Epithelioid Angiomyolipoma of kidney - An uncommon tumor mimicking renal cell carcinoma .

Kavitha K.P[1], Shalini Kuruvila[2], Jyotsna Yasodharan[3], Sajna V.M.Kutty[4], Lilly Madhavan[5]

[1]Department of Pathology.Malabar Institute of Medical Sciences Ltd.Kozhikode,Kerala.

ABSTRACT

Introduction: Epithelioid angiomyolipoma (EAML) is an uncommon variant of angiomyolipoma (AML) with malignant potential, frequently associated with tuberous sclerosis complex. Only few cases have been reported so far in the literature. Preoperative diagnosis is difficult. Differential diagnosis from renal cell carcinoma is often challenging because of its epithelioid morphology and carcinoma like growth pattern. Case report: A 52 year old man presented with progressive weight loss and abdominal pain .CT scan showed a large renal mass on right side .With a radiological diagnosis of renal cell carcinoma he underwent laparoscopic nephrectomy. With histopathological and immunohistochemical features a diagnosis of epithelioid angiomyolipoma was made .Retrospectively we came to know that he is a known case of tuberous sclerosis

Conclusion: EAML should be a differential diagnosis when we are dealing with renal tumors in young patients with tuberous sclerosis and with epithelioid morphology and high nuclear grade. It is important to have a high index of suspicion so that a correct diagnosis can potentially direct clinician to a more effective targeted treatment using mTOR inhibitors especially in TSC associated cases.

Key words: Epithelioid angiomyolipoma, mesenchymal, tuberous sclerosis,immunohistochemistry.

Corresponding author address: Kavitha Kanjirakkattu Parameswaran, Department Of Pathology. Malabar Institute Of Medical Sciences Ltd.Kozhikode,Kerala, Phone:04952300142 Mobile: 91 9447691391, **E-Mail:** kpkavi@gmail.com

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INTRODUCTION

Angiomyolipoma(AML) is a rare mesenchymal tumor frequently associated with tuberous sclerosis complex (TSC). Renal AML, also known as hamartoma, is a relatively rare benign tumor that appears in 0.3% of the general population and accounts for 3% of solid renal masses.Epithelioid angiomyolipoma (EAML) is an uncommon variant of angiomyolipoma with malignant potential and was first described in 1995 by Martignoni et al as a distinct clinicopathologic variant of AML which is mainly characterized by a predominance of epithelioid cells 1. Pea et al in 1998 described EAML as tumor composed purely of epithelioid cells arranged in sheets and are characterised by the absence of both adipocytes and abnormal vessels 2.They are usually solitary, whereas in TSC they are commonly multiple and bilateral.EAML is more frequently associated with tuberous sclerosis compared to classical variant. We hereby report a case of EAML in a 52 year old man with tuberous sclerosis.

CASE REPORT

A 52 year old male came with complaints of lower abdominal pain and progressive weight loss. There was no associated hematuria. He was a known hypertensive on treatment. Physical examination revealed a mass in the right loin. Routine blood investigation revealed mild anemia with a Hb value of 9.4 g/dl. His serum creatinine level was elevated (1.5mg/dl).CT scan showed a right renal mass . With a radiological diagnosis of renal cell carcinoma he underwent laparoscopic right radical nephrectomy.

PATHOLOGICAL FINDINGS:

Gross examination of kidney showed a large tumour measuring 10.5x8x8.5 (Fig 1). There were areas of necrosis and haemorrhage. Microscopically the tumor was composed of sheets of large polygonal cells having abundant eosinophilic cytoplasm and marked nuclear pleomorphism. Ganglion like cells and bizarre cells with multinucleation and macro nucleoli were present (Fig 2). Vast areas of necrosis and haemorrhage noted. Occasional mitotic figures were seen. Immunohistochemistry revealed Melan A positivity cytokeratin and S100 negativity in the tumor cells (Fig 3).Desmin showed weak positivity. A final diagnosis of epithelioid angiomyolipoma (EAML) was given. Retrospectively we came to know that the patient was a known case of tuberous sclerosis.

Figure 1 : Gross image of necrotic tumor mass in the kidney.

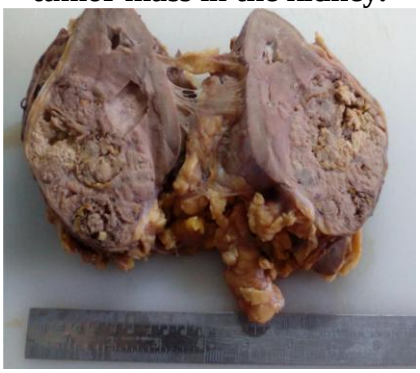


Figure2 Note the predominant epithelioid morphology. Cells polygonal having abundant eosinophilic cytoplasm and pleomorphic vesicular nuclei exhibiting macronucleoli.(Haematoxylin & Eosin, 40X).

