Hyperthyroidism in a Case of Down Syndrome

VA Londhey*, GC Rajadhyaksha**, KS Barhate***, AV More***, CR Dedhia***

Abstract
An 18 years old mentally retarded male, with morphologic features suggestive of Down syndrome was admitted with fever since 3 weeks. Karyotyping proved trisomy 21. Prominent thyroid swelling with resting tachycardia and hyper-irritability was present. He was found to have multiple renal abscesses and was treated with antibiotics. Thyroid function tests revealed hyperthyroidism which responded to anti-thyroid drugs. So, we report this case of Down syndrome with hyperthyroidism which is a rare association.

Case
An 18 years old mentally retarded male, was admitted with history of moderate grade fever with chills since 3 weeks. Fever was continuous (99-100°F) in nature not responding to antipyretics. It was associated with vomiting. There was no history of headache, cough, burning micturition, abdominal pain. Parents complained of hyperactivity and irritability with difficulty in sitting at one place. There was no past history of any other major medical illness. Patient had mongoloid features in the form of wide forehead, hypertelorism, up slanting eyes, epicanthic folds, low set ears, protruding lower jaw, hyperextensible joints, wide sandal gap and single palmar crease. (Figs. 1 and 2). Resting tachycardia (Pulse rate-104/min) with prominent thyroid swelling (Fig. 3) and staring look was noted.

On investigations, increased total WBC count (15,300 WBCs/mm³) with urinary tract infection (Urine routine showing 28-30 pus cells) was found. Urine culture did not grow any organism. Serum creatinine was 1.2 mg/dl. Ultrasonography (USG) of abdomen showed 3.7 X 3.2 cm abscess in midpole and 3.7 X 3.4 cm abscess in lower pole of right kidney suggestive of forming renal abscesses with subcapsular collection. Computed tomography (CT) of the abdomen revealed multiple right renal abscesses with subcapsular collection associated with mural thickening of right upper ureter. Mesenteric lymphadenopathy was noted. However, aspiration of the renal abscess was not possible.

USG of thyroid revealed mildly enlarged bilateral hemithyroids suggestive of goiter. Thyroid function tests showed presence of hyperthyroidism. Free T3 was 11.94 µIU/ml (Normal range:- 1.7-4.2 µIU/ml). Free T4 was 3.96 µIU/ml (Normal range: -0.7-1.8 µIU/ml). TSH was < 0.01 µIU/ml (Normal range:- 0.3-5.5 µIU/ml). 2-D Echocardiography showed visceroatrial situs solitus with thick myxomatous mitral valve with mild mitral regurgitation. Karyotyping was suggestive of Down syndrome (47XY, trisomy 21).

Patient was empirically treated with injection Ceftriaxone 1gm intravenously (IV) twice daily and injection Amikacin 500 mg IV once a day for 21 days. Repeat USG abdomen after course of antibiotics revealed complete resolution of renal abscesses. Patient was started on oral Carbimazole and Propranolol in view of hyperthyroidism. He was advised regular follow up with thyroid function tests.

Discussion
Down’s syndrome is one of the most common chromosomal disorders. Thyroid disorders are common in individuals with Down syndrome. Hyperthyroidism occurs much less frequently than hypothyroidism in this population, but is likely to be underestimated.1,2 The reported incidence of hyperthyroidism varies from 0.07-2.5 per cent. It rarely presents before eight years of age.2 The risk increases with increasing age.4

Thyroid hormones are important for the central nervous system, since they are concerned with neuronal migration and differentiation, activation of the sympathetic nervous system, synthesis and secretion of neurotransmitters, myelination, in addition to the regulation of the gene expression of neuronal
Myopathy presenting as a Sole Manifestation of Hypothyroidism


Abstract

Myopathy as the sole manifestation of hypothyroidism is rare although muscle weakness, aches and cramps, stiffness and delayed tendon jerk relaxation are the usual features of hypothyroid associated myopathy. We describe a patient with primary hypothyroidism, presenting solely with a clinical picture of myositis with very high levels of creatine phosphokinase (CPK), which normalised after 12 weeks of treatment with levothyroxine.

Introduction

Myopathy is characterized by muscle weakness, aches, cramps and stiffness with elevation of muscle enzymes. It may be associated with various clinical conditions, including endocrinopathies, electrolyte disturbances and certain drugs such as colchicine, antimalarials, cholesterol-lowering drugs, cocaine and alcohol.1 Hypothyroidism may manifest as muscle weakness with or without pain. The severity of hypothyroid myopathy ranges from an asymptomatic disease with elevation of muscle enzymes to a disease with prominent muscle weakness.23 Hypothyroid associated myopathy is seen in 30–80% of cases during the course of the disease, but myopathy as the sole manifestation of hypothyroidism is a rare presentation. We hereby present a case of 42 year old male with primary hypothyroidism with myopathy as the sole manifestation.

Case Report

A 42 yrs male presented with complaints of diffuse muscle aches, fatigue and generalized weakness for last 2 months. Patient had gradually progressive diffuse muscle aches and 1 week before presentation he could not attend his work and was forced to sit at home. The pain was severe and muscles were tender to touch. He also had gradually progressive fatigue and generalized weakness which increased after the days’ work. Patient took analgesics and Non steroidal anti inflammatory drugs without any relief.

There was no history of proximal, distal, pharyngeal, neck or ocular muscle involvement. There was no history of fever, cough, expectoration, joint pains, skin rash or ulcers. No history suggestive of hypothyroidism or hyperthyroidism was present. Patient was a non smoker and non alcoholic. There was no past history of any chronic drug intake or any other chronic illness. On physical examination his pulse was 86/min, BP was 120/70 mm Hg and weight was 55kg. Patient had grade 1 firm non tender goitre and generalized tenderness in all muscle groups. CNS examination revealed no objective evidence of proximal muscle weakness/ muscular atrophy/hypertrophy but had delayed relaxation of the ankle jerk. Rest of the systemic and general examination was within normal limits.

