techniques such as PCR of the bone marrow material can assist in rapid decision making and obviate the necessity of a long period of culture for AFB; although in majority of cases, a drug trial with ATT can be a reasonable alternative as seen in our case[6].

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CASE REPORT

JIACM 2008; 9(4): 319-20

Idiopathic Hypertrophic Osteoarthropathy

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Abstract

Idiopathic hypertrophic osteoarthropathy is a rare disorder characterised by chronic, proliferative periosteitis of long bones, clubbing of fingers and/or toes, and oligo- or polysynovitis. Patients presenting with these features should be investigated for secondary causes of this disorder. Besides this, other diseases such as acromegaly and rheumatoid arthritis may also mimic this disorder. The disease is often self-limiting.

Key words: Hypertrophic osteoarthropathy, Clubbing, Periosteitis.

Introduction

Hypertrophic osteoarthropathy (HOA) is a syndrome of chronic, proliferative periosteitis of the long bones, clubbing of fingers, toes, or both, and oligosynovitis or polysynovitis. HOA is most often secondary to the underlying neoplastic, infectious, congenital cyanotic heart diseases, etc. Primary HOA is usually a rare hereditary disorder but occasional idiopathic nonfamilial cases in adults have been reported. We report here such a patient who presented with features of idiopathic HOA beginning in adulthood.

Case report

A 28-year-old man presented with progressively increasing swelling of both wrist joints and fingers of both hands, knees, and ankles of 10-years duration. The disease was more or less static for the last 2 years. There was no associated stiffness, redness, or pain in the joints. He did not have fever, haemoptysis, chest pain, purulent expectoration, or hoarseness of voice. There was no history of cyanotic spells during childhood or history of diarrhoea with mucus or blood in stools. There was no history of pruritus, jaundice, oedema, or ascites. There was no history of similar illness in any family member. He was not a known diabetic or hypertensive, and had no history of addiction to any drug. His old photographs taken 10 and 6 years ago did not reveal any significant change of physical appearance. There was no thickening of skin, enlargement of jaw or forehead. Physical examination revealed that he had marked, painless clubbing of both hands and feet associated with enlargement of wrists, knees, and ankle joints (Fig. 1). There was evidence of mild effusion in both knee joints. Systemic examination did not reveal any abnormality. There were no features suggestive of paraneoplastic syndrome.

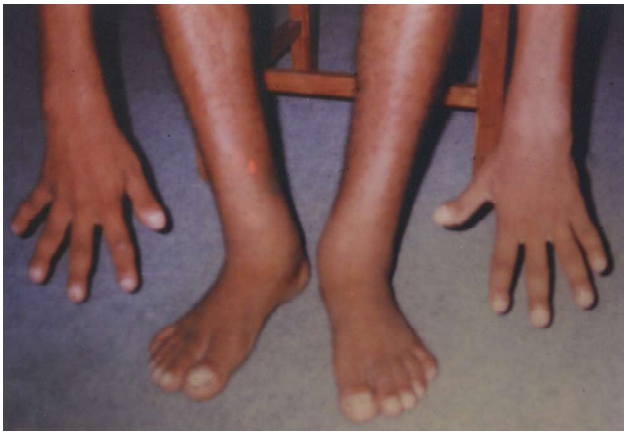

Fig. 1: *Showing gross clubbing of fingers and toes and hypertrophic osteoarthropathy involving long bones of extremities.*

Investigations revealed that his Hb was 10.2 g/dl, TLC - 4,800/cumm, differential white cell count was $N_{49}L_{48}M_{2}E_{1}$ and ESR was 56 mm in the first hour. His fasting and post-prandial blood sugar was 96 and 124 mg/dl respectively. His liver and renal function tests, chest skiagram, and ECG were found to be normal. X-rays of both knee joints and wrist joints revealed periosteal reaction and thickening. X-ray of skull did not reveal any enlargement of pituitary fossa. Fundus examination was normal and visual field charting was within normal range. There were no radiological features suggestive of acromegaly. Synovial aspirate from the right knee joint revealed: protein-5.8 g/dl, WBC count - 220/cumm, differential count - P_{36}, L_{64}, and

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glucose 76 mg/dl. Rheumatoid factor and CRP were within normal range.

