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Lymphangiomyomatosis-Tuberous sclerosis complex:A Rare Case Report presenting with weight loss.

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Abstract: *Lymphangiomyomatosis-Tuberous sclerosis(LAM) is a rare multi system involving disease which usually affects the women of reproductive age. It is estimated to affect 3.4-7.8/1,000,000 women worldwide. We report a case of 36 yr old woman who presented initially with cough and weight loss. She was evaluated and diagnosed as LAM-TSC with multisystem involvement.*

Keywords: *Lymphangiomyomatosis-tuberous sclerosis, weight loss ,multisystem involvement*

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I. Introduction

Lymphangioleiomyomatosis (LAM) is a multisystem disorder characterized by the proliferation of smooth muscle cells that result in cystic lung disease as well as extrapulmonary manifestations such as angiomyolipomas and lymphatic tumors[1].

II. Case Report

A patient aged 36 years with education of 5th grade schooling presented with dry cough for three months with no positional or diurnal variation, weight loss of 5 kgs since three months and intermittent pain abdomen since 3 months. She has multiple lesions over face since childhood. Similar family history with facial lesions in her siblings, sister's child and in mother who expired due to kidney disease. Informant was patient's sister. No history of malignancies, tuberculosis in the family. On examination patient was conscious, cooperative, oriented, poorly built, poorly nourished, emaciated. pallor noted. Vitals were stable. Respiratory system and cardiovascular system examination was normal. Per abdomen examination, tenderness was elicited in both the hypochondriac regions(right>left), tenderness in right iliac fossa. Central nervous system examination revealed abnormal higher mental function, reflexes were normal. Psychiatric evaluation by Binet-Kamath Test(BKT) of General Intelligence was done and it revealed her BKT Intelligence Quotient (LQ) was found to be 35 indicating Moderate Deficiency in Intellectual Functioning. Dermatology examination revealed adenoma sebaceum and fibro cephalic plaque on the face, shagreen patch on the trunk, mulluscum pendulum on the neck, ungual and periungual fibroma of fingers and toes. Complete blood picture showed anemia, peripheral smear showed microcytic hypochromic anemia. Renal and liver function tests were normal. In Chest x ray, no significant abnormality detected. Induced sputum for Acid Fast Bacilli (AFB) and gene expert was negative. Patient couldn't perform spirometry as she was not able to comprehend instructions. Fundoscopy revealed hamartoma in the right eye.

USG abdomen confirmed bilateral renal angiomyolipomas and hepatic angiomyolipoma. There is a large pseudoaneurysm (demonstrating in "yin yang sign" on colour doppler) with surrounding heterogenous echopattern area within the right kidney (suggestive of bleed). A small cortical cyst in the left kidney. Electrocardiogram(ECG), Echocardiography was normal.

High Resolution Computed Tomography (CT) chest showed thin walled cystic lesions in bilateral lungs with no lobar predominance. No pleural effusion/thickening / pneumothorax. CT abdomen showed Enlarged

kidneys (right more than left) and showed heterogenous attenuation suggestive of renal angiomyolipomas with hemorrhages of varying ages. Enlarged right kidney was causing mass effect upon the liver (anteriorly), right adrenal gland (superiorly), pancreas and small bowel loops (medially). There was complete distortion of right renal architecture. A small well defined fat attenuation lesion was noted in the right hepatic lobe (segment VII)-suggestive of hepatic angiomyolipoma. Multiple well defined hyperattenuation lesions were seen in sternum, bilateral lower ribs, most of the dorsal and visualized cervical vertebrae (involving vertebral bodies and posterior elements) suggestive of osteoblastic lesions. Multiple osteoblastic lesions were seen in lumbosacral spine and the pelvic bones.CT Brain study revealed multiple calcified subependymal hamartomas in bilateral lateral ventricles . A calcified subependymal hamartoma in the left foramen of Luschka . Magnetic Resonance Imaging (MRI) Brain study revealed multiple subependymal hamartomas and T2 and Fluid Attenuation Inversion Recovery (FLAIR) hyperintense cortical tubers in bilateral cerebral hemispheres.

Punch biopsy section of the skin lesions namely Fibrous cephalic plaque, Adenoma Sebaceum, Shagreen patch ,mulluscum pendulum were consistent with Tuberous sclerosis and confirmed the diagnosis.

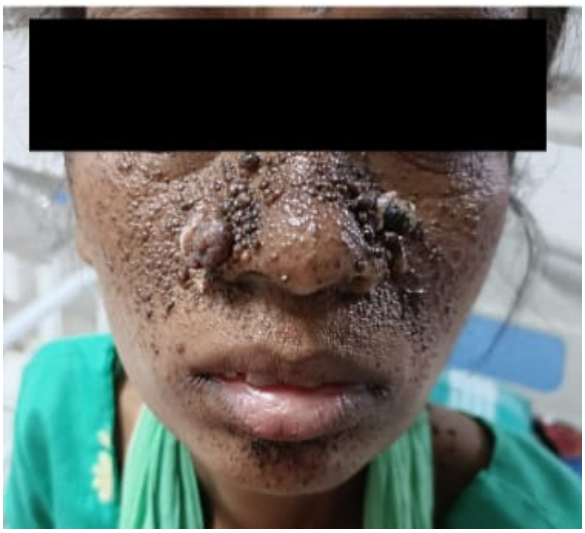


Figure 1: Adenoma Sebaceum on face.

