CASE REPORT

Renal Stones and Tuberous Sclerosis: A Rare Co-Existence

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Abstract

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome first described by Bourneville in 1880. It is a rare genetic disorder characterized by a triad of seizures, mental retardation and cutaneous lesions due to mutations in two genes, TSC1 and TSC2. We report a case of 46-years old male with generalised weakness and seizures. Patient was investigated and diagnosed after examination and investigation with tuberous sclerosis involving central nervous system i.e. sub-ependymal nodules and cortical tubers, skin manifestation adenoma sebaceum and ash leaf spots, lungs with cysts i.e. lymhangioleiomyomatosis, kidneys with angiomyolipomas and cysts . Patient also had right partial staghorn stone which was challenge for management. The patient was managed with right extended pyelolithotomy and discharged only to be re-admitted with vesical calculus after 18 months. This case report emphasizes the rare co-existence of renal stone formation with tuberous sclerosis.

Keywords: Tuberous sclerosis, Renal stones, Pyelolithotomy.

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Introduction

Tuberous sclerosis complex is an autosomal dominant, neurocutaneous syndrome described by Bourneville in 1880. It results due to mutations in TSC1 ((located at chrosome 9q34 encoding hamartin)) and TSC2 (located at chromosome 16p13.[1,2] encoding tuber in) resulting in multisystem disorder.[3] This rare genetic disorder is usually associated with a triad of seizures, mental retardation and cutaneous lesions. The diagnosis of tuberous sclerosis is established by following the revised criteria for tuberous sclerosis complex.[4]

Case Report

We report a case of 46-years old male with complaints of generalised weakness and lethargy Patient had past history of seizures for which he had received no treatment. Patient was investigated and diagnosed after examination and investigation with tuberous sclerosis involving central nervous system i.e. sub-ependymal nodules and cortical tubers, skin manifestation adenoma sebaceum, lungs with cysts i.e lymhangioleiomyomatosis, kidneys with angiomyolipomas and cysts. On examination patient had multiple papules of sebaceous adenoma over nose and malar area. [Figure 1a, b] There was ash leaf spot above right side of his umbilicus. [Figure 1c]

MRI Brain was suggestive of cortical tubers and subependyml nodules along with cerebral atrophy. [Figure 2a]

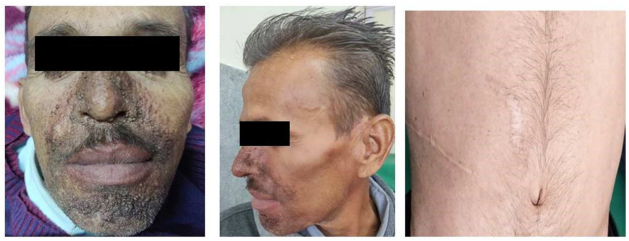

Figure 1 (a-c) a: Front view show Adenoma Sebaceum b. lateral view show Adenoma Sabaceum c. Ash –leaf spot lateral to umbilicus

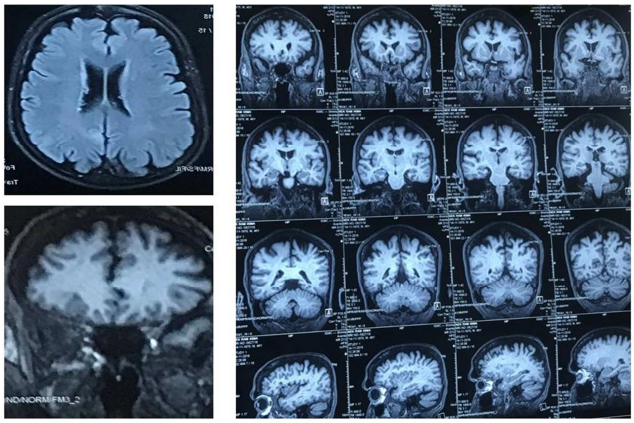

Figure 2 (a-c): MRI brain shows multiple sub ependymal nodules of varying sizes along bilateral ventricles, hypo-intense on T2 and hyper-intense on T2. Also seen are nodules bilateral parietal, right frontal and left occipital lobe of cortex.