Investigations revealed Hb 16.4 gm%, TLC 6600 cells/mm3, platelet count 231000 cells/mm3, ESR 21 mm1st hr, blood urea 12 mg/dl, serum sodium 134 meq/dl, serum potassium 4.5 meq/dl, serum calcium 9.1 mg/dl, fasting blood glucose 80 mg/dl, LFT and urine – R/M was within normal limits, total cholesterol 374 mg/dl, triglycerides 292mg/dl, LDL 273 mg/dl and HDL 43mg/dl. Muscle enzymes were markedly raised—CPK – total 15134U/L (35-232). Total T3 20.2 ng/dl (60-181), Total T4 0.8 µg/dl (4.5-12.6),

References

The prevalence of hypothyroidism in patients with myopathy is difficult to study but in a study group among 53 patients with acquired muscle diseases the incidence of hypothyroidism was found to be 5.6 per cent. In patients with myopathy is difficult to study but in a study group among 53 patients with acquired muscle diseases the incidence of hypothyroidism was found to be 5.6 per cent. Severe pain is usually not a major problem in hypothyroid myopathy but if present may be worsened in cold weather. Morbidity is significantly increased, reflected in the performance of activities of daily living and in patients’ quality of life. Symptoms in our patient had also aggravated in the month of January (Cold season in Delhi) and his daily activities were significantly affected.

Other muscle features in hypothyroidism include Carpal tunnel syndrome, Hoffmann’s syndrome (adults), Debre and Semelaigne’s syndrome (infants), pseudomyotonia, muscle cramps (pseudo-tetany), wasting, myokymia (related to a low sodium level) and delayed relaxation of the deep tendon reflexes which may be seen in 85% of the patients. Muscle involvement may be caused by (1) changes in muscle fibres from fast twitching type II to slow twitching type I fibres, (2) deposition of glycosaminoglycans, (3) poor contractility of actin–myosin units, (4) low myosin ATPase activity, (5) low ATP turnover in skeletal muscle, (6) an autoimmune reaction causing chronic thyroiditis, hypothyroidism, and polymyositis, (7) or an involvement of the muscle membrane.

Hypothyroidism induced myopathy is usually associated with modest elevation of serum CK levels ranging from 2 to 6 fold though marked elevation up to the range of 20,000-25,000 U/L may be seen. The serum enzymes may rise to very high levels, presumably because thyroid deficiency permits leakage across muscle membranes and possibly due to actual muscle necrosis. In our case the patient had very high levels of CPK-15134 U/L and high levels of TSH (>150) which reversed after LT4 replacement. The elevation of CPK correlates well with the severity of hypothyroidism. However, the increased enzymes or the severity of hypothyroidism has no correlation with muscle weakness as seen in our case that had very high levels of CPK and severe hypothyroidism but no objective signs of muscle weakness. The deranged lipid profile in our case may be ascribed secondary to hypothyroidism.

Treatment of myopathy associated with hypothyroidism is levothyroxine replacement. Myopathy improves within 2-3 weeks, but may take months to resolve completely. The pattern of improvement in our patient followed a similar course with complete improvement in approximately 12 weeks.

Hypothyroid myopathy is an uncommon sole presentation of hypothyroidism, which responds to levothyroxine and hypothyroidism should always be considered in the differential diagnosis of patients presenting with myopathic complaints even in the absence of demonstrable muscle weakness.

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**Monocular Blindness during therapy for Cerebral Neurocysticercosis**


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**Abstract**

Neurocysticercosis is endemic in India, cerebral and ocular manifestations being common. A 32 yr old man on treatment with Albendazole for cerebral neurocysticercosis for 10 days presented with 3 days of painful uniocular blindness. He had only light perception in the left eye, left pupil was non-reactive to light and left disc was edematous. B-scan of eye revealed retinal detachment due to sub retinal cyst and CT brain showed multiple parenchymal cysticerci. The natural history of ocular neurocysticercosis or enhanced sub-retinal inflammation due to Albendazole therapy could have resulted in the retinal detachment in this case.

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**Introduction**

T.solium , the pork tapeworm, is endemic in many developing countries, its larval form (cysticerci) being an important cause
Symptoms usually result from CNS or ocular cysticerci. The immune response of the host, ranging from immune tolerance to intense immune reaction, accounts for the varied clinical presentations.

**Case Report**

A 32yr old male patient presented to us with 3 days history of painful loss of vision in the left eye. Over the previous two weeks he had had 2 episodes of left sided simple partial seizures progressing to generalized seizures. He had been started on albendazole (400 mg) twice daily, with prednisolone 40 mg daily for the previous 2 weeks. Clinical examination revealed him to have only light perception at 1 foot distance, with absent pupillary reaction in left eye. Eye movements were full and painless. Disc was edematous on the left. The rest of the neurological examination was normal.

CT scan brain revealed multiple cortical hypo-dense lesions up to 1 cm in size, some with peripheral enhancement. B-scan of the eye showed sub-retinal cyst with retinal detachment (Fig. 1). No cysts were seen elsewhere in the eye. Routine biochemical and hematological tests were normal.

Albendazole was discontinued and patient was given intravenous dexamethasone 4 mg every six hours, along with oral antiepileptic medications. Surgical removal of the cyst was undertaken after 6 days.

**Discussion**

Tinea solium the pork tapeworm is endemic in most developing countries. Symptoms and signs usually result from parasite located in the nervous system or the eye. Consistently one third of seizure cases in the community are associated with NCC after subtracting background seroprevalence or asymptomatic calcifications in controls. Clinical manifestations are varied, epilepsy being present in 52% cases. Clinical pleomorphism is related to variability in number and topography of lesions and individual immune response to the parasite. Ocular cysticercosis may be associated with progressive decrease in visual acuity, related either to presence of parasite in eye or an acute inflammatory reaction causing vitreous uveitis or endophthalmitis.

This case demonstrates the occasionally malignant nature of neurocysticercosis and consequences of its treatment. Treatment options in NCC are determined by the location of the NCC as well as its evolutionary stage. Anthelmintic treatment significantly improves resolution of active parenchymal cysticerci provided they are few in number. Its beneficial effect on seizure outcome in ocular cysticercosis is less certain. A meta-analysis of 4 small clinical trials addressing the effect of albendazole on seizure outcome in 1-2 brain lesions due to parenchymal NCC, showed that 14% of treated subjects had seizures in the follow up period of 6-15 months (p<0.001 or 0.36- 95% CI : 0.21-0.62).

