Abstract
Tuberous sclerosis is characterized by typical skin and clinical manifestations with predilection to neoplasia. We describe the case of a 42-year-old female who presented with a mass and pain in right lumbar region with constitutional symptoms and generalized body aches since last one year. She had adenoma sebaceum, subungal fibromas and hepatomegaly. CT chest, abdomen and MRI revealed mass in the right renal fossa with wide spread extensions in the abdomen, left renal angiomyolipomas (AMLs) and intracerebral lesions. Her clinical and radiological findings were suggestive of tuberous sclerosis with multiple mass lesions. She had past history of being operated for right renal AML twelve years ago. In current admission she developed refractory seizures and required mechanical ventilation. Biopsies from the renal fossa mass and liver revealed epithelioid variant angiomyolipomas. It is an uncommon variant which can present with features of malignancy or local recurrence or distant metastasis occasionally. Our case emphasizes the importance of being acquainted with skin lesions which can help in early diagnosis and management of tuberous sclerosis.

Introduction
Tuberous sclerosis complex (TSC) is an inherited neurocutaneous disorder characterized by multisystem involvement and benign growths and are predisposed to develop malignancy. It occurs predominantly in females in the first decade of life. It is associated with a variety of benign tumors such as angiofibromas, rhabdomyomas, and angiomyolipomas (AML). We report a case of AML which relapsed and had widespread metastases.

Case Report
A forty-two year old female was admitted to the medical ward of the All India Institute of Medical Sciences, New Delhi in September 2014. She was the last child born out of a non-consanguineous marriage. At birth her parents noticed a hypopigmented macule over the abdomen. Her antenatal and postnatal course was normal. Her milestones were normal. By the age of 5 years, she developed hyperpigmented papules over the face. Similar lesions started appearing in the periungual regions of her fingers and toes by the age of ten years. For these skin and nail changes she had never consulted any physician.

At the age of 29 years in 2001, she developed recurrent episodes of colicky pain in the right loin. On evaluation, she was found to have a right renal mass. She underwent right nephrectomy and partial right segmental colectomy as the mass was infiltrating the colon. Histopathological examination showed features of an angiomyolipoma. She did not follow up with the clinic due to financial constraints. In 2012, at the age of 40 years, she developed a swelling in the right lumbar region associated with intermittent episodes of pain in the same region. After one year she started having bony pains in bilateral lower limbs. There was associated history of loss of appetite and significant weight loss. On detailed pedigree analysis there was no history of similar complaints in the family.

On examination, blood pressure was 128/70 mm of Hg, pulse rate -94 per minute, body mass index (BMI) was 17.3kg/m², and had severe pallor and bilateral pitting pedal edema. She had multiple firm, skin-colored to hyperpigmented nodules and plaques over the face consistent with angiofibromas (adenoma sebaceum) (Figure 1A), single hypopigmented macule was found in the epigastric region suggestive of ash leaf macule (Figure1B) and the nails showed periungual and subungal fibromas with longitudinal ridging and distal onycholysis (Figure 1C and...
A firm parietal wall swelling of size around 12cm x 10 cm was found in the right renal angle. Hepatomegaly was present with liver span of 18 cm. Rest of the examination was unremarkable.

On further evaluation she was found to have anemia with leukocytosis and deranged renal functions (Table 1). Renal function scan (DTPA) showed non visualization of right kidney and severe functional impairment of left kidney. Magnetic Resonance Imaging (MRI) of the abdomen (Figure 2) showed large heterogeneous mass lesion in the right renal fossa, which was infiltrating the posterior abdominal wall muscles, segment VII of liver and diaphragm and there were multiple metastatic nodules in the liver, lung and bones (vertebra, pelvic bones and femur). Multiple enlarged retroperitoneal lymph nodes were identified. Left kidney was studded with angiomyolipomas. In addition, a large exophytic mass was seen at the lower pole. MRI brain (Figure 2A) showed multiple cortical tubers in all the lobes and subependymal nodules in both lateral ventricles consistent with neurological manifestations of tuberous sclerosis. HRCT chest (Figure 2C) revealed multiple thin walled cysts consistent with pulmonary lymphangioleiomyomatosis.

