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Case Report

A Case of Tuberous Sclerosis: Hidden in Plain Sight

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Introduction

This case report follows a 35-year-old female who presents with vague nonspecific symptoms which she had been bearing on analgesics for the many years prior, and it was only on extensive radiological imaging that a proper, yet rare diagnosis was reached. This patient would eventually be diagnosed with Tuberous Sclerosis (TSC), a rare genetic disorder characterized by the growth of benign tumors in different organ systems, with manifestations in most organ systems.[1] It affects approximately 1 in 6,000–10,000 individuals, although the variable penetrance and subtle presentations of the disease mean that this number is likely under-representative of the true incidence.[2] This case highlights the importance of a holistic approach and sheds light on disorders that may go undiagnosed despite being rather apparent once viewed in hindsight.

Case Presentation

The patient in question was experiencing a high-grade fever, accompanied by a productive cough and vague, generalized abdominal pain along with some nausea and vomiting, all for the past 2 weeks. According to the patient, this was the first such episode of its kind. Her history was insignificant, except for a prior episode of hematuria a few months back, which led to the discovery of angiomyolipomas involving both kidneys, which she was aware of, however her previous consultation did not appear to follow up with further workup, and the hematuria eventually subsided. The patient denied any family history of the angiomyolipomas, or for any symptoms that may have followed. She also denied having smoked or using recreational drugs. There was no history of seizures or altered mentation.

Noticeable findings on her physical exam included multiple miniature, polyp like growths on the face spread in a malar distribution, and small sub centimeter hypomelanotic papules spread sporadically across the trunk and limbs. Her Respiratory exam would reveal some coarse crackles, concentrated mainly in the basal segments of the chest. On oral cavity examination, multiple cavitations in the enamel were noted across multiple teeth. The rest of her physical exams were unremarkable.

Initial serological investigations were significant for leukocytosis, with a TLC count of 20×10^9 suggesting acute inflammation and an Hb level of 8.7 g/dl, with morphological blood parameters suggesting a normocytic normochromic anemia. Creatinine was slightly elevated at 1.2 mg/dl and Urinalysis showed 4-5 RBCs.

Initial assessment pointed towards an acute bacterial respiratory tract infection, with the anemia and microscopic hematuria attributed to the known presence of renal angiomyolipomas.

The patient was initially evaluated with a high-resolution computed tomography (HRCT) scan of the chest, which revealed innumerable thin-walled rounded air-filled cysts diffusely distributed throughout both lung fields. The lung Parenchyma otherwise however appeared normal. This image was the typical presentation of Lymphangioleimyomatosis, a condition previously thought to be an interstitial lung disease but is now treated as a destructive metastasizing neoplasm.

A follow-up CT scan of the Abdomen with contrast was performed, which showed that the kidneys were enlarged, demonstrating innumerable lesions predominantly of fat density. One of the larger lesions had an exophytic component involving the upper pole of the left kidney. Another well-defined cystic lesion was seen in the middle pole on the left having an internal enhancing component, which was classified as a Bosniak Type IV lesion, highly suggestive of RCC. No evidence of retroperitoneal hemorrhage was seen. A few small fat density lesions were also seen scattered within the liver, otherwise, the liver showed normal parenchymal enhancement. The rest of the abdominal viscera were unremarkable. Multiple well-defined, rounded, sclerotic foci were seen throughout the skeleton.

Discussion

The patient in this case presented with vague abdominal pain, low-grade fever, a productive cough, nausea, and vomiting, all of which, on their own, are vague symptoms. The HRCT scan of the chest revealed numerous well defined scattered cysts in the lungs, which is consistent with LAM (Lymphangioleiomyomatosis), a complication of TSC characterized by. The follow-up CE CT Abdomen and Pelvis showed multiple bilateral renal and hepatic angiomyolipomas, as well as numerous scattered sclerotic bony lesions, which are highly suggestive of TSC.

A diagnosis for TSC requires the following, genetic testing for evidence of TSC1/TSC2 mutation, and clinical diagnosis via fulfillment of multiple criteria; either two major or one major and two minor features. Major features include the following: Lymphangioleiomyomatosis, Renal Angiomyolipomas, Shagreen Patches, Subependymal Nodules, Cardiac rhabdomyomas, Giant Cell astrocytomas, Ash Leaf spots (Hypomelanotic Nodules), Facial Angiofibromas, Retinal Hamartomas and Ungual Fibromas. Minor criteria include Dental Enamel Pits, non-renal Hamartomas, Polycystic Kidneys, Confetti Spots (Similar to ash leaf spots albeit smaller).

