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Case Report

An interesting case of Tuberous sclerosis

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ABSTRACT

Tuberous sclerosis is a genetic disorder affecting cellular differentiation, proliferation, and maturation. This cellular process gets disarranged and results in hamartomas formation in multiple organs of body the body including, the kidneys. Kidney involvement is usually bilateral and asymptomatic. We report a case of bilateral renal angiomyolipomas who presented with hematuria and pain.

Keywords: Tuberous sclerosis, renal angiomyolipoma

INTRODUCTION

Tuberous sclerosis was first described by Bournville in 1880. It is a genetic disorder with an autosomal dominant pattern of inheritance with variable penetrance and incidence of approximately 1 in 5000 to 10000 live births, occurs in all races and ethnic groups and in both genders. In tuberous sclerosis hamartomas formation also found in multiple organs of body like brain, eyes, heart, lung, liver, and skin. Its main clinical triad includes mental retardation, seizures, and facial angiofibromas. Angiomyolipomas (AMLs) and renal cysts are the common renal anomalies in TSC. Kidney involvement is usually bilateral and asymptomatic. We are presenting this case of tuberous sclerosis as patient present with hematuria due to renal angiomyolipoma.[1,2]

Case report:

A 53 year old female housewife from Bharuch, Gujarat presented to us with the complaints of hematuria since 2 months and fever since 20 days. Hematuria was Insidious in onset, Intermittent and uniform through the stream. Patient had fever which was sudden in onset, intermittent, moderate grade associated with chills, rigor and body-ache. She had no history of hematemesis, malena, rash, petechiae, bleeding gums. She had no past history of major diseases like DM/TB/IHD/HTN/Renal Disease and no history of developmental delay and mental retardation. In personal history she had no addiction and had menopause eight years back. In family history she had four sons and three daughters in which the youngest son (22 year old) had mental retardation, headache with epilepsy and facial eruptions.

On general examination patient was febrile (100^0 F) and had pallor, with normal pulse rate and blood pressure. On per abdomen examination she had mild hepatomegaly and mild splenomegaly. Kidney examination done by light palpation, deep palpation and bimanual method which suggestive of renal angle tenderness. On skin examination she had Adenoma sebaceum (Figure 1), Ash leaf macule (Figure 2), Shagreen patch (Figure 2), Skin tag (Figure 3), Periungal fibroma (Figure 4). Central nervous system and other system examination was normal.

Investigations:

Blood investigations she had hemoglobin 7.5 g/dl, total leukocyte count were 6000 cells/$mm^{3,}$ platelets were 2.3 lacs, prothrombin test was 12/14 sec. Her liver function test was normal. Her uric acid was 5.4 mg/dL and serum sodium/pottasium were 136/3.9 meq/L. Her creatinine was on slightly higher side 1.4 mg/dL. On urine microscopy examination there was plenty of red blood cells with 18-20 pus cells, 4-5

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epithelial cells and albumin was 3+. On urine culture staphylococcus saprophyticus organism was found. HIV/HB_SAG/HCV were negative.

On ultrasonography of abdomen and pelvis: Encapsulated lobular mass (13×10.7 cm^2) with low internal vascularity in left renal fossa extending from stomach to splenic hilum and another mass lesion of mixed echogenicity in right iliac fossa (20×7.9cm^2). Liver left lobe showed echogenic lesion (17×16 cm^2), and multiple small echogenic lesion in right lobe. Spleen pushed by encapsulated mass.