Albendazole therapy may cause worsening of some symptoms acutely due to death of organism and the consequent inflammatory reaction. These symptoms may be especially marked in the eye due to the restricted space. The administration of corticosteroids concomitantly with albendazole is presumed to reduce the incidence of adverse effects due to anti-inflammatory action. Three clinical trials have shown benefit in terms of clinical and radiological improvement over 6-9 months, with the addition of oral prednisolone (1 mg/kg /day x 10 days) or intravenous methylprednisolone (1 gm/day x 5 day).

Ocular cysticerci may locate in the vitreous cavity or subretinal areas. Albendazole has been shown to have cysticidal properties in ocular cysticercosis. After treatment with albendazole and dexamethasone subretinal cyst are reduced to a small chorioretinal scar, whereas cysts in the vitreous cavity are killed and once immobile, are easily surgically extracted.

Retinal detachment in ocular cysticercosis, as occurred in the present case, could be due to the natural history of the disease; or due to the inflammation being marked following Albendazole therapy. Literature search yielded data on concomitant ocular complications in cerebral neurocysticercosis, on cysticidal therapy, in a similar case reported by Rao, Vargiya et al.

**Conclusion**

Occult Subretinal cysticercosis may coexist with a manifest cerebral parenchymal neurocysticercosis. Screening of the eye with B-scan to check for ocular cysticercosis before embarking on anthelmintic therapy would be advisable to prevent ocular complications due to therapy.

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Post Varicella Angiopathy

CJ Selvakumar, C Justin, TR Gnaneswaran, M Chandrasekaran

Abstract
Varicella zoster vasculopathy is a rare complication of chicken pox. Varicella cerebellitis, a post or para-infectious condition, is a common sequela of chicken pox. Varicella angiopathy presents as acute hemiparesis, aphasia, hemianaesthesia or other focal neurologic or retinal deficits associated with mononuclear pleocytosis and VZV specific antibodies in CSF. Varicella angiopathy affecting the posterior circulation is very rare. We report a 15 yr old boy with progressive neurologic deficits over a month following a chicken pox 3 months prior to the onset of symptoms. On investigation he had infarcts both in the anterior and posterior circulation territories in CT and MRI with mononuclear pleocytosis in CSF elevated IgG and IgM in CSF. He was treated with intravenous acyclovir and corticosteroids.

Introduction
Varicella zoster virus or herpes virus – 3 is an alpha herpes virus belonging to herpesviridae family was isolated in 1958. 90% cases occur in children under 13. Incubation period is 2 weeks (10-20days). After primary infection VZV becomes latent in dorsal root ganglia. Reactivation appears clinically as herpes zoster (shingles) which can affect all people especially elderly and immunocompromised. Chicken pox can lead on to varieties of complications, but recurrence of stroke and involvement of posterior circulation is very rare. We present here a case of post chicken pox vasculopathy affecting both anterior and posterior circulation.

Case History
15 year old male patient had chicken pox infection and recovered over 15 days. After that patient was perfectly normal. 2 months later he developed giddiness, vomiting and developed weakness of the left upper and lower limbs. There was head nodding and swaying to the left side while walking. After 15 days he suddenly developed weakness of right upper and lower limbs with aphasia. No history of bowel, bladder, sensory and cranial nerve involvement. On examination vitals were stable. He was conscious, aphasic with bilateral cerebellar signs. Both right and left hemiplegia was present.

His blood sugar, urea, creatinine, homocysteine levels, coagulation profiles were normal. TC, DC, Hb, platelet count were normal with ESR-25mm/Hr. ANA and APLA, HIV, VDRL were negative. CSF study – glucose-88mg/dl, protein- 35mg/dl, globulin negative, cell count- 1-3 lymphocytes/HPF. AntiVZV IgM and AntiVZV IgG levels were raised in CSF. X-ray chest, ECG and ECHO were normal. MRI brain which was done earlier revealed ill defined lesion involving major part of left cerebellum and vermis which was iso to hyperintense in T1 and hyperintense in T2 and FLAIR sequences [Figure 1]. T1 contrast showed heterogenous enhancement of left cerebellar lesion with hypointensity noted in superior cerebellum. MRA-
Varicella zoster virus, the cause of chickenpox and shingles, has been associated with several neurologic conditions including acute ataxia, myelitis, stroke, post herpetic neuralgia, Bell’s palsy, Ramsay-Hunt syndrome, aseptic meningitis, encephalitis, congenital varicella syndrome and Reye’s syndrome. Less than 0.1% of otherwise healthy children with chickenpox experience neurologic complications. Varicella-associated arterial ischaemic stroke accounts for nearly one third of childhood ischaemic stroke. Acute cerebellar ataxia, the most common complication begins approximately 10 days after the onset of the rash. Varicella encephalitis usually appears 3-7 days after the onset of the rash and produces headache, fever, seizures, coma or paralysis. Stroke and herpes zoster ophthalmicus has been reported after chickenpox. Usually occurring within 2-10 weeks of Varicella zoster infection these disorders are characterized by headache, acute hemiparesis, hemianesthesia, aphasia or other focal neurologic or retinal deficits and seizures. Hemiparesis can occur after a delay of 1 week to 12 months. Basal ganglia infarcts, infarcts in the anterior circulation and very rarely posterior circulation are reported. An entirely different type of delayed vasculitis that affects small vessels is being reported in patient with AIDS and other forms of immunosuppression. Delayed hemiparesis following intrauterine Varicella exposure has been reported in a 17 month old baby. Rare complication of stroke seen after Varicella infection is not seen after vaccination with live attenuated Varicella vaccine.