Figure 2 : periungual and ungual fibromas.

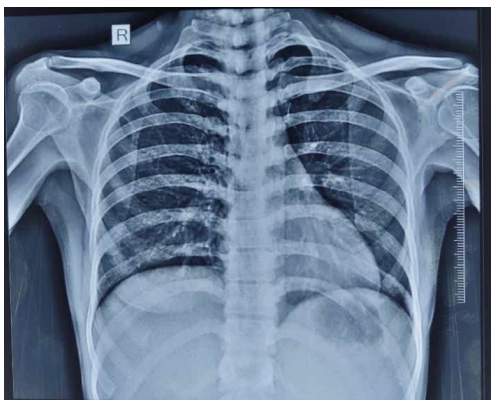


Figure 3: Normal chest x ray.

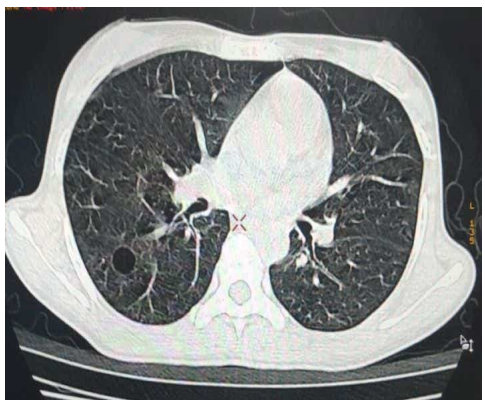
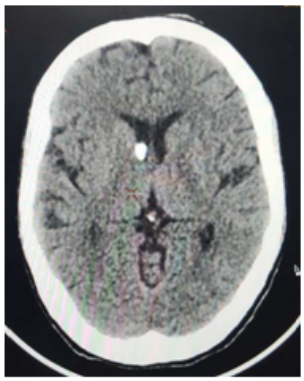
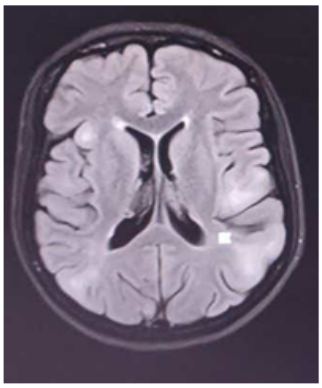
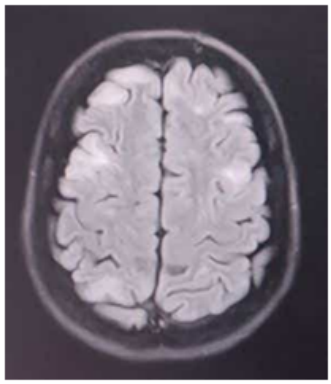


Figure 4: HRCT chest showing thin walled cyst.

Figures 5, 6, 7: CT and MRI Brain showing multiple subependymal hamartomas and cortical tubers.

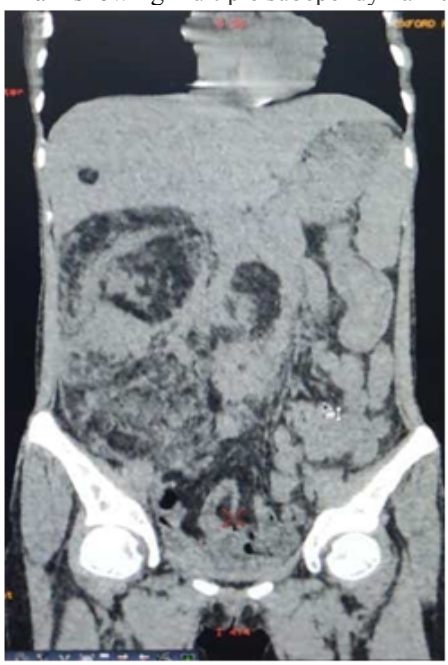


Figure 8: CT Abdomen showing hepatic angiomyolipoma, enlarged and distorted kidneys with renal angiomyolipomas and displaced bowels.

III. Discussion

Patients with LAM often present with pleuritic chest pain, increasing dyspnea, and decreased breath sounds on the affected side due to spontaneous pneumothorax[2] but our patient presented with cough and weight loss and intermittent pain abdomen. The weight loss in our patient may be because of renal angiolipoma on the right side extending from right hypochondrium to right iliac fossa and causing compressive symptoms on bowel. Anaemia in this patient is probably due to nutritional and intra-organ bleeding in the kidney due to pseudoaneurysm.