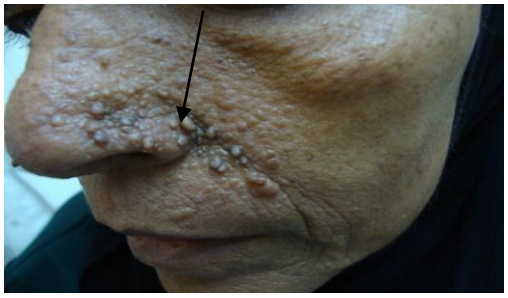

Figure 1 Adenoma Sebaceum

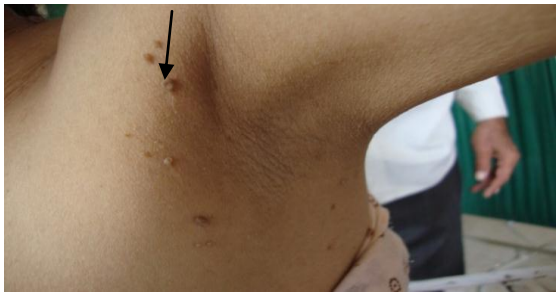

Figure 2 Skin Tag

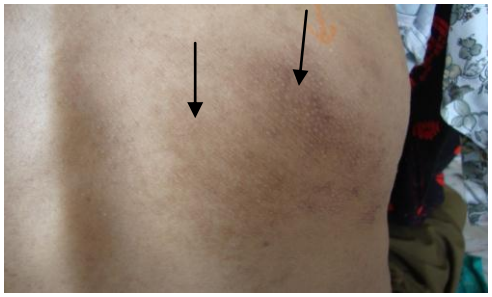

Figure 3 Shagreen patch and ash leaf macule

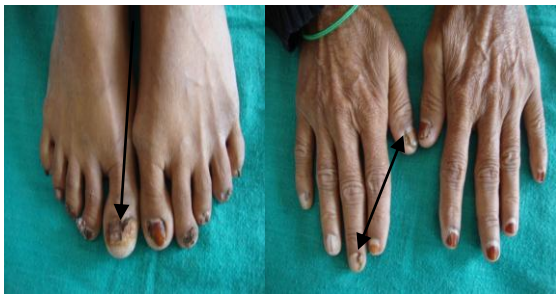

Figure 4 Periungal Fibroma

CT scan thorax, abdomen and pelvis: Both kidneys were enlarged and showed multiple mixed density lesions and calcification with multiple cysts involving upper, middle, and lower poles of both kidneys, suggestive of angiomyolipoma (Figure 5A). Multiple bilateral thin walled cysts distributed through both lungs suggestive of lymphangiomyomatosis (Figure 5B). Mild hepatosplenomegaly. Multiple small hypodense nodules with peripheral enhancement seen in both lobes of thyroid (Figure 5C). Multiple sclerotic nodules involving spine and pelvic bones.

CT Head: Bilateral Multiple hyper dense nodules seen along the walls of ventricles (Figure 5D). Thickening of the cranial vault with irregular hyper dense area were seen (Figure 5E). Hyperdense area seen in C2 and C3 vertebral bodies.

Thus, this case had multiple lesions which involve multiple organs like lungs, liver, kidney and brain. Also there were cutaneous lesions and nodular lesions in thyroid.

DISCUSSION

Tuberous sclerosis is an autosomal dominant condition which results from mutation in one of the genes TSC1 on chromosome 9q34 and TSC2 on chromosome 16p13 that encode distinct proteins, hamartin and tuberin. In most cases it is due to mutation of these genes, hence positive family history may not be present in all cases but disease might be carried to next generation.[3-5]

There are no pathognomic clinical signs for tuberous sclerosis. A combination of signs, classified as major or minor required for making diagnosis. The diagnostic criteria for tuberous sclerosis were revised at the Tuberous Sclerosis Complex Consensus Conference, July 1998. The second International tuberous sclerosis complex consensus conference was held in June 13-14, 2012 in Washington. The most significant change recommended to the diagnostic criteria was the incorporation of genetic testing.[6]

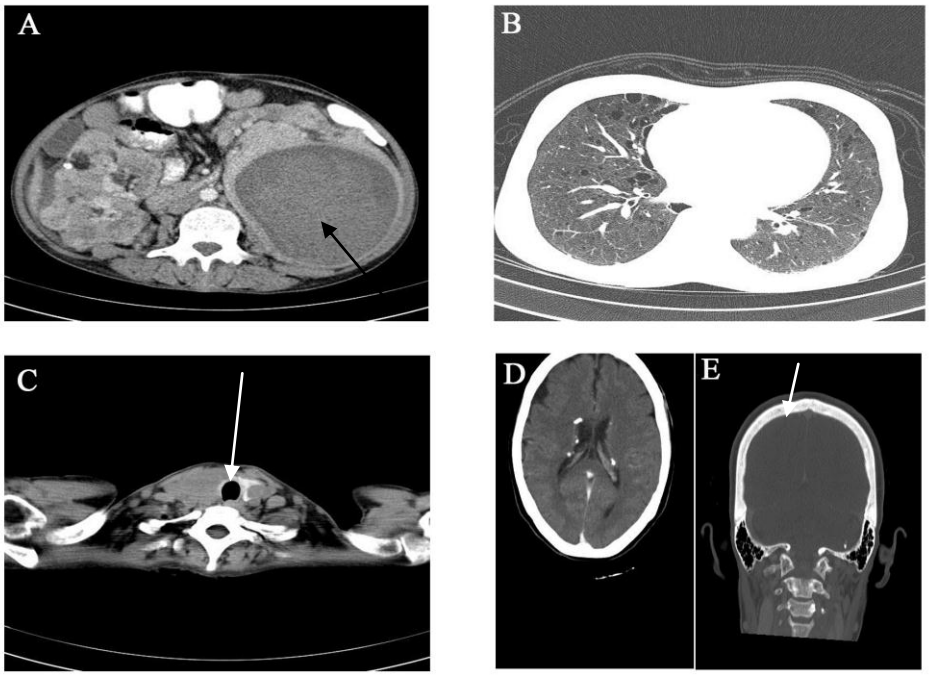

Figure 5 (A) CECT Abdomen shows Angiomyolipoma in kidney (B) HRCT Thorax shows Lymphangiomyomatosis in Lung (C) CT Neck showing hypodense nodules in Thyroid (D) CT Brain Plain shows Hyperdense nodules (E) CT Brain Coronal section shows Thickening of the cranial vault, Hyperdense area seen in C2 and C3 vertebral bodie

For making the definite diagnosis of tuberous sclerosis - either 2 major (or) 1 major + 2 minor features will be require, for probable diagnosis - 1 major + 1 minor and for possible diagnosis - 1 major (or) 2 or > minor features will require. Our patient had six major (Facial angiofibroma or forehead plaque, Non traumatic ungula or periungual fibroma, >3 hypomelanotic macules, Shagreen patches, Lymphangioleiomyomatosis, Renal angiomyolipoma) and two minor (Non renal hamartomas, Multiple renal cysts) features; which confirms the diagnosis of definite tuberous sclerosis, and patient managed conservatively with antibiotics and supportive treatment.

