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CASE REPORT

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Simultaneous presentation of Wunderlich's syndrome and thyroid nodule in a patient with tuberous sclerosis: Are thyroid lesions a part of tuberous sclerosis complex?

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ABSTRACT

A multisystem involvement is seen in tuberous sclerosis with a variety of manifestations, but thyroid lesions are rarely reported in this syndrome. Angiomyolipomas (AMLs) of the kidney are common in tuberous sclerosis, and when present, it is a significant cause of morbidity. Wunderlich's syndrome is the most dreaded complication in such patients. We present the case of a 25-year-old male patient who had tuberous sclerosis and presented to us with flank pain and hematuria. On evaluation, he was found to have bilateral AMLs along with a thyroid nodule and also had Wunderlich's syndrome.

ARTICLE HISTORY

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Tuberous sclerosis; Wunderlich's syndrome; thyroid; angiomyolipoma

Case Report

A 25-year-old male presented to us with complain of right flank pain for 2 months and recurrent episodes of gross hematuria. The pain was intermittent, colicky in nature, and got relieved by taking over the counter analgesics, but the present episode of pain was intractable. There was no history of fever, lower urinary tract symptoms, trauma, seizure, or any previous surgery. On examination, there was a bimanually palpable abdominal lump on his right flank. His pulse rate was 126 per minute and blood pressure was 90/54 mm of mercury. The patient gave a history of skin lesions at various places on his body. On examination, he was found to have adenoma sebaceum (Fig. 1), hypo-melanotic macules (Fig. 2), Shagreen patch on the sacral region (Fig. 3), and peri-ungal fibromas (Fig. 4). The patient had a visible swelling on the neck, which moved with respiration (Fig. 5). On palpation, both lobes of the thyroid gland were enlarged with a palpable nodule in the right lobe. The patient had no visual



Figure 1. Adenoma sebaceum (facial angiofibromas).



Figure 2. Hypo-melanotic macule on the arm.

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Figure 3. Shagreen patch.



Figure 5. Enlarged thyroid lobes on inspection.



Figure 4. Peri-ungal fibromas.



Figure 6. CECT showing heterogeneous enhancing fat containing lesion (9 × 8.5 × 6 cm) at the lower pole of the RK (AML) with a non-enhancing heterogeneous area with hyper dense component (hematoma with active bleed). A pseudo-aneurysm is seen (arrow)..

complaints and was not on spectacles. The patient had no neurological or respiratory symptoms. He was hemodynamically stabilized with intravenous crystalloids and investigated. The patient's hemoglobin was 8.5 g/dl and total leucocyte counts were 10,900/mm^3. His kidney function tests were normal (Blood urea 34 mg/dl, serum creatinine 0.85 mg/dl, serum sodium 145 mmol/l, and serum potassium 4.2 mmol/l). Serum tri-iodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone were within normal limits, at 121 ng/dl, 7 µg/dl, and 1.58 mIU/l, respectively. Ultrasonography (USG) of the abdomen was suggestive of irregularly enlarged bilateral kidneys with multiple hypo-echoic renal lesions. Once the patient was stabilized, then further investigations were done. Contrast-enhanced computed tomography (CECT) scan of the abdomen and thorax was done which showed a heterogeneously enhancing fat containing lesion (9 × 8.5 × 6 cm in size) at the lower pole of the right kidney (RK). Within this lesion, there was a non-enhancing heterogeneous area with hyper dense components and a small enhancing aneurysm projecting into it, suggestive of right renal angiomyolipoma (AML) with active bleeding (Fig. 6). A similar

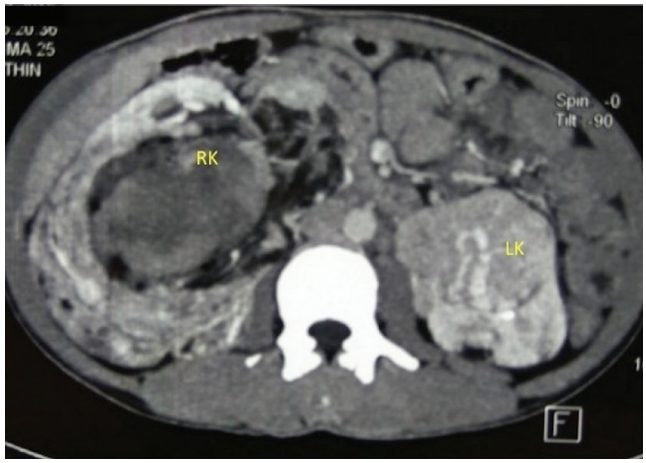


Figure 7. Axial section on CECT abdomen showing AML with hematoma in the RK and a lower pole AML in the LK.