The underlying mechanism for Varicella causing arterial ischemic stroke is not known. Multiple mechanisms have been suggested. VZV vasculopathy is caused by chronic active virus infection in cerebral arteries. At autopsy there was granulomatous angiitis of the large vessels and electron microscopy revealed virus like particles in the outer layer of the vessel walls but not the endothelium. The most plausible mechanism involves intraneuronal migration of the VZV from the trigeminal ganglion along the trigeminal nerve to the cerebral arteries. Defective anticoagulant mechanism and low levels of protein C and S have been documented. Autoantibody mediated protein S deficiency, anticaldilipin antibody and post varicella vasculitis may also occur.

CSF shows a lymphocytic pleocytosis and elevated protein content. Diagnosis can be made by PCR demonstration of VZV DNA in CSF or by demonstration of VZV immunoglobulin M (IgM) or intra thecal synthesis of VZV immunoglobulin G (IgG) in CSF. There will be reduced serum – CSF VZV IgG ratio (compared with normally high ratios of total IgG and albumin). MRI or CT brain shows a large single infarct most commonly in the internal carotid, middle cerebral and anterior cerebral artery territories and rarely in the posterior circulation. In immunocompromised individuals VZV reactivation produces a multifocal vasculopathy with involvement predominantly of small and medium sized arteries. Neuroimaging shows multifocal hemorrhagic and ischaemic cortical and subcortical infarcts. Autopsy reveals viral particles, antigen and DNA in the involved artery. Cerebral angiography revealed focal stenosis of proximal portions of major cerebral arteries.

Rash or CSF pleocytosis is not required to diagnose VZV vasculopathy whereas MRI/CT abnormalities will be seen in all patients. Detection of anti VZV IgG antibody in CSF is a more sensitive indicator of VZV vasculopathy than detection of VZV DNA.

Our case developed ischaemic stroke 2 months after chickenpox in anterior and posterior circulation. He developed a recurrent stroke on the opposite side within 15 days. CSF studies confirmed Varicella zoster infection and MRI/CT showed infarcts in the anterior and posterior circulation.

Patients with VZV CNS vasculopathy should receive a combination of intravenous acyclovir 30mg/kg/day in three divided doses as infusion over 1 hour for a minimum of 7-14 days combined with Prednisone 60-80 mg/day for 3-5 days. Long term therapy with aspirin has been suggested for secondary prevention. More effective but potentially less safe treatment with warfarin or LMWH should be reserved for children in whom stroke recurs while on aspirin until these treatments have been studied in clinical trials.

Although mortality is low and morbidity is high, outcome of varicella related stroke in children seem to be more favourable than the outcome in adults.

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Early Posttransplant Erythrocytosis in Renal Allograft Recipients

Jai Prakash†, Shivendra Singh‡, Sanjeev Kumar Behura§, Biplab Ghosh∥, LK Sharatchandra¶, US Dwivedi**

Abstract

Posttransplant erythrocytosis (PTE) is defined as a persistently elevated hematocrit to a level greater than 51% after renal transplantation. It usually develops 8 to 24 months after transplantation. We report occurrence of PTE in two male renal allograft recipients within first 8 months of transplantation.

Introduction

Renal transplantation, the preferred form of renal replacement therapy, is associated with certain hematological complication in the post transplant period. Anemia, Hemolytic uremic syndrome (HUS), Posttransplant erythrocytosis (PTE), Leucopenia, Thrombocytopenia and Hemophagocytic syndrome are some of the hematological complications in the renal transplant patients besides transplant renal artery stenosis.1 Although various authors have used different values of hematocrit (50% to 54%) to define PTE, most agree that a persistently elevated level of hematocrit more than 51% suffice to define PTE. PTE is known to occur in allograft recipients with good graft function, mostly after 8 months following transplantation and in patients who required minimal iron and EPO therapy to maintain adequate hemoglobin level in pretransplant period.2 It occurs in 10% to 15% of graft recipient, varying from as low as 2.5% to as high as 22.2%.2

Case Presentation

Case 1

A 20 year male presented in Nov 2007 with progressive generalized swelling for last 5 months along with clinical features of severe renal failure. He was given two session of hemodialysis for control of uremic symptoms. In view of normal sized kidney on sonography and presence of active urinary sediment, a kidney biopsy was done. Serological tests revealed ANA and dsDNA to be positive. Biopsy showed features of WHO class IV lupus nephritis with both active and chronic changes. Three pulse of methylprednisolone (500 mg IV) was given followed by pulse cyclophosphamide and oral prednisolone. Cyclophosphamide was later replaced by mycophenolate mofetil (MMF), in view of cyclophosphamide toxicity. Despite immunosuppressive therapy patient went into ESRD over next 5 months. Maintenance hemodialysis was started and continued till transplant. He was noted to have severe anemia (3.8gm/dl) and 2 units of blood was transfused in pretransplant period. Erythropoietin (EPO) and iron therapy was given as per need in standard doses. Patient was worked up for renal transplant with patient’s mother as prospective donor. HLA typing showed 1 mismatch at A, B and DR locus and cross match was negative. Both donor and recipient were IgG positive and IgM negative for CMV. Live renal allograft transplantation was done on 22/8/08. Two units of blood were transfused during the surgery. He was put on triple immunosuppression with steroid, MMF and cyclosporine. Post operative period was uneventful. At discharge patient had a good urine output (UO – 4 to 5L/day), BP of 126/86 mm of Hg (on Nifedipine and Metoprolol), Hemoglobin (Hb)- 11.1gm/dl and serum creatinine of 0.94 mg/dl. Patient was followed up in transplant OPD twice weekly. During the first three months of follow up, he maintained UO (4-5L/day); compliance with medication was good; and gradual improvement in Hb. level (13.6gm/dl ).He did not have any acute rejection episode. However, patient developed features of steroid toxicity (moon facies, acne) and hence steroid dose was reduced to 10mg/day. In Nov 2008, 3 months after transplant he was noticed to have a flushed face and suffused conjunctiva. His Hb. was 16.7gm/dl. Color Doppler study did not reveal evidence of transplant renal artery stenosis. On the basis of elevated hematocrit diagnosis of PTE was made. He was started on Theophylline 300mg/OD in view of progressive erythrocytosis (Hb.-17.9gm/dl). However 2 weeks later his Hb. was 18.5 gm/dl and Angiotensin converting enzyme inhibitor (ACEi) Ramipril 5mg /OD was added. In spite of this his Hb. level was 19.5 gm/dl. Theophylline added; ACEi started; Phlebotomy done.

