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Case Report

Surgery Section

A Case Series & Review of Literature of Angiomyolipoma with Medical & Surgical Perspective

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ABSTRACT

The angiomyolipoma of renal origin is a rare benign tumour composed of fat cells, smooth muscle cells, and thick-wall blood vessels. Mostly these are sporadic origin, asymptomatic and benign in nature.

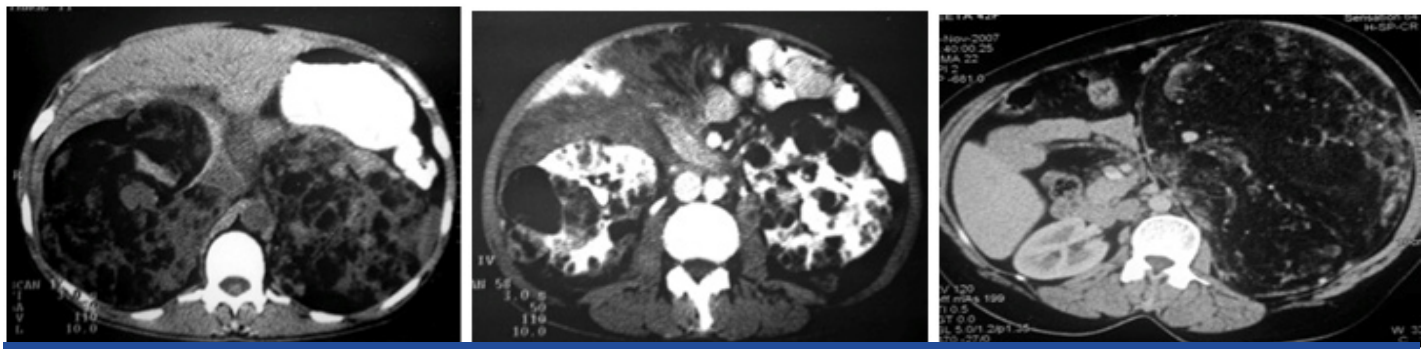
Here we present two cases of Renal angiomyolipoma (AML) presenting as fever, pain, perirenal haematoma & frank haematuria. After initial stabilization, evaluated by contrast enhanced computer tomography (CECT) & diagnosed as renal angiomyolipoma because of low Hounsfield areas (10-20HU) suggestive for fat. Patient later underwent angiography with selective angioembolisation. Post intervention period was uneventful and was treated by an oral Everolimus 10 mg daily for a period of one year in first case & partial resection was done in second case. On two year follow-up both patients were doing well & had normal renal function without any recurrence.

Embolisation is the emergency treatment of choice for bleeding angiomyolipoma. When preventive treatment is considered a nephron sparing approach by either transarterial embolisation or partial nephrectomy is clearly important. While angiomyolipoma in both kidneys or in solitary functioning kidneys, renal preservation is mandatory in order to avoid need for renal replacement therapy. Also, recently approved drug Everolimus may be considered for patients not suitable for surgery particularly in tumour seen with tuberous sclerosis.

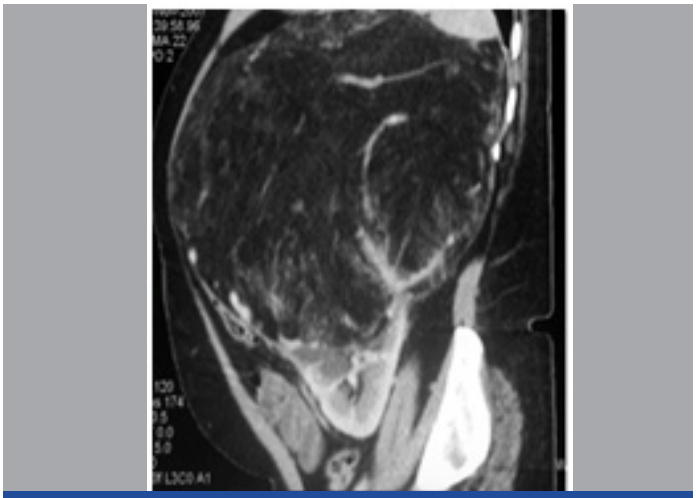
Keywords: Embolisation, Mesenchymal renal tumours, Tuberous sclerosis