During the hospital stay, she developed refractory seizures and deterioration of sensorium requiring mechanical ventilation. Subsequently, she succumbed to the illness due to sepsis and multiple organ dysfunction. Post-mortem biopsies were done from the renal fossa mass, liver and the lung. The biopsies from the renal fossa mass and the lung both showed a similar tumor (Figure 3), composed of sheets of medium to large polygonal cells with abundant pale eosinophilic cytoplasm, round vesicular nuclei and prominent nucleoli. Areas of necrosis were identified. On morphology, the possibilities of renal cell carcinoma and epithelioid angiomyolipoma were considered. On immunohistochemistry, the tumor cells were immunopositive for HMB-45, vimentin, and smooth muscle actin (SMA), but were negative for cytokeratin (CK), epithelial membrane antigen (EMA) and CD10. Based on the histomorphological and immunohistochemical features, a final diagnosis of renal epithelioid angiomyolipoma (EAML) involving the renal fossa, infiltrating the liver and metastasizing to lung was made.
Discussion

This patient presented with history and clinical examination suggestive of tuberous sclerosis. Previous surgery had revealed angiomyolipoma. Surgery alone is associated with high rate of recurrence especially in tumors of large size (>9 cm), and those displaying nuclear atypia on histology as seen in our case. The diagnosis of TSC is based upon clinical criteria and/or genetic testing. Genetic testing is not required to make a diagnosis in patients who fulfil criteria for definite TSC. The classic TSC diagnostic triad of seizures, mental retardation, and facial angiofibromas (Vogt triad) occurs in less than one-third of patients with TSC. Thus, clinicians need to be familiar with the full spectrum of TSC-associated diagnostic features. Furthermore, there is a range of phenotypes between and within families that includes patients with normal to severely impaired neurologic function.

Current diagnostic criteria for tuberous sclerosis is from the International Tuberous Sclerosis Complex Consensus Conference. Our patient fulfilled six major criteria, including angiofibromas, ungual fibromas, subependymal nodules, cortical dysplasia, angiomyolipomas (AML) and lymphangioleiomyomatosis making it a very conspicuous presentation of tuberous sclerosis. She had no previous history of neurological manifestations, though she developed refractory seizures during hospital stay. Based upon an estimated prevalence of TSC of 1 in 15,000 children in the United Kingdom, the relative risk of malignancy in children with TSC was 18-fold higher than for those without TSC. It has been suggested that the risk of invasive cancer is higher in patients with TSC2 than TSC1 mutations. The malignancies associated with tuberous sclerosis include renal cell carcinoma (RCC), invasive EAML, glioblastoma multiforme and rhabdomyosarcoma.

Benign AML is a common renal manifestation of tuberous sclerosis. Its two histological types: classical and epithelioid variants have been described. The latter is a rare tumour, accounting for about 10% of AML and arises from the perivascular epithelioid cells. It can be benign, aggressive or malignant. Malignant variant closely resembles renal cell carcinoma.

Radiologically and histologically, it is difficult to differentiate epithelioid AML from renal cell carcinoma. On radiology, the reduced fat content in EAML leads to difficulty in differentiation from RCC. Novel techniques like chemical shift MRI can help in early detection of the disease.

Similar to classical AML, EAML stains positively with melanocytic markers viz. HMB-45 and Melan A, as well as smooth muscle markers viz. SMA, and is negative for epithelial markers viz. CK and EMA, and CD10 that are positive in renal cell carcinoma. While the cells of clear cell RCC are arranged in nests separated by thin fibrovascular septae, those...
of EAML are more discohesive and are usually seen in sheets. In the present case, on imaging RCC was kept as the first diagnosis. However, histological examination and use of an appropriate immunohistochemical panel helped to resolve the diagnostic dilemma.

Composite tumors comprising of RCC and AML within the same lesion are known to occur, especially in patients with tuberous sclerosis. Core biopsy can often pick up only one of the tumor components, leading to under-diagnosis.9

Certain gross and microscopic features, when present, should raise concern for malignant behavior, including size >15 cm, presence of necrosis, mitotic activity, nuclear anaplasia, and extra renal spread. These patients require close follow-up for early detection of local recurrence or distant metastases.8

Management options include active surveillance for small asymptomatic masses. In general, symptomatic masses and masses of a size greater than four centimetres should be treated. Therapies include radical or partial nephrectomy, selective arterial embolization and ablative therapies like cryo-ablation and radiofrequency ablation. mTOR inhibitors like everolimus have been shown to decrease tumour volume and progression with acceptable safety profile in both AML and EAML.10,11 Definitive role of the same as neoadjuvant or nephron sparing therapy requires further research.

References