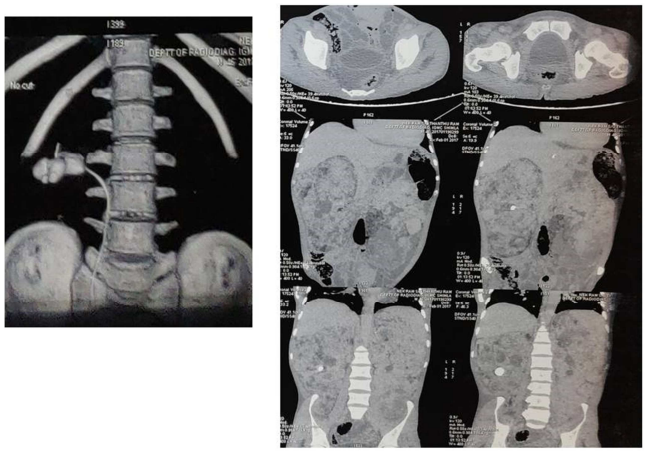

Figure 3 (a-b): X Ray KUB shows right partial staghorn stone, b. Coronal section of CECT KUB shows bilateral enlarged kidneys with bilateral angiomyolipoma and bilateral renal cysts

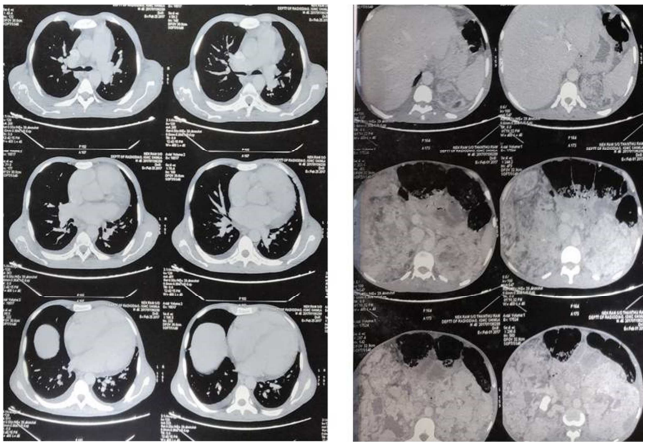

Figure 4 (a-b): CECT thorax shows bilateral pleural effusion with diffusely scattered lung cysts suggestive of lymhangioleiomyomatosis, markedly enlarged kidneys with multiple cystic lesions and hypo-dense areas in between suggestive of angiomyolipoma with right renal calculi with ascites with portal hypertension and hepatomegaly

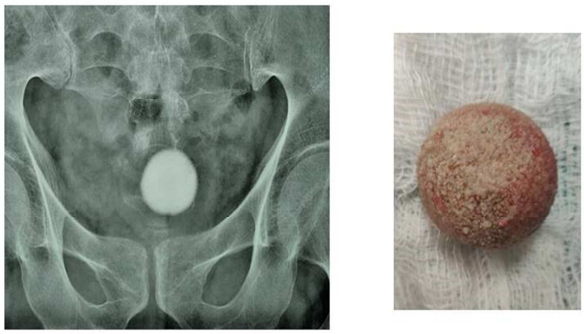

Figure 5(a-b)" a. X-ray Pelvis showing Bladder stone b. Bladder stone after cystolithotomy

His ocular examination including anterior segment and fundus examination of both eyes were normal.

MRI brain shows multiple sub ependymal nodules of varying sizes along bilateral ventricles, hypo-intense on T2 and hyper-intense on T2. Also seen are nodules bilateral parietal, right frontal and left occipital lobe of cortex.

Patient was investigated and diagnosed with tuberous sclerosis involving multiple systems with CECT abdomen and pelvis [Figure3a-b,4b] showing markedly enlarged kidneys with multiple cystic lesions and hypodense areas in between suggestive of angiomyolipoma with right renal calculi with ascites with portal hypertension and hepatomegaly . 2-D echo showing non-contracting left ventricle with mild Tricuspid regurgitation (TR) and Pulmonary Arterial Hypertension trivial Mitral regurgitation (MR) and left ventricular diastolic dysfunction (LVDD) with circumferential pericardial effusion. CECT thorax (Figure 4a) showed bilateral pleural effusion with diffusely scattered lung cysts suggestive of lymhangioleiomyomatosis. Pulmonary function tests show moderate restriction. Patient underwent right DJ stenting followed by extended pyelolithotomy. Postoperatively patient recovered well and no residual stone was found. Metabolic evaluation after 6 weeks suggestive of hypercalciuria, furthermore; stone analysis suggestive of ammonium phosphate, calcium phosphate, calcium oxalate. Patient again presented in department of urology after 1 year with complaints of pain in hypogastrium which on investigations turned out to be vesical calculus. The patient was managed by cystolithotomy. Patient was started on everlimus for bilateral angiomyolipoma. At 6 months patient is asymptomatic for renal stones, and kept on follow up for bilateral angiomyolipomas.