CASE REPORT-1

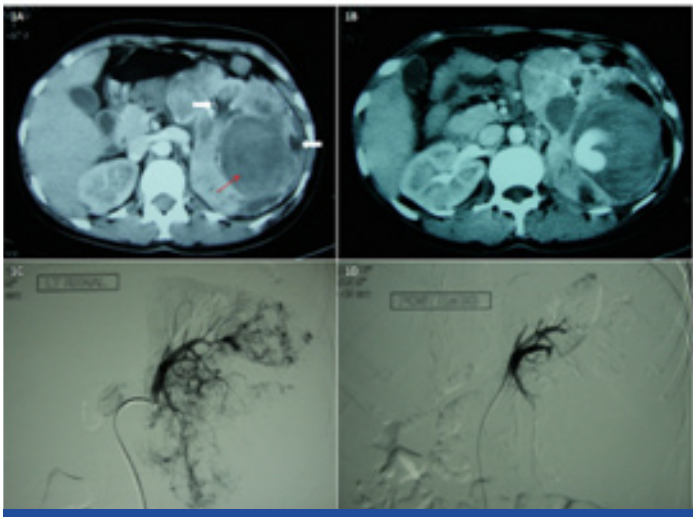
A 45-year-old man presented with profuse haematuria and agonizing right flank pain in a state of shock with severe pallor. Patient's intial vital's were pulse rate was 130/minute, blood pressure of 90/48 mmHg, respiratory rate of 30/minute and afebrile. Immediate resuscitation was started with intravenous fluid and blood was sent for cross-match and investigations. On examintion, his looks were pale with a huge palpable lump in his abdomen. Per abdominal examination revealed diffusely tender and distended abdomen with guarding and a mass occupying the right flank and epigastric area. Per rectal examination was unremarkable. Blood investigations revealed a haemoglobin of 5.8 g/dL, a total leukocyte count of 12000/mm^3, and a platelet count of 148 x 10^3/mm, creatinine of 1.63 mg/dL and a blood urea nitrogen (BUN) of 60 mg/dL. Abdominal sonography revealed bilateral highly echogenic renal masses with a large perinephric haematoma over the right renal area. He was a known epileptic since 3 years, and was previously diagnosed as a case of adenoma sebaceum documented by skin biopsy, and had a significant positive family history suggestive of cerebrovascular accident with hemiparesis in his one of the siblings and renal cell carcinoma in another. An immediate suspicion of tuberous sclerosis was raised. Following resuscitation and stabilisation abdominal contrast enhanced computed tomography (CECT) was done, which revealed heterogeneous mass of size 16 X 12 & 22 X 18 cm containing fat density (11-18 Hounsfield unit) with hypervascularity in both kidneys confirming it to be a bilateral giant angiomyolipoma replacing both the kidneys [Table/Fig-1,2]. MRI brain showed two areas of subependymal giant cell astrocytomas. Renal biopsy was performed which showed tumour composed of variable amounts of three components; blood vessels spindle cells and adipose tissue & further immunohistochemical analysis revealed tumour positive for HMB-45 and p53 protein (95%), but negative for epithelial markers and S-100 protein. Patient later underwent angiography, which revealed multiple aneurysmal dilations and arteriovenous fistulae. Actively bleeding vessels were identified and selective angioembolisation was done with gel foam particles and steel coils. Post intervention period was uneventful and he was started on oral Everolimus 10 mg daily for a period of one year. Monthly follow-ups for three months were done with USG KUB, showed progressive decrease in size and after one year a response assessed by Response Evaluation Criteria in Solid Tumours (RECIST) criteria showed >50% decrease (14-16 cm) in size along with improvement in renal function. After assessing the response we considered to continuing the therapy with sirolimus. As



[Table/Fig-1]: Non Contrast CT scan showing bilateral Angiomyolipomas **[Table/Fig-2]:** Contrast enhanced CT scan showing bilateral giant Angiomyolipomas
[Table/Fig-3]: Contrast CT showing giant Angiomyolipoma of left kidney



[Table/Fig-4]: Contrast CT showing Angiomyolipoma arising from upper and interpolar region of left kidney. Good amount of renal parenchyma seen in the lower pole



[Table/Fig-5]: Showing Angioembolisation of the tumour of left kidney(Pre & Post embolisation)

patient was asymptomatic so we recommended ultrasonography or CECT every 6 months for tumours 4 cm or larger and was doing well without any recurrence.

Ethical approval: Written informed consent to publication was obtained from the patient.