A diagnosis of primary hypertrophic osteoarthropathy was made after exclusion of secondary causes of HOA, rheumatoid arthritis, and acromegaly with which it closely resembles. The patient was prescribed NSAIDs in the form of oral diclofenac for symptomatic relief for a period of 4 weeks. The disease has been self-limiting.

Discussion

The triad of periosteitis, clubbing, and arthritis has been associated with various disorders such as bronchogenic carcinoma, suppurative lung diseases, congenital cyanotic heart diseases, infective endocarditis, and various gastrointestinal, and hepatobiliary disorders. Presence of these osteoarticular changes not associated with any underlying disease (primary HOA) is very rare. Sometimes, isolated clubbing not associated with periosteitis or polyarthritis may occur[1]. The clubbing develops over a period of months to years as compared to secondary causes where it develops rapidly. This familial condition may be a separate entity or an incomplete expression of HOA. Primary HOA (pachydermoperiostosis or Touraine-Solente-Gole syndrome) occurs most often within families. Symptoms usually begin at about 1-year of age or in adolescence, either before or after puberty, more commonly in males[2]. It is probably transmitted by an autosomal dominant gene with variable expression, and symptoms often decline within 1 or 2 decades. There is insidious development of clubbing with "spade like" enlargement of hands and feet[3]. The patient often complains of cosmetic unsightliness and decreasing dexterity or awkwardness when using the fingers. Symptoms may include vague pains in the joints and along the bones[4]. Examination reveals marked clubbing with cylindrical thickening of forearms and legs, corresponding with radiographic periosteal changes[5]. Recurrent joint effusions are mildly symptomatic[6]. Acro-osteolysis may occur with resorption of distal phalanges of hands and feet. There is thickening and furrowing of facial features giving coarse "leonine-like" appearance. The skin of the face and scalp is "greasy" with excessive sweating which also affects the hands and feet. The latter features are uncommon in secondary HOA. Some patients demonstrate gynaecomastia, striae, and acne vulgaris.

Laboratory tests are not useful in the diagnosis. These patients have raised ESR and CRP. Rheumatoid factor and antinuclear antibody tests are negative. Synovial fluid is non-inflammatory in nature. Periosteal thickening is the characteristic radiographic finding. It occurs along the shaft of long and short bones, most often in the tibia, fibula, radius, ulna, and femur. Radiographs of the hands may reveal tufting of the terminal processes and osteophytosis in more advanced stages of clubbing. Whenever HOA is diagnosed, it is essential to exclude secondary causes before labelling it as idiopathic. Evaluation should include assessment of cardiopulmonary and gastrointestinal systems. When the primary presenting complaint is polyarticular pain and swelling, the picture may resemble rheumatoid arthritis. However, typical history and clinical findings alongwith negative rheumatoid factor and non-inflammatory nature of the synovial fluid exclude this diagnosis. Similarly, acromegaly should also be thought of as a possible differential diagnosis for this condition.

The exact aetiopathogenesis of HOA is unknown. However, various mechanisms such as vagal stimulation, growth factor, immune mechanisms, platelet endothelial interaction, etc., have been implicated in the pathogenesis of HOA. Primary HOA is a self-limiting disease, although recurrent episodes of synovitis are common. This disorder is frequently asymptomatic and therapy with NSAIDs is rarely required.