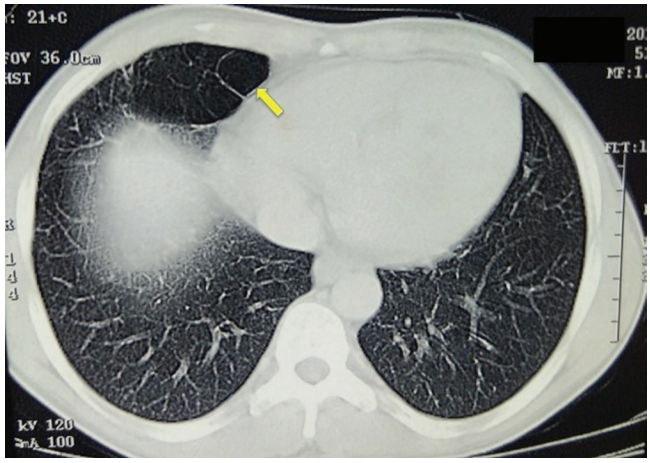


Figure 8. CECT thorax demonstrating thin walled cysts along the medial segment of the middle lobe of the right lung suggestive of para-septal cysts (yellow arrow).

enhancing lesion (suggestive of AML) without any bleeding/hematoma was also seen in the lower pole of the left kidney (LK) (Fig. 7). In the thorax, there were radiolucent thin-walled cysts along the medial segment of the middle lobe of the right lung, suggestive of para-septal cysts (Fig. 8). On USG neck, he was found to have a well-defined hypo-echoic nodule (9.2 × 8.0 mm) arising from the right lobe of the thyroid gland with the normal left lobe. Fine needle aspiration cytology of the nodule was done, which was suggestive of colloid goiter. Visual acuity was 6/18 in both eyes. Fundus examination revealed a nodular mass in the supra-temporal region of retina about 1.5 × 0.5 disc diameters (DDs) in size along with a satellite lesion in the far temporal lesion and an atrophic satellite lesion about two DD infero-nasally, suggestive of retinal astrocytoma. Non Contrast Computed

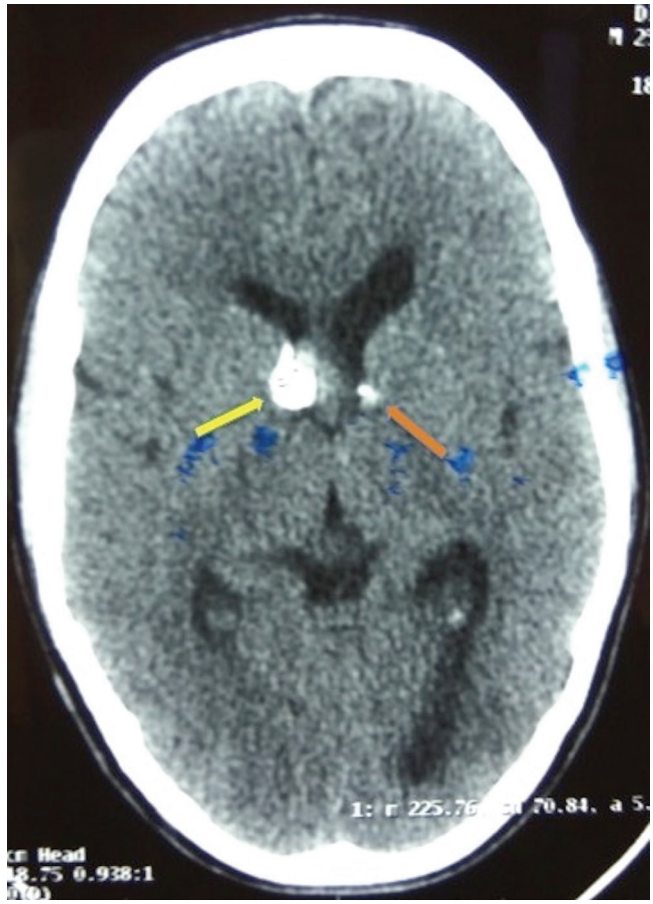


Figure 9. CT head demonstrating subependymal calcified lesion with soft tissue component at the level of the right foramen of monro (yellow arrow) suggestive of giant cell astrocytoma with another subependymal tuber at the region of the left foramen of monro (red arrow).

Tomography (NCCT) head revealed subependymal calcified lesions with soft tissue components suggestive of subependymal giant cell astrocytoma (Fig. 9). Electrocardiogram of the patient was suggestive of left ventricular hypertrophy while echocardiography suggested left ventricular hypertrophy with an ejection fraction 66%. The patient was given the option of trans-catheter arterial embolization (TAE) but as he was from the poor economic background and had no insurance, it could not be performed. The patient was counseled and was planned for partial nephrectomy, explaining him clearly that total nephrectomy may have to be performed due to extensive involvement of the RK. As the AML involved almost the entire RK, we performed right open radical nephrectomy with a flank incision. The patient faired well post operatively and was discharged on the sixth day. The thyroid swelling was asymptomatic and he has been kept on regular follow-up for it. For the AML in his contralateral kidney, he is on semi-annual follow-up.