CASE REPORT-2

A 42-year-old female presented to our outpatient department with fever since last one month, left flank pain and lump in left half of abdomen. Examination revealed a stable patient with a 15X20 cm lump in left hypochondrium and lumber region. Blood investigations revealed a haemoglobin of 10.9 g/dL, a total leukocyte count of 9900/mm^3, and a platelet count of 189 x 10 ^{3} /mm, creatinine of 1.72 mg/dL and a blood urea nitrogen (BUN) of 58 mg/dL. Chest X-ray, urine analysis and blood culture were negative. An ultrasound scan of the abdomen revealed a mass of mixed echogenicity involving and expanding the upper pole of the left kidney. CECT revealed a 15 x 18 cm heterogeneous mass containing fat density 12 Hounsfield units with hypervascularity arising from upper and interpolar region of left kidney confirming it to be a giant angiomyolipoma [Table/Fig-3,4]. As the patient was diabetic with borderline renal function, angioembolisation followed by left partial nephrectomy was done [Table/Fig-5]. Resected specimen was sent for histopathological analysis which revealed the tumour free margins and was composed of variable amounts of three components; blood vessels, spindle cells and adipose tissue & immunostaining for vimentin, smooth muscle actin, desmin, and HMB-45, but negative for cytokeratin & S-100 confirming the diagnosis of angiomyolipoma. On two year follow-up patient was doing well without any recurrence.

DISCUSSION

We performed English literature search using Pubmed and Crossref on 10th May 2015, which yielded more than 1110 results of published material on Pubmed & Crossref. The search terms used were “angiomyolipoma renal cell cancer” and “angiomyolipoma carcinoma pathology/metastasis/immunohistochemistry” and “mesenchymal renal tumours”. We have critically analysed and included most of the important case series, reports and previous reviews from 1970- May 2015 in our review. Cases appear to be focusing on tumour histology and differentiation with other similar subtypes of renal tumours. There has been a surge in the reports and reviews in the past 10 years indicating a recent interest among researchers in the study and management of this tumour. Here in, we present a case series of Renal angiomyolipoma (AML).

Renal angiomyolipoma (AML) is a benign mesenchymal tumour of the kidney composed of blood vessels, smooth muscle cells, and adipose tissue. They are of two types, the first type, are sporadic (80%), unilateral and are typically identified in adults (mean age 45 years), with a strong female predilection (F:M of 4:1). Nearly all patients i.e. there about 77% of tumours that are less than 4 cm in size are asymptomatic, however 82% of AMLs that are bigger than 4 cm exhibit symptoms that include fever, nausea, vomiting, pain, palpable mass, haematuria, hypertension, anaemia, and shock. Retroperitoneal haemorrhage (Wunderlich syndrome) usually seen in up to 50% of cases with large tumours [1].

The second type is inherited AML(10-20%) are seen in association with phakomatoses, the vast majority in the setting of tuberous sclerosis, although they have also been described in setting of von Hippel Lindau syndrome (VHL) and neurofibromatosis type 1 (NF1). In these cases they present earlier (usually identified by the age of 10 years), much larger, far more numerous and seen in both sexes. They are more likely to be fat-poor, which accounts for their earlier presentation. The clinical presentations of inherited AML are similar to that of sporadic AML, but also include neurological & cutaneous symptoms of tuberous sclerosis as mental retardation, seizure and adenoma sebaceum [2]. The renal failure is seen in nearly 15% of patients with tuberous sclerosis and numerous confluent AMLs.

AMLs in patients with tuberous sclerosis associated with mutations in the hamartin gene (TSC1) or the tuberin gene (TSC2). These mutations are also seen in sporadic AML. The TSC1 and TSC2 genes encode the hamartin-tuberin complex that negatively regulates the activity of mammalian target of rapamycin (mTOR). TSC1 or TSC2 genes mutations spearhead mTOR activation leading to tumour growth. Upregulation of mTOR is found in TSC AML and sporadic AML. Sirolimus (mTOR inhibitor) showed promising results by down grading these tumours [3,4].

The management of AML must take into account the natural history and, in particular, the risk of haemorrhage. In general, most symptomatic AMLs have been relatively large, and the most studies in the literature have focused on a 4-cm cut-off point [5]. On the basis of an extensive literature review, Oesterling et al., reported that 82% of patients with AMLs larger than 4 cm in diameter were symptomatic, with 9% in haemorrhagic shock at the time of presentation; in contrast, patients with smaller tumours were symptomatic 23% of the time [6].

The treatment approach of these tumours lies in parenchymal preservation which is adroited by nephron-sparing surgery or preferably by selective embolisation, particularly in patients with TS, multicentric AML or patients with compromised renal function. The feasibility and efficacy of partial nephrectomy in patients with AML are established even in patients with large bilateral lesions or lesion in a solitary kidney and it is always better to have some functioning tissue than making the patient anephric.

Preventive embolisation may be feasible even for large asymptomatic tumours, in females of childbearing age or in patients in whom follow-up or access to emergency care may be inadequate [7]. