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Case Report

Pathology Section

Bilateral Multifocal Renal Angiomyolipoma Associated with Wunderlich's Syndrome in A Tuberous Sclerosis Patient

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ABSTRACT

Renal Angiomyolipoma (renal AML) is a benign clonal neoplasm with a incidence of 0.3-3%, occurring as isolated sporadic entity or in association with Tuberous sclerosis (TS) in 80% cases. Multiple, bilateral renal AML are considered diagnostic of Tuberous sclerosis. Wunderlich's syndrome, a urological emergency is a spontaneous nontraumatic bleeding into subcapsular and or peri-renal space and is a life threatening complication of renal AML occurring in 10% cases which has to be timely diagnosed and treated. Here, we present an unusual case of TS with bilateral, multifocal renal AML in a 25-year-old female who presented with Wunderlich's syndrome, which is a rare but life threatening complication that has to be suspected, timely diagnosed and treated. We have discussed the importance of early diagnosis, timely treatment, follow up and education of patient and relatives of the possible complications associated.

Keywords: Bilateral, Female, Life threatening

CASE REPORT

A 25-year-old female presented to urology OPD with complaints of abdominal pain, mass in right side of abdomen, fever since two months. She gave history of sudden increase in pain and size of the mass and frank haematuria. On examination, patient was pale, had multiple adenoma sebaceum on her face [Table/Fig-1]. Abdominal examination revealed tender, firm, bimanually palpable mass extending from the right hypochondrium to right lumbar region.

A positive history of mother and brother having adenoma sebaceum was present. There was no history of seizures, loss of vision. Haemoglobin was 9gm/dl. Urine microscopy showed red cell casts and RBC's. Further investigations were done. Ultrasonography revealed bilateral enlarged kidneys showing multiple, nodular, hyperechoic lesions with right kidney showing a large haematoma.

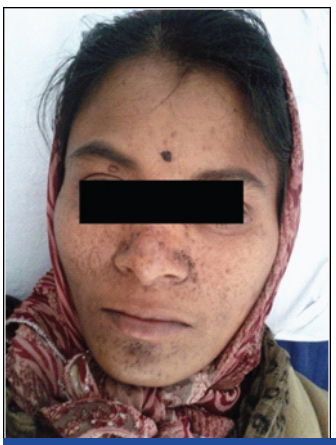
Contrast enhanced CT abdomen revealed bilateral enlarged kidneys showing multiple fat densities. Right kidney showed a large heterogenous lesion measuring 13.2 x 11.5 x 7.5 cms and large sub acute haematoma measuring 8.2 x 8.1 cms in the lower pole suggestive of ruptured AML [Table/Fig-2]. CT brain revealed multiple calcified sub ependymal nodules [Table/Fig-3].

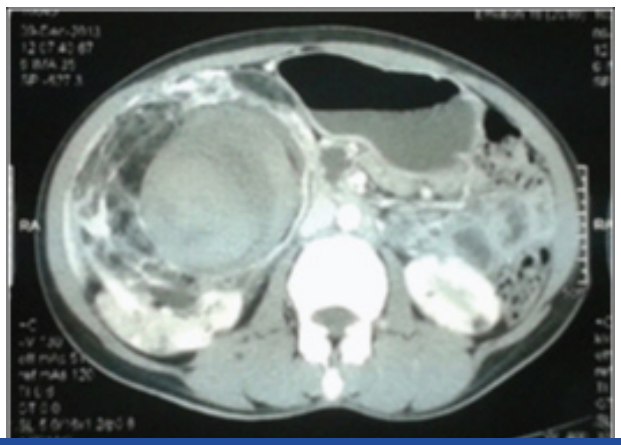
A diagnosis of TS with bilateral, multifocal renal AML with Wunderlich's syndrome was made. Patient was transfused 2 pints of packed RBCs. Exploratory laprotomy and enucleation of tumour in right kidney along with the haematoma was done. Histopathology showed a well encapsulated globular soft tissue mass measuring 15 x 11x 8cm weighing 850g, with the haematoma measuring 8x8 cm with compressed renal tissue on one side. Cut surface showed yellow to tan tumour mass with areas of haemorrhage.