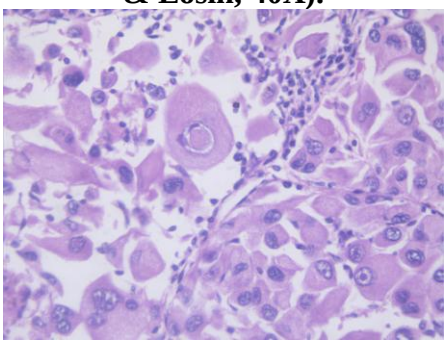
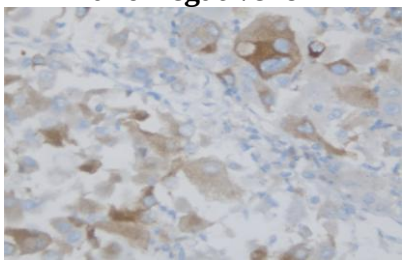
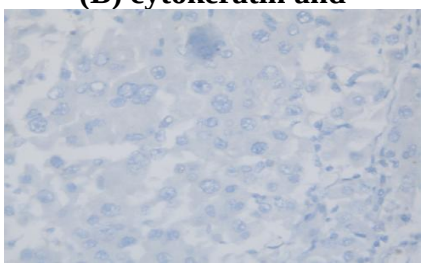


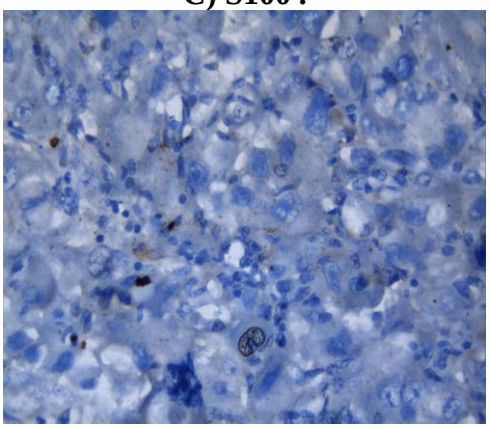
Figure3.Immunohistochemistry. A)Tumor cells are positive for melanA and negative for

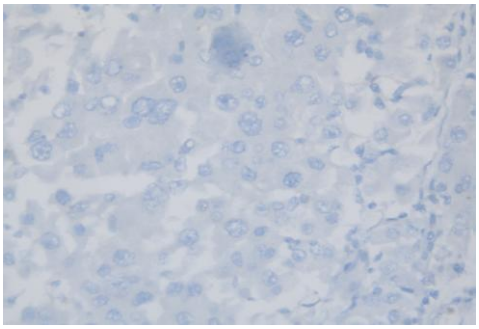


(B) cytokeratin and



C) S100 .





DISCUSSION

Epithelioid angiomyolipoma (EAML) is a rare variant of AML and is composed of purely epithelioid cells with melanogenesis markers. EAMLs account for about 8% of renal AMLs 3. Eventhough the classical variant of angiomyolipoma is a benign lesion , epithelioid angiomyolipoma is described as potentially malignant. Malignant behaviour including local recurrence and distant metastasis, has been reported in EAML4,5. Therefore, the current

World Health Organization Classification of Renal Neoplasms regards EAML as ‘‘a potentially malignant mesenchymal neoplasm’’ with adverse outcomes in approximately one-third of cases. It is proposed that p53 mutation may play an important role in malignant transformation of renal AML 6 . EAML affects both sexes almost equally, with an average age at diagnosis of 38 years 7 . Patients can be asymptomatic or can present with flank pain, a palpable mass and hematuria. A few of the patients may present with renal failure due to compression and replacement of renal parenchyma..Genetically, like classical angiomyolipoma, EAML is characterised by the loss of allelic short arm of chromosome 16.

There are no specific features of EAML in terms of clinical manifestations and imaging modalities. Renal EAML can have a range of imaging appearances and can be indistinguishable from renal cell carcinoma7. Hence preoperative diagnosis is difficult. In our case the radiological diagnosis was renal cell carcinoma. However EAML can be considered when a mass is found that has small foci of macroscopic fat without calcification or when acute hemorrhage of a renal mass occurs 8 .

