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Case report

Missed tuberous sclerosis complex with multi-system complications in a single patient☆,☆☆

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ABSTRACT

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by widespread clinical manifestations. Early diagnosis is usually possible when typical TSC related skin lesions and neurologic presentations are detected in young patients. Undiagnosed TSC patients are at increased risk of morbidity and mortality as disease progression will inevitably lead to complications. While case reports of single complications in pediatric patients have been documented, to the best of our knowledge, multi-system complications of TSC in adults have yet to be reported in the literature. We present a case of tuberous sclerosis diagnosed in adulthood with complications involving the central nervous, renal and respiratory systems. This case highlights the need for a multidisciplinary approach in the management of TSC as well as the role of imaging in both diagnosis and intervention.

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder with widespread clinical manifestations. Patients are typically diagnosed in early childhood owing to the characteristic clinical manifestations of infantile spasm, learning disabilities, facial angiofibroma, shagreen patch, or hypomelanotic macules.

Patients can present with various symptoms and severity, ranging from mild to life-threatening seizures or intraabdominal hemorrhage. Common complications include intractable epilepsy and renal angiomyolipomata which lead to hemorrhage or destruction of viable renal tissues causing renal failure. Pulmonary lymphangioleiomyomatosis is a well-known pulmonary involvement that may cause recurrent pneumothorax or chylothorax. Causes of death vary and up to 40% of TSC patients die by 35 years old [1]. The most common cause of mortality in TSC patients is status epilepsy or sudden unexpected death in epilepsy [2]. While case reports of single complications in pediatric patients have been documented, to the

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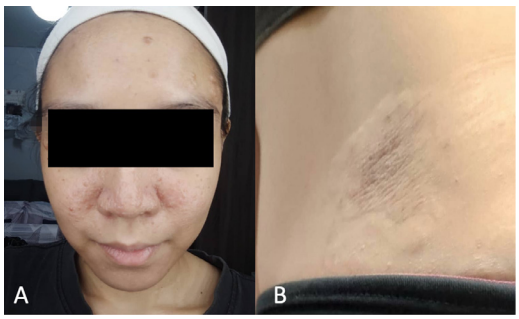

Fig. 1 – Clinical photographs of the face and right flank. There are neurocutaneous manifestations of tuberous sclerosis, namely, (A) adenoma sebaceum and (B) shagreen patch.

best of our knowledge, multi-system complications of TSC in adults have yet to be reported in the literature.

Imaging plays an important role in establishing the diagnosis, determining the extent of disease, and surveilling disease progression. Timely and appropriate imaging studies facilitate early detection of TSC associated complications and helps in the treatment decisions.

Case report

A 24-year-old woman presented to the Ophthalmology Department with sudden blurry vision and headache. She denied other neurological or systemic symptoms. General examination showed sebaceous adenoma and a shagreen patch at her right lower back (Fig. 1). She experienced one episode of seizure at the age of 6 months but did not receive further medical attention. There was no family history of seizures or learning disabilities. She developed skin lesions on both her cheeks and the flank region at the age of 7 years.

Fundoscopic examination revealed bilateral swollen optic discs, loss of cup-disc ratio, and silver wiring retina. Contrasted CT brain demonstrated an enhancing intraventricular mass with foci of calcifications arising from the right lateral ventricle (Fig. 2). Avidly enhancing intraventricular masses arising from the foramenina of Monro with obstructive hydrocephalus and midline shift was seen on MR brain. Also, multiple cortical and subcortical T2W/FLAIR linear hyperintensities were noted on T2 weighted MR images seen adjacent to the left lateral ventricles (Fig. 3). Excision of the intraventricular lesion was undertaken. Histological findings of the resected lesion were in keeping with subependymal glial cell tumor. Diagnosis of TSC was then established based on her clinical and neuroimaging findings. Screening ultrasound abdomen showed bilateral large renal echogenic masses (Fig. 4). CT of the abdomen and pelvis revealed bilateral angiomyolipomata, and she was referred to Urology for further management. However, she refused treatment and was temporarily lost to follow-up.

A year later, she presented to the Emergency Department with acute generalized abdominal pain and distention.

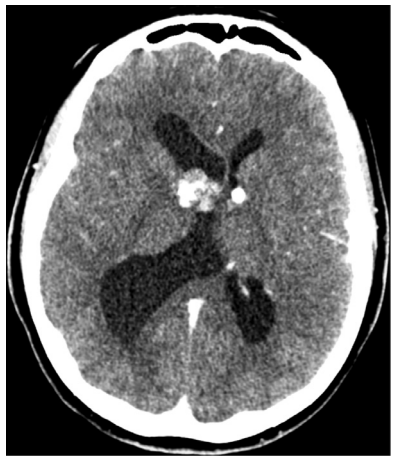

Fig. 2 – Contrasted axial CT brain image at the level of the basal ganglia showing lobulated enhancing mass (white arrow) in both ventricles.