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CASE REPORT

JIACM 2008; 9(4): 321-5

CT Diagnosis of Pulmonary Wegener's Granulomatosis: A Case Report and Review of Literature

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Abstract

The diagnosis of Wegener's granulomatosis which is a rare disease involving the small vessels of lungs and kidneys has traditionally been carried-out by biopsy. In the last decade, imaging has evolved greatly and it is possible to diagnose Wegener's granulomatosis by conventional CT or high resolution CT because of the characteristic radiological findings on CT images. There are certain characteristic pulmonary imaging features of Wegener's disease; and nodules randomly distributed in the bilateral lung fields with cavitation are diagnostic in appropriate clinical settings. Other lesser known radiological manifestations of the disease are being discussed and reviewed.

Keywords: CT, HRCT, Acinar opacities, Pulmonary nodules, Bronchocentric distribution, Bronchocentric, tracheobronchial stenosis, Interstitial opacities.

Introduction

Wegener's granulomatosis is a multi-system disease characterised by necrotrising granulomatous inflammation and small vessel vasculitis. The aetiology of this disorder is unknown; an autoimmune mechanism is probable, and the mean age of presentation is 40 to 55 years with a male to female ratio of 1:1[1]. The pulmonary disease occurs almost always in Wegener's granulomatosis with a 95 – 100% incidence of involvement of upper and lower respiratory tracts and it manifests as intractable cough with bouts of haemoptysis and dyspnoea[2]. In 85% patients, the kidneys are involved by a focal necrotising vasculitis and glomerulonephritis. The renal involvement may be asymptomatic or associated with microscopic haematuria and proteinuria. Skin and muscle involvement is seen in 44% patients with inflammatory macules and rashes, joint involvement occurs in 56% patients with migrating polyarthopathy and middle-ear involvement occurs in 29% cases with proptosis and otitis media, while heart and pericardium are affected in 28% patients with myocardial ischaemia[3]. The presenting symptoms and clinical course of the disease depend on the specific organs involved. Wegener's granulomatosis has been reported in the peadiatric population also.

An accurate diagnosis of this rare, aggressive vasculitis is important as 90% patients show partial or complete remission with cyclophosphamide and corticosteroid therapy. Radiological imaging has a great role in detecting and diagnosing this unusual disorder using plain radiographs, conventional computed tomography (CT), or high resolution computed tomography (HRCT).

We report the radiological findings in two cases of pulmonary Wegener's granulomatosis. Both the cases histologically proved to have necrotrising vasculitis.

Case 1

A 46-year-old man presented with malaise and weakness for two months, low-to-moderate fever since three weeks associated with dyspnoea and four-to-five episodes of nasal bleeding and discharge. The laboratory tests showed leucocytosis with high level of antinuclear cytoplasmic antibodies. Spiral CT of the chest as well as the paranasal sinuses was performed on Siemens Somatom balance spiral scanner. The scout view showed multiple, large, well-defined nodules randomly distributed through out bilateral lung fields (Fig. 1). Cavitation was seen in most of the nodules with thick irregular walls of the lesions (Fig. 2a and 2b). Pleural effusion was seen as well. CT images of the paranasal sinuses revealed soft-tissue thickening of the mucosa of the sphenoid sinuses with obliteration and mucosal involvement of the anterior and posterior ethmoid cells and mucosal involvement of bilateral maxillary sinuses. The nasal cavity also demonstrated mucosal thickening.