There are two types of LAM, sporadic and congenital. The congenital form is an autosomal dominant genetic disorder as a result of mutations in the tuberous sclerosis complex (TSC) genes 1 and 2, Tsc1 and Tsc2, respectively. The genetic type of LAM is associated with a more severe form of disease and is characterized by involvement of the brain, kidney, skin and severe mental retardation. Pulmonary symptoms are less frequent in the genetic form of LAM. The sporadic form of LAM may also be caused by mutations in the Tsc genes [3-7].Sporadic LAM may represent up to 85% of the total cases of LAM[8].Our patient presented with congenital form of LAM which is autosomal dominant so she had multiorgan involvement like brain, eye, lung, kidneys, skin, liver and mental retardation. She had few small thin walled cysts in bilateral lung but the lung manifestations were not very severe in contrast to sporadic LAM.

In 2021, the International Tuberous Sclerosis Complex Consensus Group reviewed prevalence and specificity of TSC-associated clinical manifestations and updated the TSC diagnostic criteria published in 2013.

Clinical features of TSC and genetic testing provide two ways of obtaining a diagnosis of TSC.
The clinical and genetic diagnostic criteria of 2021 are summarized below.

(1) Clinical Criteria:
Definite Diagnosis:
A definite diagnosis of Tuberous Sclerosis will be made when an individual has either: 2 major features; or 1 major feature with 2 minor features.A combination of the two major clinical features Lymphangioleiomyomatosis (LAM) and Angiomyolipomas without other features does not meet criteria for a Definite Diagnosis.
Possible Diagnosis:
A possible diagnosis of Tuberous Sclerosis will be made when an individual has either: 1 major feature; or 1 major and 1 minor feature; or more than 2 minor features.

Major Features
1. Angiofibromas (3 or more) or forehead plaque
2. Hypomelanotic macules (3 or more at least 5 mm diameter)
3. Ungual fibromas (2 or more)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Multiple cortical tubers and/or radial migration lines. This includes tubers and cerebral white matter radial migration lines.
7. Subependymal nodule(s) (2 or more)
8. Subependymal giant cell astrocytoma(s)
9. Cardiac rhabdomyoma
10. Lymphangioleiomyomatosis (LAM)
11. Angiomyolipomas (2 or more)

Minor Features
1. Dental enamel pits (more than 3)
2. Multiple renal cysts
3. Sclerotic bone lesions

(2) Genetic Testing Criteria:
Either a TSC1 or TSC2 pathogenic mutation is sufficient to make a Definite Diagnosis of TSC. A pathogenic mutation is defined as a sequence variant that clearly prevents TSC1 or TSC2 protein production. Additionally, some mutations compatible with protein production (e.g., some missense changes) are well established as disease-causing and as sufficient to make a Definite Diagnosis of TSC. Other variants should be considered with caution.
Our patient has 8 Major criteria namely Angiofibromas, forehead plaque, Ungual fibromas , Shagreen patch, Multiple retinal hamartomas, Multiple cortical tubers, Subependymal nodules, Lymphangioleiomyomatosis (LAM), Angiomyolipomas and 1 Minor criteria namely Sclerotic bone lesions. As per the International Tuberous Sclerosis Complex Consensus group 2021 diagnostic clinical criteria our patient was diagnosed definitive TSC.
Serum VEGF-D >800pg/ml is a useful diagnostic and therapeutic biomarker for sporadic LAM according to American Thoracic Society guidelines.
According to European Respiratory Society guidelines for management of LAM-TSC, requires multidisciplinary approach as follows.
a) General advice and intervention - Maintaining normal weight and refrain from smoking.
b) Advice for patients on risk for pneumothorax: Education
c) Advice patients to warn risk of pneumothorax and chylous effusions during pregnancy and risk for genetic predisposition in the child.
d) Avoidance of estrogen and hormonal therapies like contraceptives pills.
e) Information for patients concerning air travel on risk for pneumothorax.
f) Pulmonary rehabilitation for LAM patients limited with dyspnea.
g) Prophylactic Infleunza and Pneumococcal vaccination
h) Assessment by Bone Mineral Density and management of osteoporosis by weight bearing and strength training apart from pharmacological therapy
i) Inhaled bronchodilators for patients with Obstructive Airway Disease.
j) mTOR inhibitors can be used with caution in certain candidates and further studies are required.
k) In bleeding renal angiolipoma, embolisation and nephron sparing surgeries can be considered.
l) Patients should be considered for lung transplantation when they reach New York Heart Association (NYHA) functional class III or IV with severe impairment in lung function and exercise capacity (VO2max -50%

predicted, hypoxemia at rest). Transplantation in patients > 65 yrs of age may only be considered exceptionally. Both single, and more commonly, bilateral lung transplantations have been performed for LAM. Although a bilateral lung transplant is associated with better post-transplant lung function and a reduction in LAM-related complications there is no difference in survival between single and double lung transplant.

For skin lesions, cosmetic procedures and topical rapamycin application has been tried with temporary clearance of lesions with non-promising results as there is recurrence of skin lesions[9].

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