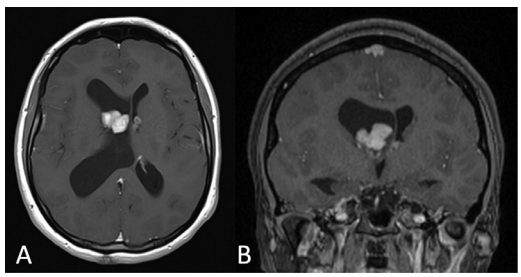

Fig. 3 – Axial (A) and coronal (B) post-contrast T1-weighted MR images demonstrating enhancing masses at the foramina of Monroe in keeping with subependymal giant cell astrocytoma.

An abdominal radiograph showed dilated small bowel loops and bedside ultrasound demonstrated free fluid at Morrison's pouch. Provisional diagnosis included intestinal obstruction secondary to huge renal masses or rupture renal AML. Multiphase renal CT showed multiloculated cystic pelvic abscess with larger bilateral renal AML (Fig. 5). She was admitted and underwent laparotomy for pelvic abscess drainage. Intra-operatively a large right adnexal cyst containing pus and mucoid material was removed. This cyst was adherent to the small bowel, oomentum, and the rectosigmoid colon. Histopathological diagnosis was reported as infected right ovarian cyst containing pus.

During her admission, she developed sudden onset of shortness of breath with S1Q3T3 electrocardiogram findings. CT pulmonary angiogram was negative for pulmonary embolism, with diffuse well-circumscribed thin wall cystic lesions distributed equally in both lung fields in keeping with lymphangioleiomyomatosis (LAM) (Fig. 6). However, there were CT findings of left pleural effusion with consolidation which were thought to cause the sudden episode of breathlessness. She was treated with a course of antibiotics and her symptoms resolved.

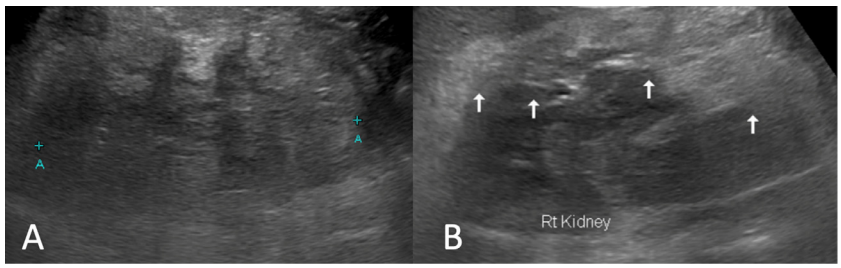

Fig. 4 – Longitudinal ultraound images of both kidneys. There are hyperechoiec lesions with no significant posterior acoustic shadowing in the right kidney (A). Ultrasonogram of the right kidney demostrates similar large hyperechoiec lesions (B).

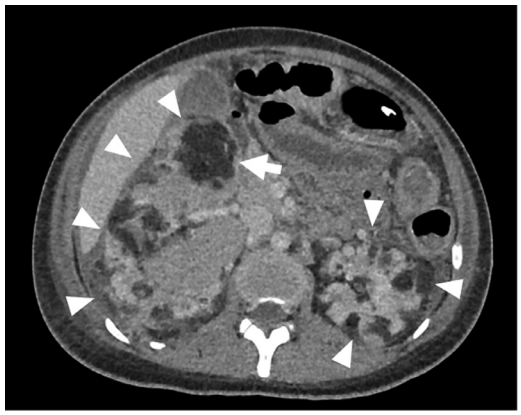

Fig. 5 – Axial contrasted CT abdomen image showing bilateral large renal masses (white arrow heads)with macroscopic hypodense fat densities within (white arrow).

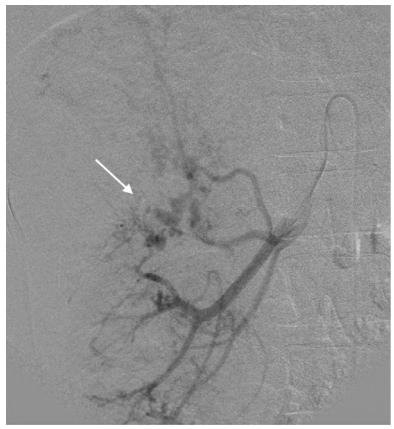

Fig. 7 – Digital subtracted angiography of right renal artery showing multiple midpole and lower pole pseudoaneurysms (white arrow).

Two months after her laparotomy, she complained of frank hematuria and she was referred back to the Urology team. Her pulse, blood pressure, and hemoglobin level were normal. Emergent renal angiogram demonstrated segmental mid and lower pole pseudoaneurysms in the right kidney and selective arterial embolization was performed in the same setting (Fig. 7). During her subsequent follow-up no further evidence of hematuria.