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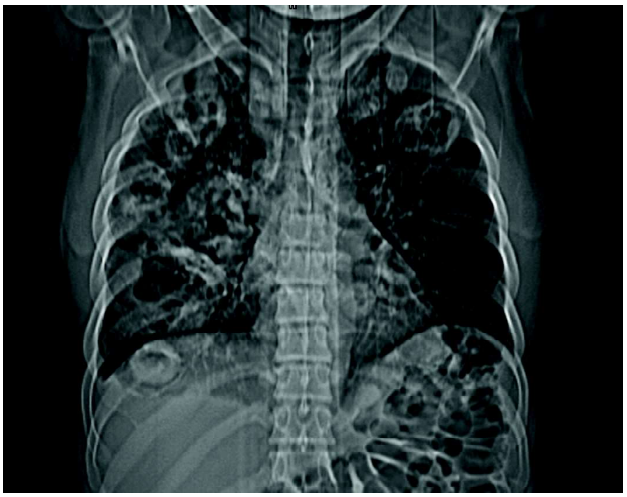
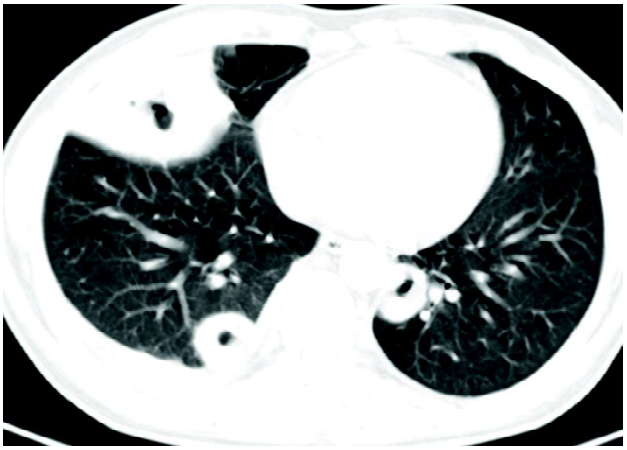


Fig. 1: *Scout film of the chest showing multiple, large, 4 – 5 cms nodules in bilateral upper, mid- and lower zones of the lungs. Most of the nodules show cavitation and thick walls.*



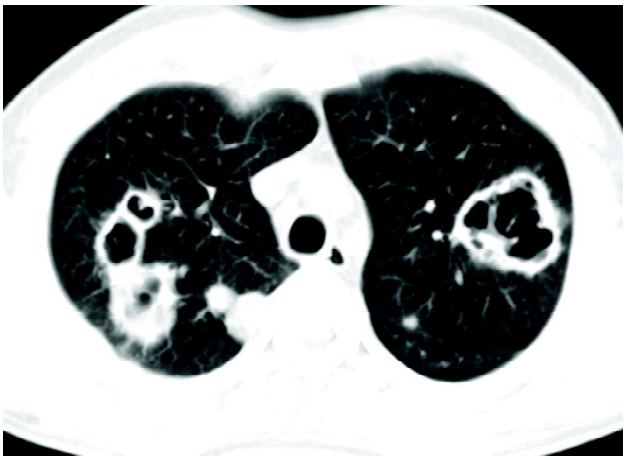
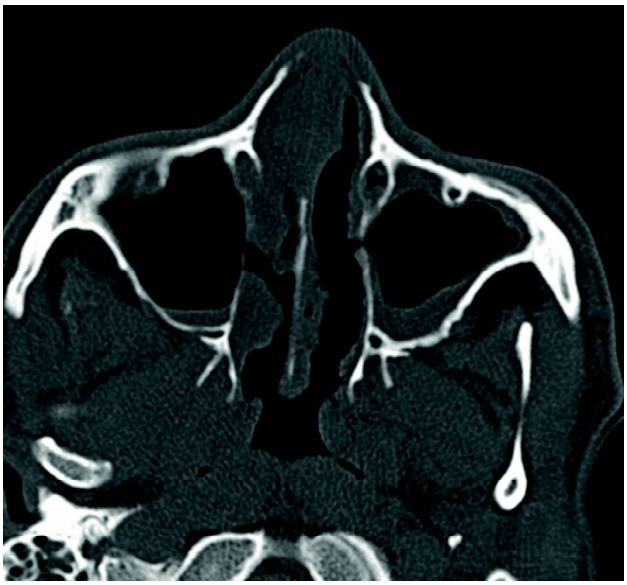


Fig. 2A, b: *Axial CT scans through the upper and lower zones of the lungs show thick-walled, cavitating nodules distributed in bilateral lungs. Some of the nodules show coalescence.*

Thinning of the nasal septum was also present (Fig. 3a and 3b). CT guided lung biopsy was performed from one of the pulmonary nodules and the specimen showed necrotising vasculitis of the small vessels with a granulomatous component.