In tuberous sclerosis approximately 20-30% patients have renal cysts and 60-80% patients have benign tumous of the kidneys called angiomyolipoma which can cause symptoms, while dermatological signs will be present in 96% of individuals with tuberous sclerosis. Neurological menifestations like learning difficulties and low IQ will be present in 50% individuals with tuberous sclerosis.[7]

Most of the TSC patients can be diagnosed clinically due to typical triad of fascial nevus, seizures, and mental retardation. Sometime a clear diagnosis cannot be made on clinical finding alone, and then genetic screening testing is useful. It helps (1) confirmation of diagnosis made on clinical grounds; (2) carrier testing for other at-risk family members; and (3) prenatal diagnosis (4) where it is difficult for individual (newborn) to go through imaging studies required for the clinical diagnosis.[8]

However, due to wide variety of mutations leading to tuberous sclerosis, neither simple genetic tests nor any biological markers are available to diagnose the disease. Clinical genetic test identifies approximately 80% of the mutations in samples that are submitted and facilities for this test are limited even in developed countries. But, once a person has been clinically diagnosed the genetic mutation can be used only for prenatal diagnosis of the disease in next generation.[8]

So, the investigations and management of these patients has to be coordinated between specialities

with periodic imaging assessments including brain imaging studies, ophthalmic evaluation, electrocardiography, and echocardiography, ultrasound, looking for neurocutaneous markers and keeping in mind developmental delay in milestones if any.

Diagnostic criteria for tuberous sclerosis:

Major features:

- Facial angiofibromas or forehead plaque
- Nontraumatic ungula or periungua; fibroma
- Hypomelanotic macules
- Shagreen patch
- Multiple renal nodular hamartomas
- Cortical ulcer
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma
- Lymphangiomyomatosis
- Renal angiomyolipoma

Minor features:

- Multiple randomly distributed pits in dental enamel
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter migration lines
- Gingival fibromas
- Nonrenal hamartomas
- Retinal achromic patch
- Confetti skin lesions
- Multiple renal cysts

As no specific medication for tuberous sclerosis is available till today, treatment of the disease is cure the symptoms. The goals of the treatment for patients with tuberous sclerosis are providing the best possible quality of life with fewest complication from the underlying process, fewest adverse treatment effects, and fewest medications. Hence, awareness regarding different organ manifestation of tuberous sclerosis is important.

Rapamycin is an immunosuppressant which forms an inhibitory complex with the immunophilin FKBP12, which binds to inhibit the ability of mTOR to phosphorylate downstream substrates, such as the S6Ks and 4EBPs. It also inhibits T cell proliferation. Other drug is Sirolimus which was used to treat renal angiomyolipomas and showed good results in recent studies. Vigabatrin and lamotrigine are useful drugs in spasms and seizures. Adrenocorticotropic hormone (ACTH)/ steroids are also useful to treat symptoms.

Surgery including dermabrasion and laser treatment may be useful for treatment of skin lesions. CO_2 laser, provides efficient and bloodless extraction of the lesions.[9,10] or phenolization that allows for a better cosmetic result. Complete excision is required to achieve a permanent cure.[10-13] Surgical care for seizures in a patient with tuberous sclerosis can involve focal cortical resection, corpus callosotomy, or vagus nerve stimulation.

Focal cortical resection: In patients with tuberous sclerosis resection of a cortical tuber is considered palliative rather than curative. In this surgery the problem is after removal of one epileptic focus other focus can take its place and produce the seizures. So the surgery is helpful in selected cases.

Corpus callosotomy: It can be effective in reducing atonic and tonic seizures but not helpful for other type of seizures.

Vagus nerve stimulation: Studies shown that patients with tuberous sclerosis and treatment resistant epilepsy had approximately 50% reduction in seizure frequency. Simple and complex partial seizures also respond better to vagus nerve stimulation.

SEGA resection: Subependymal giant cell astrocytoma require resection if they produce hydrocephalus or significant mass effect. If a total resection can be done than recurrence is unlikely.

Ketogenic diet is also reported by some to be beneficial in patients with tuberous sclerosis as it can decrease the frequency of seizures, cause less drowsiness and better behavior. Prognosis of tuberous

sclerosis patients mainly depends on the severity of symptoms. Those who have mild symptoms live long productive life, while patients with more severe form may have serious disabilities. However, with appropriate medical care, most patients with the disease can have normal life.

CONCLUSION

Although tuberous sclerosis is very rare and difficult to manage, if we diagnose the disease earlier we can cure the symptoms and provide better life. Hence, awareness regarding different skin manifestations and various organ involvement of tuberous sclerosis is very important.

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