Discussion

TSC affects 1 in 6,000 births, caused by mutations in either TSC1 or TSC2 genes which are the tumor-suppressor [3]. More than 80% of TSC are diagnosed during early childhood [4]. Severe complications arise from associated manifestation in cardiac, ophthalmic, renal, neurologic and pulmonary systems. Cardiac rhabdomyoma is the most frequent benign childhood cardiac tumor which often related to TSC. It can be diagnosed prenatally in ultrasound. It affects 60% of TSC chil-

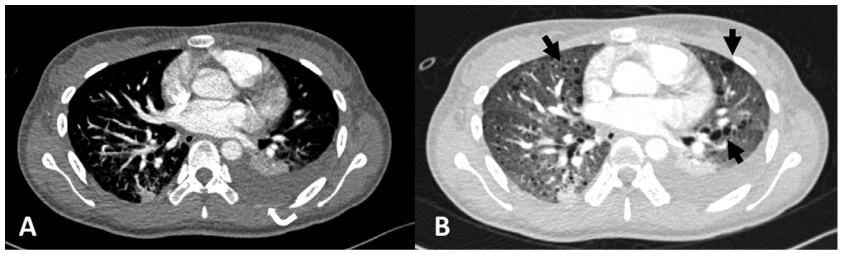

Fig. 6 – Axial contrasted CT thorax images in lung (A) and adjusted soft tissue window (B). There were multiple scattered well-defined air-filled cystic lesions with intervening normal lung tissue bilaterally (black arrow). Pleural effusion and consolidation noted on the left (white curved arrow).

dren however only involve 20% of TSC adults [5]. Cardiac rhabdomyomas are typically asymptomatic and usually regress spontaneously by first year of life. Retinal hamartoma affects 30%-44% of TSC patients [2]. Most common type of retinal hamartoma is a flat, translucent, and circular lesion located in the superficial retina detected during dilated fundoscopy. It is rarely progressive and cause visual disturbance. Annual evaluation is recommended for the identified ophthalmologic lesions.

Uncommonly, the diagnosis can be delayed until late childhood or adulthood when the characteristic neurodevelopment and cutaneous features are absent [6]. Early diagnosis of TSC is paramount to avoid complications as a result of delayed treatment [4]. Our patient did not have cognitive impairment nor a family history of clinical manifestation of TSC. She had a single episode of seizure when she was a 6-month-old infant, which did not receive further investigation. Facial angiofibroma only developed at the age of 7 years and she led a relatively normal life, unaware of her condition until she presented to us with blurring of vision. She fulfilled the diagnostic criteria of TSC by having histologically confirmed glial cell tumor, renal AML and LAM in imaging, sebaceous adenoma and a shagreen patch [7].

Our patient presented with acute visual disturbance caused by the mass effect from an intraventricular subependymal giant cell astrocytoma (SEGA) which mandated immediate surgical resection. SEGA is the most common TSC-related brain tumor and serial CT or MRI is helpful in early detection and monitoring of SEGA before the lesions become symptomatic in a child with established TSC [8]. Good outcome and low recurrence rates have been reported in post-excision SEGA patients [9].

The incidental finding of bilateral large renal AML was an indication for close urology follow-up as renal AML are highly vascularized. AMLs are composed of smooth muscle, adipose tissue, and blood vessels [10]. In general, about 80% of AML are sporadic, single, small, and asymptomatic. The remainder 20% of AML are TSC-related, usually numerous, large, bilateral, and likely to grow aggressively and lead to alarming complication [11]. One life-threatening complication is retroperitoneal hemorrhage secondary to ruptured vasculature in a renal AML.

In our patient, her second contrasted CT abdomen, which done 1 year after the first study, demonstrated significantly larger bilateral renal AML. The rapid increment of size could be attributed to hormonal influences of estrogen and progesterone [12]. A common complication is ruptured pseudoaneurysms found within the tortuous vessels. Patients may experience hematuria, flank pain, or a felt abdominal mass with tenderness. AML larger than 4cm or intralesional aneurysms larger than 5 mm increase the risk of rupture [1]. Contrasted CT abdomen has been shown to aid in identifying the abnormal tortuous or dilated vessels which are prone to bleed before embolization [13]. Embolization is considered the first-line therapy in cases of acute renal hemorrhage. On the other hand, when a growing AML is asymptomatic (> 3 cm in diameter), mammalian target of rapamycin (mTOR) inhibitors can be used as first-line treatment. Selective embolization or kidney-sparing resection have also been shown to be effective second-line therapies in asymptomatic patients [14].

LAM is a rare disorder which predominantly affects females in the reproductive age group. It is seen in 30% of young women with TSC [15]. Well-defined, thin-walled lung cysts that distributed diffusely in both lungs is the hallmark imaging finding of LAM in CT thorax. The major complications are pneumothorax and chylothorax [16]. LAM usually progresses slowly but ultimately leads to respiratory failure . These patients should have yearly pulmonary function testing and surveillance with high resolution CT imaging every 2-3 years [14]. The definitive treatment for LAM is lung transplantation .

Conclusion

A multidisciplinary approach is needed for TSC in view of its multiorgan involvement. Early detected of TSC will help manage the disease progression, possibly averting neurologic, pulmonary, renal and cardiac complications. This case demonstrates how advanced TSC can incur significant morbidity in an adult patient and the role radio-imaging plays in its management.

Guarantor

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Patient consent

Written informed consent was obtained from the patient's next of kin for the publication of this case report.

Ethical approval

Not required.

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