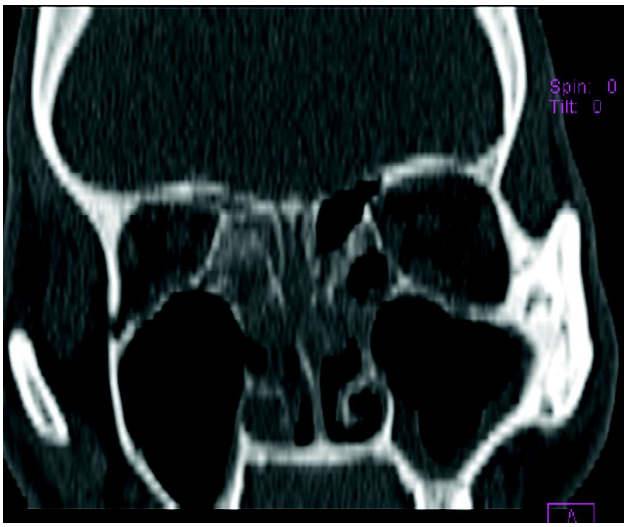


Fig. 3A, b: *Axial and coronal reformatted CT images of the paranasal sinuses demonstrate obliteration of bilateral anterior and posterior ethmoid air cells by a soft-tissue density with mucosal thickening of bilateral maxillary sinuses involving the osteomeatal complexes. Soft-tissue thickening is seen in the nasal cavity as well as around the nasal septum with thinning of the septum.*

Case 2

A 41-year-old woman presented with a history of recurrent epistaxis, productive cough over 2 months, and pyrexia

for two weeks. She had also suffered two bouts of haemoptysis in quick succession. A history of myalgia and headache was present for 2 months. On clinical examination, mucosal ulcerations were found in the oral cavity and on the gums. The laboratory investigations revealed an elevated erythrocyte sedimentation rate and anaemia, and few active sediments were detected in the urine examination. A chest radiograph was done which showed large nodules distributed randomly in bilateral lungs.

Conventional tomography of the chest was done on a Siemens spiral scanner keeping a protocol of 5 mm section thickness. HRCT scans using Siemens algorithms were also performed taking 1 mm thickness scans through the upper, mid- and lower lung zones. Well-defined nodules ranging between 3 to 5 cm were seen in bilateral upper, mid- and lower zones in a random distribution. The walls of the nodules were thick and the margins irregular, with cavitation seen in the upper lobe lesions (Fig. 4 and 5). The surrounding parenchyma demonstrated interlobular interstitial thickening, and minimal left-sided pleural effusion was also present.

CT scan of the paranasal sinuses was performed for the persistent headache complained by the patient; and the axial sections revealed pansinusitis. In view of the pulmonary, renal, joint, and mucosal involvement, a diagnosis of Wegener's granulomatosis was made. A biopsy was performed from the gum lesions and the diagnosis of Wegener's granulomatosis was confirmed.

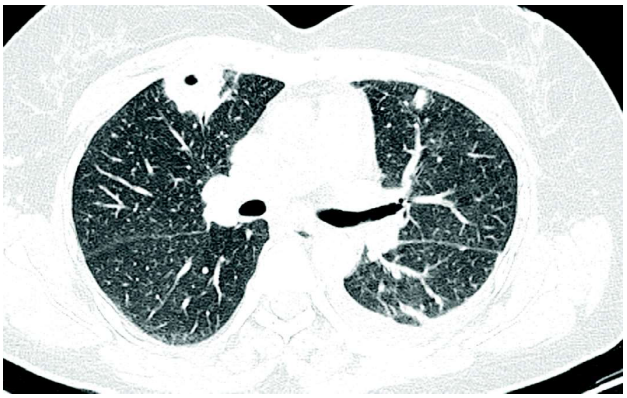


Fig. 4: *In this HRCT chest at the level of upper lobe, the axial image shows a cavitating thick-walled nodule in the anterior segment of the right upper lobe. Another smaller nodule is seen in the anterior segment of the left upper lobe.*