Table 1: Serial Hemoglobin and Creatinine level for case 1 (Date of Tx - 22/08/08)

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†Theophylline added; ‡ACEi started; ‡Phlebotomy done.

*Professor and Head, Dept. of Nephrology, **Lecturer, Dept. of Nephrology, ***Senior resident, Dept. of Nephrology, ****Reader, Dept. of Urology, Institute of Medical Science, Banaras Hindu University, Varanasi 221005, INDIA

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Table 2: Serial hemoglobin and creatinine level of case 2 (Date of Tx - 11/04/08)

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</table>

1Phlebotomy done and ACEI started

of these measures, a week later, patients Hb. level was noted to be 19.5 gm/dl (Hematocrit - 58%); patient was advised phlebotomy. One unit of blood was removed. ACEI and theophylline was continued. Patient is on weekly follow up. Hemoglobin concentration decreased to 16gm/dl, 2 months after starting the combination of ACEI and theophylline. His current hemoglobin at last follow up was 16.8 gm/dl with serum creatinine of 1.05 mg/dl (Table 1).

Case 2

A 24 year male presented in Feb. 08 with complaints of swelling of body, breathlessness, and loss of appetite for 2 months. Patient had received 1 unit of blood transfusion outside in view of severe anemia. On examination he had severe anemia and blood pressure was 200/100 mm Hg. Ultrasound scan showed small contracted kidney. Patient was diagnosed to have ESRD of uncertain etiology. Maintenance hemodialysis was started. Transferrin saturation was 7%. IV iron (1000mg) was given and EPO therapy started. Anti-hypertensive was adjusted (Nifedipine, Clonidine, Prazopress, and Atenolol) to achieve adequate blood pressure control. Pre-transplant work up started with mother as prospective donor. HLA typing showed 1 mismatch at A locus and no mismatch in B and DR locus. Cross match was negative. Both donor and recipient were IgG positive and IgM negative for CMV. Pretransplant hemoglobin ranged around 6 – 7 gm/dl. Live related renal transplant was done on 11/4/08 with his mother as kidney donor. Two units of blood was transfused during surgery. Total ischemia time was 55 minutes. Immediate post operative period was complicated by development of P. falciparum malaria and pneumonia, which responded to appropriate treatment.

Triple immunosuppression with azathioprine, steroid and cyclosporine was started. Cyclosporine dose was reduced on POD 6 in view of suspected cyclosporine toxicity (progressive rise in serum creatinine). Following reduction in dose of cyclosporine serum creatinine settled. Patient was discharged on POD 16 in stable condition. At discharge, serum creatinine was 1.46mg/dl, Hb. of 7.4gm/dl and UO was 3 to 4L/day. At 10 days of follow up, creatinine was 2.02 mg/dl with urine showing 15-30 RBC/hpf and 10-15 WBC/hpf. Clinical diagnosis of acute rejection was made and he was given 500 mg methyl prednisolone IV for 3 consecutive days. Creatinine settled to 1.92 mg/dl. Tacrolimus was added replacing cyclosporine. Creatinine remained stable at 1.5-1.6 mg/dl over next 3 months.

Six months following transplant, patient was noted to have a rise in creatinine again. He was given 3 doses of methyl prednisolone assuming diagnosis of acute allograft rejection. Color Doppler study revealed minimal fluid collection on both upper and lower pole of graft kidney. There was no evidence of transplant renal artery stenosis. Azathioprine, steroid and tacrolimus was continued. S. creatinine settled to 1.55 mg/dl. Eight months posttransplant, patient gave history of headache and tinnitus. His BP was 126/86 mm Hg. and Hb was 18.5gm/dl. Diagnosis of PTE was made on the basis of rising hematocrit. One unit of blood letting was done and he was started on Ramipril 2.5 mg/OD. Hemoglobin dropped to 16.7gm/dl, 2 weeks after the start of Ramipril (2.5mg/day). He is continuing on Ramipril and hemoglobin was 13.5 gm/dl with serum creatinine of 1.69 mg/dl at last follow up (Table 2).

Discussion

Prevalence of posttransplant erythrocytosis is 10-15 % in graft recipient and usually develops 8 to 24 months after engraftment. The pathogenesis of PTE still remains to be elucidated completely. At least three hormonal systems are implicated in the development and propagation of PTE: Erythropoietin, Renin angiotensin system (RAS) and endogenous Androgens. EPO, the major promoter of erythropoiesis is secreted from cells present in the peritubular area of kidney. An inappropriately excessive production of EPO from native and transplanted kidney leads to increased erythropoiesis. Also the normal negative feedback balance between EPO production and hematocrit is disturbed in PTE. RAS system has been implicated in development of PTE. Angiotensin II is known to activate AT1 receptors present on erythroid progenitors leading to enhanced erythropoiesis. Androgens also cause a dose dependent direct stimulation of erythroid progenitors that have already been differentiated by erythropoietin. Androgens can even promote erythropoiesis indirectly via stimulatory effect on endogenous erythropoietin or via RAS activation. Insulin-like growth factor binding protein – 1 (IGFBP-1) is noted to be increased in patients with Polycythemia Vera and this has shown to stimulate erythroid burst formation. Transplant recipients with PTE are noted to have elevated IGFBP1 compared to those recipients with normal hematocrit, suggesting a role of IGFBP 1 in PTE.