Based on the patient's presentation and imaging findings, along with the fulfillment of three major and, the diagnosis of TSC (Tuberous Sclerosis Complex) was eventually made, as at least two major criteria for its diagnosis were fulfilled.[3] TSC is a rare genetic disorder characterized by a genetic mutation in the genes TSC1 (on Chr. 9) or TSC 2 on (Chr.16) that code for the proteins Hamartin and Tuberin respectively.[4] These proteins are tumor suppressors and act to regulate and control cell growth. TSC follows an autosomal dominant inheritance pattern but also exhibits variable expressivity, which means that two individuals with TSC may lie at vastly different ends of the severity spectrum and the disease may bring about significantly more morbidity in one affected individual than another. This is because these two genes follow the "Two-Hit Hypothesis" which means that in addition to the original primary gene mutation a second, random, sporadic gene mutation is needed to bring about phenotypical change[5]. Despite its autosomal dominant nature, more than half of all TSC cases have been found to originate from random mutations rather than direct vertical transmission. Due to the adjacent proximity of the TSC 2 Gene with the PKD1 gene, it is possible for a mutation to affect the latter as well, provided it is extensive enough. This is why patients with TSC are at a greater risk of also developing Polycystic Kidney Disease.

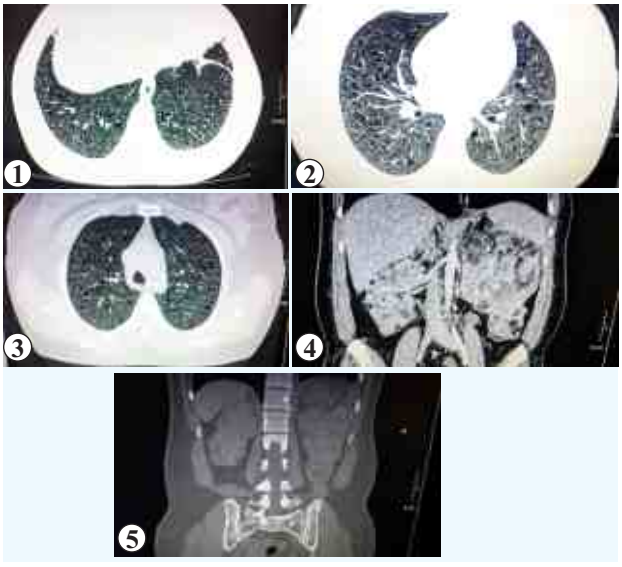
Patients with TSC will develop multiple hamartomatous lesions throughout multiple organ systems, ranging from angiofibromas along the skin, particularly in a butterfly pattern on the face, to angiomylipomas in the Kidneys and Liver, to Subependymal Nodules and Giant Cell Astrocytomas in the Brain, the latter of which can bring about CSF flow obstruction and may lead to obstructive hydrocephalus. Hence epilepsy is another common finding in affected populations. TSC also has a high relation with Neurodevelopmental delay and hence can be a significant source of morbidity. Cardiac Rhabdomyomas, despite being very uncommon in the general population, are also a common finding in TSC[6]. TSC is also associated with an Increased risk for RCC however recent research has not been able to identify anything along the lines of a directly causal relationship.[7]

Conclusion

This case report highlights the importance of a thorough evaluation and imaging in patients with TSC, as the disorder can present with a wide range of symptoms and can affect multiple organ systems. The patient in this case was diagnosed with TSC based on her imaging findings, but due to affordability issues, she did not follow up with further imaging to confirm the diagnosis and to evaluate other organs that can be affected by TSC. Nevertheless, this case report illustrates the importance of a multidisciplinary approach in the management of TSC, as the disorder can affect multiple organ systems and requires specialized care.

Ideally further investigations warranted in this patient would include an echocardiogram to look for Rhabdomyomas and a CT Brain to look for any growths that may result in debilitating levels of morbidity and even mortality.

It is important that we recognize such cases and facilitate them both emotionally and financially as the burden of such systemic diseases is vastly spread and significant.



Legend: *Pictures labelled 1, 2 and 3 demonstrate thin-walled cystic changes in transverse HRCT sections, consistent with the classic appearance of Lymphangioleiomyomatosis (LAM). Picture 4 Demonstrates Renal Angiomyolipomas, with a suspicious exophytic cystic component in the left kidney, classified as a Bosniak Type IV cyst, possibly suggestive of malignancy. Picture 5 highlights the sclerotic foci seen within the vertebral as well as the Sacro-Ileac region.*

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