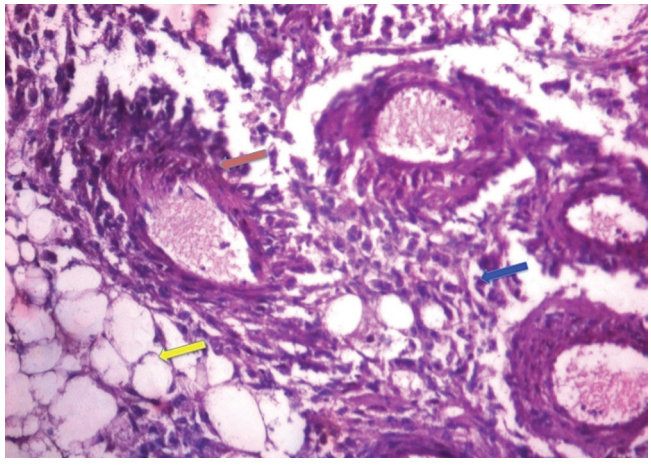


Figure 10. Photomicrograph at 10× magnification showing mature adipocytes (yellow arrow), thick walled blood vessels (red arrow), and mature smooth muscle cells (blue arrow), all characteristic of AML.

Histo-pathological examination of the resected kidney revealed a tumor composed of mature adipocytes, smooth muscles, and thick walled blood vessels. These features were consistent with a diagnosis of AML (Fig. 10). The resection margins were free and there was no capsular breach. Six months after the surgery, the patient is presently asymptomatic and the thyroid swelling has not increased in size on repeat USG scan.

Discussion

Tuberous sclerosis or tuberous sclerosis complex (TSC) is a genetic neurocutaneous disorder with multisystem involvement and an incidence of approximately 1/10,000 births. The inheritance pattern is autosomal dominant with incomplete penetrance. The two main genes implicated for its pathogenesis are TSC1 and TSC2 located on chromosomes 9q34 and 16p13, respectively. TSC traditionally is said to have multi-organ involvement and is characterized by a multitude of clinical features including seizures, mental retardation, hamartomatous lesions such as facial angiofibroma, shagreen patches, cardiac rhabdomyoma, subependymal giant cell astrocytoma, and renal AML. There are clearly defined major and minor criteria and based on them a patient is said to have TSC when he has two major criteria or one major criterion and ≥2 minor criteria present. If a pathogenic mutation in the TSC1 or TSC2 gene is found, then by itself it is sufficient for a definite diagnosis [1]. A variety of lesions have been reported in TSC but associated lesions in the thyroid gland are rare. AML is the commonest renal lesion reported in TSC and when present, it is the most common cause of morbidity in these patients. AMLs are prone to spontaneous renal hemorrhage leading to Wunderlich's syndrome, more so when they are associated with TSC [2]. Close to 300 cases of Wunderlich's syndrome have been reported in the literature, whereas incidence of thyroid lesions in TSC is even rare, confined to anecdotal case reports. In 1856, C.R.A Wunderlich first described a rare clinical condition with spontaneous renal bleeding of non-traumatic origin contained within the Gerota's fascia. This condition with a triad of acute flank pain, palpable flank mass, and clinical hemodynamic deterioration (Lenk's classic triad) was thus named Wunderlich's syndrome in 1910 [3]. AML is a benign neoplasm characterized by having variable amounts of mature adipose tissue, smooth muscles, and thick walled vessels. AML is the most common cause for Wunderlich's syndrome. AML is seen in 60% to 80% of patients with TSC. In these patients, AML is usually bilateral and more often symptomatic [4]. The vessels inside AMLs are often dysmorphic and can have micro or macro aneurysms, which may spontaneously rupture leading to Wunderlich's syndrome. If this complication develops, then the management options include conservative (only when the patient is hemodynamically stable), selective TAE, and nephrectomy. In AML associated with TSC, usually total nephrectomy has to be done because the lesions are multifocal [5]. There have been anecdotal reports of thyroid disease in patients with TSC. Hypothyroidism, thyroid dysgenesis, goitre, thyroid adenoma, thyroid papillary carcinoma, and medullary thyroid carcinoma have been reported in patients with TSC. Currently, to look for thyroid disease or its surveillance is not standard of care in patients with TSC [6,7]. In a recent retrospective study of thoracic CT scans, the authors found thyroid lesions (incidental as well as symptomatic) in 19 of the 93 cases of TSC. They concluded that as there is the potential of malignancy in thyroid nodules and because patients with TSC undergo multiple CT scans, follow-up with USG is warranted in cases of TSC with incidental thyroid lesions [6,8]. Though there are many case reports describing an associated thyroid lesion in TSC, there is yet no definite evidence establishing thyroid lesions as a part of TSC. It probably requires a well-conducted prospective study to find out whether there is an increased incidence of thyroid lesions in TSC or is it the same as in the general population.

Conclusion

Renal AML is the most important cause of morbidity in patients with TSC and its appropriate management is imperative. When a patient of AML develops Wunderlich's syndrome, total nephrectomy has to be done most of the times but TAE may be tried where facilities are available. Lesions of the thyroid gland are not considered as a part of TSC at present, but recent reports suggest that a patient with concurrent TSC and thyroid lesion should be carefully monitored.

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