Both the above cases had some peculiarities which were slightly different from conventional cases of PTE. It usually occurs after 8 – 24 months post transplant. However, both our patients developed PTE at a very early period. Early development of PTE has been noted by Quinibi et al and can occur as early as 1 to 2 months post transplant. Patients prone to develop PTE are those who have had least requirement of iron, EPO, or blood products in pre transplant period. In contrast both our patients were severely anemic requiring blood transfusion. Although case 1 had a good graft function from the very beginning in the posttransplant period, case 2 had a slow graft recovery and also had two documented episodes of acute rejection. Episodes of acute rejection and poor graft function are known to cause fall in hemoglobin concentration. However, in spite of acute rejection and poor graft function, case 2 continued to have rise in hemoglobin and was symptomatic because of severe erythrocytosis. Quinibi et al had also documented PTE in posttransplant patients with a serum creatinine as high as 2.4 mg/dl and with two rejection episodes. Male gender and young age are known risk factor for development of PTE. More than 80% of patients with PTE reported in American studies in the mid -1990s were males. Both our patients were male and below...
Bone Mineral Disorder Resulting from Secondary Distal Renal Tubular Acidosis due to Overlap Syndrome (Mixed Connective Tissue Disorder) Associated with Coronary Artery Disease

SM Yeli*, Vinay Yeli**, Tittu Oommen***, Rajaneesh Mittal†

Abstract
A 35 year old female presented with chronic bone mineral disorder which was due to secondary renal tubular acidosis – type 1 (RTA₁). Serologically there was definite evidence of overlap syndrome (mixed connective tissue disease – M.C.T.D.), which was the cause for RTA₁. During hospitalization she developed coronary artery thrombosis.

Introduction
Bone mineral disorder with renal rickets and Osteomalacia is reported as presenting feature resulting from renal tubular acidosis Type – I (RTA₁). Renal tubular acidosis is a disorder of renal tubular acidification characterized by hyperchloremic acidosis, hypokalemia and inability to lower urinary pH below 5.5. In this disorder distal nephron does not lower urine pH either because of collecting duct permits back diffusion of hydrogen ion from lumen to blood or because of inadequate transport of hydrogen ions. Chronic acidosis lowers tubular absorption of calcium causing renal hypercalciuria and mild secondary hyperparathyroidism. In adults bone marrow disorder with Osteomalacia occurs because of acidosis induced loss of bone material and inadequate production of 1,25-dihydroxy vitamin D₃. Majority cases of secondary type-1-RTA result form Sjogren’s syndrome, SLE which are part of overlap syndrome. In these cases there is interstitial nephritis resulting in tubular dysfunction with defective ‘H⁺’ ion secretion and distal renal tubular acidosis.

Overlap syndrome (MCTD) is a clinical feature of Sjogren’s syndrome, SLE, Systemic Sclerosis, Polymyositis, Rheumatoid arthritis and is having high titer of circulating antibodies to nuclear RNP – anti U, RNP. There could be predominant vasculitis other than features of underlying disorder.

A case of bone mineral disorder with Osteomalacia following secondary Type 1 Renal tubular acidosis with Overlap syndrome, which manifests as acute coronary artery disease is discussed.

Case Report
A 35 year old female presented with generalized weakness, body pain, joint pain and difficulty in walking.

On examination – she had chest deformity – pelvic and leg deformity. Bones, joints, muscles were mildly tender and there was a wound in gluteal cleft. Deep tendon reflexes were showing...
hyporeflexia and there was epigastric tenderness. Two days after admission as she had myocardial ischemic chest pain, she was shifted to ICU and at that time there was mild tachycardia, maintaining normal blood pressure – i.e., 110/70 mm Hg and there were few respiratory rhonchi and crepitations.

### Investigations

Total WBC 15,200/mm³. P-72%, L-23%, M-5%, ESR: 23mm/hour. Platelets 436/mm³, Hb – 10.7 gm%, Peripheral blood picture – Normocytic hypochromic. Urine: Albumin – Traces, 20-25 RBCs/HPF on one occasion later it was normal. Urine pH 7.5. Urine calcium 181.7 mg/dl (Normal 100-320 mg/dl), 24 hour urine protein 743 mg (Normal upto 150mg), urine phosphorous 211.6 mg/dl (Normal 400-1300). Stool exam – occult blood test was positive on one time, later it was normal. Fasting blood sugar 100 mg%, Blood Urea 21 mg%, S. Creatinine 1.2 mg%, S. Total cholesterol 110mg%, S. Triglycerides 74 mg%, S. HDL Cholesterol 30 mg%, S. LDL Cholesterol 50mg%, S. LDH 156.0 U/L, S. CPK 79 U/L, SGOT 14 U/L, S. Calcium – Varied from 7.9 to 8.7 mg%, S. Phosphorus 2.7mg%, S. Alkaline phosphatase 417 U/L, S. Sodium 137.2 mmol/L, S. Potassium 2.7mm/L, S. Chloride 112 mmol/L, Liver function test – Normal, Except – Mild Hypoalbuminemia 3.0 gm%, and mild increase in alkaline phosphatase 148.0 U/L. Thyroid function tests – Normal. (Tests done prior to present admission)

ANA +++, Rheumatoid factor 588.9 U/ml (N<20U/ml)- 30-6-2003 done prior to present admission) Ab to JO -1 +, RNP/SM +, SSA ++, SS –B+; - 2.7.2003


- X-ray chest – Lungs and cardia – normal. All bones were osteoporotic with few areas of sclerosis. There were multiple fractures of various ages of – ribs, humerii, clavicles and scapulae.
- Ba swallow screening – normal with normal transit time. X-ray fractures of various ages of – ribs, humerii, clavicles and scapulae.

Bone density test was suggestive of osteoporosis.

Abd. USG – Normal.

ECG – Non Q wave myocardial infarction.

**ABG – Study**

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### Management

**A. For bone mineral disorder and renal tubular acidosis** – Tab. Calcium 500mg tid, Tab. Calcitriol 0.25 µg or Intramuscular Vit. D₃ – 3 lacs – when she was unable to take orally. Potassium 40-60 mEq, Sod. bicarbonate 2-3 gms 8th hourly /day. Protein supplements

**B. For coronary artery disease in I.C.C.U.**

Inj. Heparin 25000 units in saline for 24 hour – then 5000 units IV twice a day for 5 days. Tab. Clodigorel 75 mg and Aspirin 150mg daily – continued further. Tab. Isosoribide dinitrate 10mg 8th hourly – continued. Inj. Cefotaxime 1gm IV – twice a day for 7 days for respiratory infection.