Discussion

Tuberous sclerosis complex (TSC) is a rare, multi-system genetic disease characterised by non-malignant tumors to grow in the brain and on other vital organs such as kidneys, heart, eyes, lungs, and skin. A combination of symptoms may include seizures, developmental delay, behavioural problems, skin abnormalities, lung and kidney disease. TSC is caused by a mutation of either of two genes TSC1and TSC 2, which encode for the proteins hamartin and tuberin respectively. These proteins act as tumor growth suppressors agents that regulate cell proliferation and differentiation. TSC most often presents with neurologic symptoms with 90% of affected individuals experience seizures. Renal manifestations are the second most common findings associated with TSC, with Angiomyolipomas occurring in 80% and renal cystic disease in ~50% of patients. Pulmonary involvement, specifically lymphangioleiomyomatosis (LAM), is the third most common cause of TSC-associated morbidity, occurring in approximately 35% of female TSC patients.[3-5]

The full triad of seizures, mental retardation and cutaneous lesions is only seen in a minority of patients (~30%). The criteria for diagnosis of tuberous sclerosis include-Definitive TS complex: either 2 major features or 1 major and 2 or more minor and Possible TS complex: either 1 major or ≥2 minor. Major features include angiofibromas (3 or more) or fibrous cephalic plaque, non-traumatic ungual or periungual fibroma (2 or more), hypomelanotic macules (3 or more, at least 5mm diameter), Shagreen patch, multiple retinal nodular hamartomas, cortical dysplasia's (include tubers and cerebral white matter migration lines), subependymal nodule,

subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis (LAM) and angiomyolipomas(2 or more). Minor features include dental enamel pits (3 or more for the entire dentition), intraoral fibromas (2 or more), non-renal hamartomas, retinal achromic patch, 'confetti' skin lesions and multiple renal cysts.

In the present case there were subependymal nodules in brain, multiple angiomyolipoma in bilateral kidney, LAM in lungs, adenoma sebaceum. Interestingly the patient was also diagnosed with renal calculi in his first visit and subsequently in his second visit he developed vesical calculus along with renal calculus. This rare association of tuberous sclerosis with renal stones has not been reported. However following reasons have been suggested for Nephrolithiasis. Firstly drugs like topiramate have proven to be a very effective therapy for some forms of TSC-associated epilepsy by enhancing GABA-activated chloride channels and inhibiting excitatory neurotransmission. In kidney, topiramate inhibits carbonic anhydrase (II and IV) leading to decreased citrate excretion and subsequently increased risk of nephrolithiasis. Secondly, the seizure frequency of some TSC patients responds well to the ketogenic diet. The associated diet-stimulated hypercalciuria and hypocitraturia synergize to increase the risk of nephrolithiasis, and this effect is further facilitated by the resulting decrease in uric acid solubility caused by the low urine pH. Thirdly, significant renal cystic disease, as disruption of distal tubular function by a significant cyst burden leads to hypocitraturia.6 As there were no records available regarding the antiepileptic treatment in the present case, the most probable cause of nephrolithiasis in this patient was metabolic abnormality in urine and renal cystic disease.

Ureteroscopic stone removal is the treatment of choice in nephrolithiasis as extra-corporeal shockwave lithotripsy (ESWL) and percutaneous Nephrolithotomy (PCNL) put the kidneys to potential risk of haemorrhage. However in view of staghorn stone, risk of haemorrhage and large size of kidneys, open extended pyelolithotomy was done. This is very unusual combination and very challenging to treat. However, it requires multidisciplinary team, including urologist, ophthalmologist, anaesthesia, neurologist, physician, cardiologist, pulmonologist. The surgery cleared all renal stones with minimal complications. Further patient developed bladder stone after 1 year, in view of large stone open cystolithotomy was done.

Conclusion

It is therefore emphasized to have detailed evaluation of a case presenting with tuberous sclerosis. Although these patients have no cure, they can be relieved symptomatically to ameliorate morbidity associated with this syndrome. Renal stones in these patients are challenging and with multimodal treatment patient may be managed. Follow up of these patients is important as these have metabolic abnormality, anatomic predisposition and renal cystic disease.

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