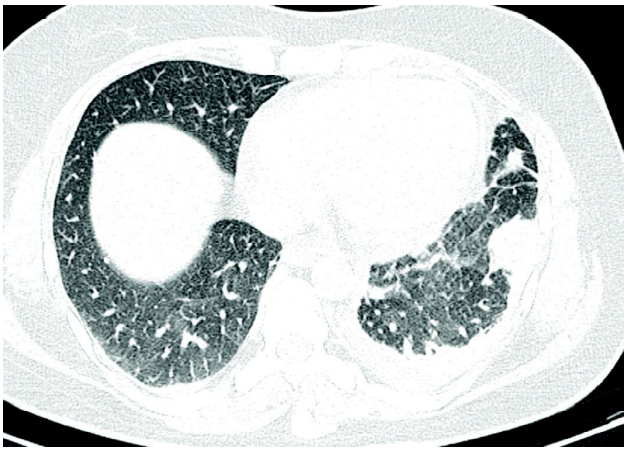


Fig. 5: *Axial HRCT image through the lower lung fields shows a small nodule in the anterior segment of left lower lobe and a subpleural larger, well-marginated nodule in the lateral segment of the left lower lobe. Interlobular septal thickening is seen surrounding the nodules. A small left pleural effusion can also be seen.*

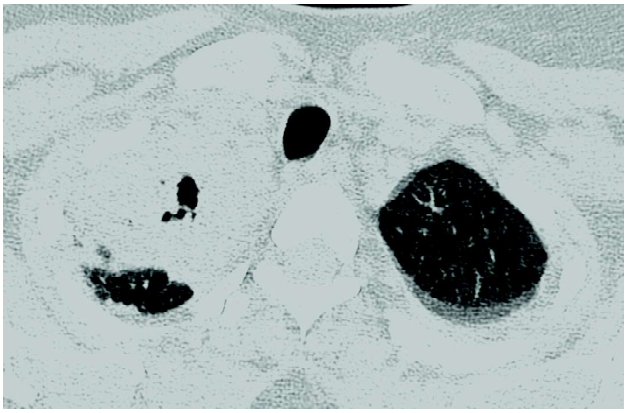


Fig. 6: *Axial image shows a large, well-marginated, cavitating nodule with thick walls in the apical segment of the right upper lobe with pleural thickening seen posteriorly.*

Discussion

The roentgenographic patterns obtained by CT scanning of the chest in Wegener's granulomatosis follow and trace the underlying histologic lesions of intraluminal fibrosis, alveolar haemorrhage, eosinophilic infiltrates, bronchiolitis, and acute or chronic and organising pneumonia[4]. Computed tomography therefore plays a major role in the diagnosis of this vascular disease which could otherwise be diagnosed accurately only by either biopsy demonstration of granulomatous inflammation and vasculitis in the tissues or by laboratory demonstration of antineutrophil cytoplasmic antibodies

by immunofluorescence. HRCT is useful for detecting the interstitial or ground glass opacities as well as the nodular opacities.

A radiologist is often the unsuspecting imagologist who views the chest radiograph or the CT images of a patient who may come with a clinical suspicion of Wegener's granulomatosis or merely for the investigation of haemoptysis or other upper airway symptoms. It is indeed possible to diagnose this uncommon disorder because of the specific imaging features seen on both conventional CT as well as HRCT. CT imaging can detect the disease even when the radiograph appears normal and of course in case opacities have been already detected in bilateral lung fields on the plain radiograph of the chest, their distribution and characterisation is possible with CT scanning. Moreover, CT has the advantage over biopsy of being noninvasive.