### Discussion

Rickets in children, and Osteomalacia in adults are bone mineral disorders in which mineralization of organic matrix of the skeleton is defective. These disorders are caused by a number of different conditions associated with Vitamin D deficiency or resistance. Large numbers of disorders are associated with bone mineral disorder – Osteomalacia, primarily through alterations of Vit. D nutrition or metabolism or because of phosphate wasting. Thus it could be due to chronic tubular acidosis. Renal tubular acidosis is a disorder of renal tubular acidification out of proportion to the reduction in filtration rate. Distal renal tubular acidosis- RTA-1 is characterized by hyperchloremic metabolic acidosis with normal serum anion gap, inappropriately high urinary pH and nephrocalcinosis. In RTA, distal nephron does not lower urine pH normally, either because of collecting ducts permit excessive back diffusion of hydrogen ions from lumen to blood or because of there is inadequate transport of H⁺ ions. Excretion of tubule acid and ammonia is low. Potassium conservation tends to be impaired.

Pathophysiological abnormality includes impaired H⁺ ions secretion by distal nephron leading to reduced acidification of urine and defect in H⁺ ATPase and H⁺ K⁺ ATPase. Hypocitraturia occurs due to increased absorption facilitated by acidosis and hypokalemia. Hypokalemia is caused by defect in H⁺ K⁺ ATPase and secondary hyperaldosteronism due to sodium loss in urine. Chronic metabolic acidosis induces inadequate production of 1, 25 dihydroxy Vit. D₃ and loss of bone material leading on to bone mineral disorder – Rickets and Osteomalacia.

Our present case with bone mineral disorder had high urinary pH, hyperchloremic metabolic acidosis, near normal anion gap, hypokalemia, hypocalcaemia and features of Osteomalacia. However there was no nephrocalcinosis and hypercalcuria.

Overlap syndrome is mixed connective tissue disease characterized by features of Systemic Lupus Erythematosus (SLE), Systemic Sclerosis, Polymyositis, Rheumatoid arthritis and could be associated with Sjogren’s syndrome and presence of high titer of circulating antibodies to nuclear RNP antigen. About 25% develop renal disease of all types – including, tubule interstitial disease presenting as renal tubular acidosis.

Overlap syndrome (MCTD) can present with coronary artery disease.45 Coronary arteries are frequently involved in systemic arteritis. Inflammatory infiltrate damages the intima and may trigger the occurrence of coronary artery thrombosis.

In present case though there were no obvious clinical features of overlap syndrome (MCTD), there was definite serologic evidence of it (MCTD). Antibodies detected were – ANA strongly positive, Abs to SS – A (RO), SS-B (LA), RO – S2 – were positive. Rheumatoid factor – positive, JO – 1 positive and RNP/SM was positive though not in high titers as expected.

This case is being presented manifesting predominantly with...
bone mineral disorder – Osteomalacia caused by renal tubular acidosis RTA, due to overlap syndrome – (Mixed connective tissue disease) evidenced by positive serological tests and this was associated with coronary artery vasculitis and thrombosis. This case was being managed as mentioned in case report, she was showing signs of improvement clinically and by laboratory evidence. However she was lost for further follow up.

References

Sweet’s Syndrome with Subacute Intestinal Obstruction

MVRJ Somayajulu, G Raghu Rama Rao, A Amareswar, N Ramkoteswar Rao

Abstract
A 48 year old woman presented with high grade fever, arthralgia and multiple tender papules and plaques over the face, neck, back, arms and forearms with distension of abdomen. Investigations revealed leukocytosis with neutrophilia, high ESR and increased C-reactive protein. Skin biopsy showed neutrophilic infiltration in the dermis. Plain x-ray abdomen is suggestive of subacute intestinal obstruction. We report this case of classic Sweet’s syndrome with uncommon presentation.

Introduction
Sweet’s syndrome (the eponym for Acute Febrile Neutrophilic Dermatosis) was first described by R.B.Sweet in 1964 is characterized by sudden onset of fever, leukocytosis and cutaneous eruptions. The eruption consists of tender, erythematous, well demarcated papules and plaques which show dense neutrophilic infiltrates microscopically. The lesions may appear anywhere, but favour the upper body including the face. Extra cutaneous manifestations of Sweet’s syndrome like conjunctivitis, episcleritis, arthritis, osteomyelitis, tenosynovitis, tendinitis, alveolitis, renal, hepatic and central nervous system involvement have been reported. Neuropathilic infiltration of intestines, ileum and colon can also occur in Sweet’s syndrome. Sweet’s syndrome may present as a paraneoplastic syndrome with acute leukemias and other myeloproliferative disorders. The condition is more common in women and the mean age of onset is the mid to late fifties. Recurrence is a common feature. Though Sweet’s syndrome has been described very well in the standard text books, but very few cases have been reported from India. We report a rare case of Sweet’s syndrome with subacute intestinal obstruction.

Case Report
A 48 year house wife was admitted with high grade fever, arthralgia, multiple skin lesions with abdominal distension. The present complaint started ten days ago with irregular fever and constipation for which she was given antibiotic and laxatives with temporary response. She is non-diabetic, non-hypertensive, had no past history of chronic diarrhea or any other GI disturbances. There was no history of drug intake for any ailment in the recent past. On examination, the patient was acutely ill with body temperature of 103°F, BP 130/90 mm Hg, PR 100/min, and RR 20/min. The patient was conscious and coherent. There were multiple, erythematous, tender papules arranged in groups and arcuate fashion and also tender plaques over the face, neck, chest, back, arms and forearms (Figs. 1, 2). There were no lesions over the abdomen, thighs, legs, palms and soles. Some of the papules were shiny and clinically appear as vesicles (pseudo vesiculation), but there were no true vesicles and bullae. There were no mucosal lesions, no lesions over the genitalia, no lymphadenopathy, no jaundice nor anemia. Conjunctival catarrh of both eyes was present. Abdomen was distended with mild diffuse tenderness. On auscultation, peristaltic sounds were heard. There were no joint effusions. All other systems were normal.