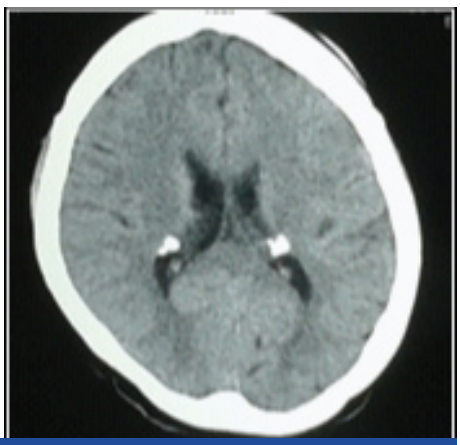
Microscopy revealed a tumour composed of areas of mature adipose tissue, thick walled, hyalinised blood vessels and bundles of smooth muscles with perivascular epitheloid cells [Table/Fig-4]. No evidence of nuclear atypia or increased mitoses seen. Immunohistochemistry with HMB-45 showed immunoreactivity in the perivascular epitheloid cells [Table/Fig-5]. The diagnosis of renal AML was made. Patient recovered uneventfully and was discharged from the hospital on the 5th postoperative day. At 6 months follow up, there was neither evidence of tumour recurrence on same side nor evidence of an obvious increase in size of nodules in the opposite kidney.

DISCUSSION

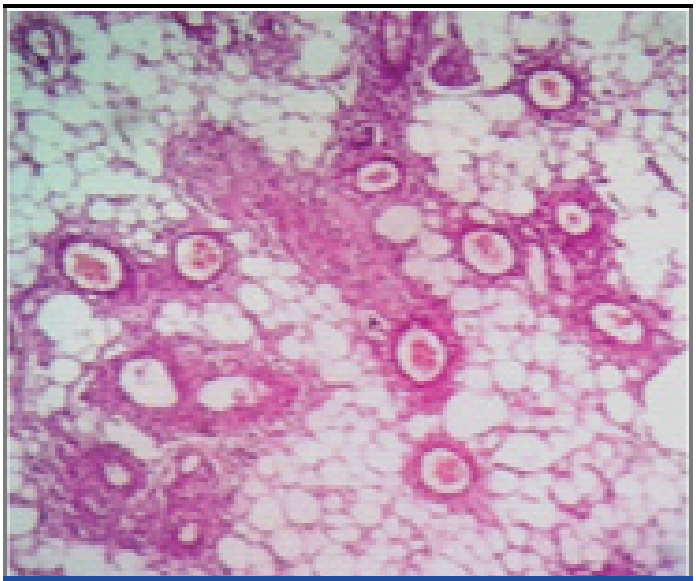
Tuberous sclerosis (TS) or Bournville-Pringle disease is a relatively rare autosomal dominant disorder with variable penentrance affecting approximately 1 in 10,000 population [1,2]. Classically the disease is described as a clinical triad of adenoma sebaceous, mental retardation and seizures. The pathophysiology can include



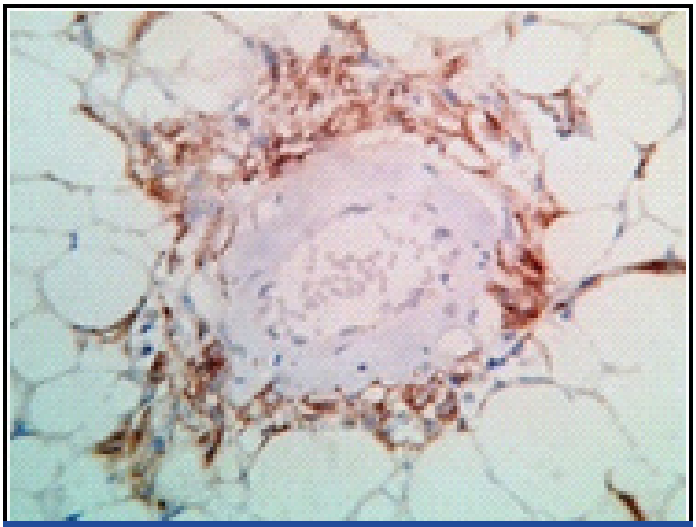




[Table/Fig-1]: Multiple adenoma sebaceum on face **[Table/Fig-2]:** CT abdomen showing bilateral renal AML with large intratumoural bleed on right side
[Table/Fig-3]: CT brain showing calcified Sub ependymal nodules



[Table/Fig-4]: Angiomyolipoma showing fat, hyalinised blood vessels and smooth muscles (H&E,x100)



[Table/Fig-5]: Perivascular epitheloid cells showing HMB-45 immuno reactivity (IHC, x100)

glial tumours of brain, adenoma sebaceus of skin, rhabdomyoma of heart and hamartomatous tumours of thyroid, retina, liver, pancreas, lung, kidney, adrenals and ovaries [1,2]. Three types of renal involvement have been described in TS: a) Renal AML (40-80%); b) Cystic disease (occasionally); c) Renal cell carcinoma, with the most common renal lesion being AML [3]. A rare concurrence of Bilateral RAML and Renal cell carcinoma was reported by Khallouk A et al., in a 35-year-old man with TS [4].

Histologically AML is a benign renal neoplasm composed of mixture of 3 tissue types- benign smooth muscle in sheets and bundles, thick walled muscular blood vessels which lack elastic lamellae and mature fat [1]. One of the most feared complications of renal AML is Wunderlich's syndrome, occurring in 10% of patients. By definition, Wunderlich's syndrome is a spontaneous non traumatic bleeding into the sub capsular and or peri renal space, and is characterized by the classic triad of symptoms of acute abdominal pain, a palpable mass and hypovolemic shock [5], as seen in the present case. Similar cases of Wunderlich's syndrome have been described in the literature which are tabulated below [Table/Fig-6].

AML occur as isolated sporadic entities and in association with TS [1]. They are typically large, multifocal, bilateral and occur in younger patients when associated with TS. In 70 to 80% of patients with AML without TS, a more pronounced female predominance is found and most patients present later in life, during fifth or sixth decade [5]. These findings are supported by the literature review shown in the

Author	Age of patient	Sex of patient	Laterality	Association with TS	Year of reporting	Maximum diameter of index lesion
Khan AS et al.,[1]	29	F	Bilateral	Present	2003	40 cm
Mongha R et al., [5]	32	F	Bilateral	Present	2008	Not mentioned
Nabi N et al., [6]	47	F	Bilateral	Present	2007	Not mentioned
Medda M et al., [7]	50	F	Unilateral	Absent	2009	22 cm
Kushwaha R et al.,[8]	35	F	Unilateral	Present	2010	15 cm
Lin CY et al., [9]	57	F	Unilateral	Absent	2011	Huge
Vaddi et al., [10]	25	F	Bilateral	Present	2011	Not mentioned
Ploumidis A et al., [11]	32	F	Unilateral	Absent	2013	7.6 cm

[Table/Fig-6]: Table showing cases of Wunderlich's syndrome from the literature

[Table/Fig-6]. Benign and malignant renal tumours, renal infections, nephritis, vascular lesions like PAN, anatomical lesions like cysts and hydronephrosis, previously undiagnosed haematological conditions are the common causes of Wunderlich's syndrome [12]. The commonest cause of renal haemorrhage is an AML [12]. Lesions greater than 4 cms, multicentric lesions and those associated with TS have increased risk of haemorrhage [1,7].

AML's can exhibit areas of hypercellularity with atypia, posing specific diagnostic challenges. In such cases sarcomas including fibrosarcoma, leiomyosarcoma, liposarcoma, and sarcomatoid renal cell carcinoma need to be considered in the differential diagnosis depending on the predominant component present. Positive immunoreactivity for HMB-45 is characteristic of AML and positive in 100% of tumours, thus clinching the diagnosis [13].

Malignant transformation of AML, if it does occur is extremely rare. Two such cases were reported by Takahashi N et al., in the absence of association with TS. AML with many perivascular epitheloid cells should be classified as epitheloid AML. Malignant AML is considered to be a transformation of benign epitheloid AML. Diagnosis of malignancy can be made only on the basis of presence of metastases. On IHC, malignant AML are negative for epithelial markers (EMA, Keratin), but are positive for HMB-45 [14].

In general, asymptomatic AMLs with a diameter of 4 cm or smaller can be followed up. For larger and symptomatic tumours, surgical intervention should be considered [7]. Nephron sparing approach such as angio-embolisation or partial nephrectomy is preferable, especially in TS with bilateral, and multiple AML [15] as was done in the present case.

CONCLUSION

Renal AML are unusual lesions that behave in a benign fashion, however when associated with TS, can result in life threatening haemorrhage. So, an early diagnosis and timely treatment is important in these cases to prevent life threatening complications. Regular follow up of smaller lesions for progression and a thorough search for hamartomas in other sites, which are a part of tuberous sclerosis complex, is warranted. Patients and the relatives have to be educated about the pathology of the disease and to report immediately in case of appearance of sudden abdominal pain / haematuria.

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