Due to the variable histologic lesions associated with Wegener's granulomatosis on biopsy, the CT images too reveal a spectrum of radiologic features. There may be multiple nodules, focal or diffuse areas of consolidation, a ground-glass appearance better appreciable on HRCT, or even an interstitial pattern of reticular densities[5].

The most frequent radiologically encountered pattern on axial CT images is of multiple, irregularly marginated nodules ranging from 2 to 20 in number and 2 to 10 cm in size seen as rounded opacities in bilateral lung fields[6]. Nodules which have a diameter greater than 2 cm are prone to cavitation. The cavities in the nodules may show thick, irregular walls or thin, smooth walls[7]. Bilateral lung involvement by these randomly distributed pulmonary nodules is the most typical radiological feature of Wegener's disease. Cavitation in these nodules is specially pathognomonic of Wegener's disease. A subpleural peripheral or bronchocentric distribution of the nodules in the lung parenchyma may also be seen[7,8]. These patients have severe respiratory symptoms.

Patients of Wegener's disease who develop pulmonary haemorrhage show a different radiological picture on axial CT images. These patients present commonly with haemoptysis and the axial images of chest show focal, patchy, or diffuse areas of alveolar opacificaion appreciated as ground-glass opacities or even in the form of consolidation with air bronchogram within[8]. These acinar opacities may show a subpleural distribution in the lung fields. When parenchymal consolidation is encountered in CT images, it has a non-specific appearance and can pose diagnostic difficulty with consolidation due to infection or drug-related alveolar damage. It is equally important to know that both nodular opacities and acinar opacities or consolidation can coexist in the same patient.

Yet another CT manifestation of Wegener's granulomatosis is an interstitial pattern of reticular opacities with a characteristic bronchocentric distribution, the underlying histology being cuffing around the lobar, segmental, or subsegmental bronchi[9]. This pattern is better appreciated on HRCT images. It has to be differentiated from other causes of interstitial lung involvement where fibrosis, bronchiectasis, etc., are usually the accompanying findings. A vasculitis sign has recently been described in Wegener's granulomatosis on axial HRCT images. This sign presents as a peripheral pulmonary artery much larger in size than the corresponding bronchus and having an irregular and stellate shape. The location of this artery has been described in the lower and posterior lung fields. When recognised alongwith acinar pulmonary parenchymal involvement, this sign is extremely useful in diagnosing Wegener's granulomatosis.

Hilar adenopathy is very rare in Wegener's disease, but can sometimes be encountered on CT images. Pleural disease in the form of small pleural effusions may coexist in some patients with the parenchymal opacities[6,8,9].

Tracheobronchial involvement also occurs with mural thickening and luminal narrowing and presents with stridor clinically. The site of tracheal involvement is the subglottic region in 90% cases. On CT images, subglottic stenosis is seen as distortion and irregularity of tracheal cartilage and should be specifically looked for. The ancillary features seen with trachedobronchial stenosis are areas of lobar or segmental atelectasis.

Conclusion

The four diagnostic criteria as specified by the American

College of Rheumatology for Wegener's disease are: the presence of an abnormal chest radiograph or abnormal CT images, an abnormal urinary sediment due to renal vascular involvement, cutaneous involvement in the form of oral ulcers, nasal discharge, skin macules, papules, or a rash; and the granulomatous inflammation demonstrated by tissue biopsy which is the fourth and final criteria which confirms the pulmonary form of the disease in patients with a history of haemoptysis. The presence of two of the four above-mentioned criteria has a diagnostic sensitivity of 87% and a specificity of 94%. In the limited form of the disease, there is absence of renal involvement and this is considered as early stage disease by some authors.

CT imaging helps in arriving at an early diagnosis by detecting the characteristic pulmonary lesion and follow-up scan can also be performed to assess the response to treatment. The role of CT has zoomed because of its ability to demonstrate the spectrum of radiological findings associated with Wegener's disease which cannot be visualised by the chest radiograph or any other imaging modality.

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