The investigations revealed- hemoglobin[Hb] 8.4 gm%, total leukocyte count [TLC] 21,310 cells/cu mm, differential count [DC] neutrophils 92, lymphocytes 6, macrophages 2, erythrocyte sedimentation rate [ESR] by seditainer method of 90 mm at the end of one hour, platelets 3.41 lakhs/cu mm, C-reactive protein 16.9 mg/dl, serum antinuclear antibody [ANA] and anti neutrophil cytoplasmic antibody[ANCA] were negative. Serum rheumatoid factor was non-reactive and ASO titres were within normal limits. Biochemical investigations like liver function tests, renal function tests and serum electrolytes were within normal limits. Peripheral smear showed leukocytosis with neutrophilia. Urine microscopic examination revealed no pus cells, no casts and 24 hrs urine protein was 66 mg. ELISA for HIV
was negative. Plain X-ray abdomen (Fig. 3) showed no evidence of pneumoperitoneum. A small air-fluid level was seen in the distal ileal loop suggestive of subacute intestinal obstruction. Faeces loaded large bowel loops were seen. X-ray chest PA view was normal. Ultrasonogram abdomen revealed multiple dilated gas and fluid filled bowel loops suggestive of subacute obstruction. Skin biopsy showed dense neutrophilic infiltration in the papillary dermis, perivascular and periappendageal spaces (Fig. 4). There is no true vasculitis. In view of high grade fever, leukocytosis with neutrophilia and characteristic skin rash, a diagnosis of Sweet’s syndrome was made. The patient was given oral prednisolone 1 mg/kg body weight i.e. 60 mg/day in two divided doses along with injection ceftriaxone 1 gm i.v. BD, oral metronidazole 400 mg TID for 7 days. The patient dramatically improved within 48 hours after administration of systemic steroids. Fever, arthralgia and abdominal distension subsided and all the skin lesions disappeared without any residual sequelae. Her leukocyte count has decreased to 13,600 cells/cumm, ESR and C-reactive protein became normal after one week of steroid therapy. Repeat ultrasound abdomen revealed no evidence of any intestinal obstruction. Systemic steroids were continued in tapering doses for 4 weeks. After 4 weeks, upper GI endoscopy and colonoscopy were carried out and there was no evidence of Inflammatory Bowel Disease (IBD). Patient has been under follow-up and there is no recurrence till now.

**Discussion**

Sweet’s syndrome may be subdivided into 4 groups-classic/idiopathic (71%), para inflammatory (16%), paraneoplastic (11%) and pregnancy related (2%).\(^1\) The diagnosis of classic Sweet’s syndrome is established by the presence of 2 major criteria (skin eruptions and neutrophilic infiltration) along with 2 of the 4 minor criteria (high grade fever; leukocytosis with 70% neutrophils, high C-reactive protein, high ESR; good response to systemic steroids and systemic associations).\(^2\) The systemic associations with Sweet’s syndrome are hematological or visceral malignancy, IBD, pregnancy, upper respiratory and gastrointestinal infections and autoimmune diseases like polychondritis, rheumatoid arthritis, dermatomyositis, SLE, Sjogren’s syndrome, sarcoidosis and Behcet’s disease.\(^1,2\) A drug induced Sweet’s syndrome has also been recognized and a variety of drugs like trimethoprim-sulfamethoxazole, G-CSF, all trans-retinoic acid, hydralazine, oral contraceptive pills and minocycline are implicated.\(^2\) Sweet’s syndrome may result from a hypersensitivity reaction to a variety of triggers like bacterial, viral or tumour antigens and variety of cytokines directly or indirectly may have an etiological role in the development of Sweet’s syndrome. However, the exact mechanism is not yet known.\(^2\)

Our case fulfills the above diagnostic criteria for classic Sweet’s syndrome and there was no clinical or laboratory evidence of rheumatological disease, IBD and malignancy. The association of Sweet’s syndrome with IBD is very rare where it may be an extra intestinal manifestation of IBD, may precede or may be seen in all stages of Crohn’s disease.\(^3,4\) Extensive and diffuse neutrophilic inflammation of the intestines, ileum and pancolitis have been described in Sweet’s syndrome.\(^2\) In our case, the sudden onset of intestinal obstruction along with high grade fever and leukocytosis with neutrophilia could be due to acute inflammation of the intestines by the influx of neutrophils. Hence, along with the other symptoms, the intestinal obstruction was also dramatically relieved with systemic corticosteroid therapy.

Sweet’s syndrome is one of the groups of neutrophilic dermatosis that include pyoderma gangrenosum and whose association with ulcerative colitis and Crohn’s disease is well established. Sweet’s syndrome can be distinguished from pyoderma gangrenosum by the abrupt tendency to form multiple eruptions on the upper half of the body, lack of ulceration, absence of vasculitis and lack of dermal necrosis.\(^2\) The other differential diagnostic conditions are bowel bypass-related dermatosis, cellulitis, erysipelas, disseminated erythema nodosum, erythema elevatum diutinum, erythema multiforme and leukocytoclastic vasculitis.\(^1\)

Sweet’s syndrome if left untreated, usually heals within 6-8 weeks. Oral prednisolone at an initial dose of 40-60 mg/day with gradual tapering for over 4-6 weeks is the standard treatment for Sweet’s syndrome.\(^2\) Relapses are common if steroid is tapered too quickly. If steroids are contraindicated or not tolerated or in cases of recurrent relapses, potassium iodide can be given. Colchicine, dapsone, doxycycline, indomethacin, clofazimine, isotretinoin and cyclosporine have all been tried.\(^1,2\) Our case responded very well to systemic corticosteroid therapy. During the follow-up
Fig. 3: Plain X-ray abdomen showing a small air fluid level in the distal ileal loop.

Fig. 4: Skin biopsy specimen showing neutrophils in papillary dermis (H&E; 100X).

period of 6 months after stopping steroids, no recurrence was observed. Though there are a few cases of Sweet’s syndrome with other associations\(^3,^4\) in Indian literature, but to our knowledge, there is no reported case of Sweet’s syndrome with intestinal manifestation. This prompted us to report this case.

References


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