EAMLs are usually larger tumors compared to the usual type with mean size 8.6cm versus 5.6 cm 3,7.Microscopically these are composed polygonal cells with clear to eosinophilic cytoplasm and round to oval nuclei that may show varying degree of nuclear atypia. Ultrastructurally, EAMLs show evidence of melanogenesis by the presence of premelanosomes. Under light microscope main differential diagnoses of EAML include renal cell carcinoma with rhabdoid features, renal oncocytoma, epithelioid smooth muscle tumor, epithelioid melanoma etc. Some tumors originally diagnosed as renal cell carcinoma are actually found to be EAML on review. Such misdiagnosis occurs particularly when other components of AML are obscure and atypia is prominent. In our case also we could not demonstrate abnormal blood vessels and intratumoral fat in multiple sections of the tumor studied. Our morphological differential diagnoses were renal cell carcinoma with rhabdoid features and epithelioid angiomyolipoma.Immunohistochemical evaluation helped us arriving at the right diagnosis of EAML,as the tumor cells expressed melanogenic marker and lacked cytokeratin and S100 positivity.

There has been no consensus as to the percentage of epithelioid cells required for diagnosing epithelioid-AML . Aydin et al set a minimum of 10% of epithelioid component to include the case in the EAML group. While Nese et al included only pure EAML(tumors with >95% epithelioid component) as epithelioid-AML in their study . Wenlei et al 9 considered only tumors with more than 80% epithelioid histology. The present case showed >95% epithelioid component .Immunohistochemical markers for AML include melanocytic markers such as HMB-45 , HMB-50, Mart-1/Melan-A, tyrosinase, and microphthalmia-associated transcription factor.Myoid markers such as smooth muscle actin, muscle specific actin, desmin . Other markers CD63and CD117 show variable immunopositivity.Epithelioid angiomyolipomas are typically negative for S100 protein and epithelial markers such as cytokeratin and epithelial membrane antigen 2,3,7 .

Malignant behavior, including local recurrence and distant metastasis, has been reported in approximately one-third of EAMLs1,7.According to Nese et al recurrence was seen in around 17% of patients and metastasis in about 50% of patients, out of which about 30% had metastatic disease at presentation. Metastatic sites included the liver , lung ,peritoneum , colon, pelvis and diaphragm . Regional lymphnode metastasis was also seen 10 . EAML can exhibit extension into perirenal soft tissue and involvement of the regional lymph node. Some authors regard this as an expression of multicentricity rather than metastases 11.According to Brimo et al. the rate of malignancy in EAML is around 26%. However, Aydin et al. 3 described benign clinical outcomes in all 15 of their patients. Wenlei at al 9 also found out that the incidence of malignant behaviour is very low. One reason for the variability in outcome among reports could be the small sample sizes in many of them, a consequence of the rarity of this entity and also the difference in selection of study population and design.

Currently there are no definite criteria for predicting malignancy in EAML . Different studies have put forward the features which can have association with the malignant behaviour . According to Brimo et al >70% epithelioid cells,>2 mitotic figures /10 high power field,atypical mitotic figures and necrosis are associated with malignant behaviour. Nese et al found that tumor necrosis ,primary tumor size >7cm,nuclear atypia,renal vein invasion and mitotic activity are associated with recurrence and metastasis . However, not all cases with cytologic atypia correlate with poor prognosis. Diagnosis of malignancy can be made only on the basis of the presence of metastases. In our case, there were worrisome histologic features like diffuse cytological atypia, carcinoma-like growth pattern, coagulative tumor necrosis and mitosis. Post operative work up did not reveal any evidence of metastasis. Patient is now under regular close follow up. To date there is not much data regarding the treatment aspect of this entity. Due to the difficulty in differentiating EAML from RCC, nephrectomy is a common procedure for large EAMLs. Resection alone may not be curative. Adjuvant therapy should be considered. In AML and TSC patients, there is disruption of TSC1 and 2 genes which results in inappropriate activation of mTORC1 . Recent studies have shown functional activation toward the mTOR pathway and sirolimus as a potential therapeutic target underscoring the need for accurate diagnosis 7,10,12,13. A multimodality treatment approach needs to be explored for this newly recognized malignant variant of renal angiomyolipoma.

To conclude we report a very rare variant of angiomyolipoma ,which is a potentially malignant tumor often misdiagnosed as renal cell carcinoma radiologically and histologically. The awareness of this entity and careful interpretation of histopathological and immunohistochemical features are needed to accurately classify this tumor. Properly designed studies are necessary to determine with more certainty which clinical and pathological features affect disease progression and to optimize their management.

CONCLUSION

EAML should be a differential diagnosis when we are dealing with renal tumors in young patients with tuberous sclerosis and with epithelioid morphology and high nuclear grade. It is important to have a high index of suspicion so that a correct diagnosis can potentially direct clinician to a more effective targeted treatment using mTOR inhibitors especially in TSC associated cases.

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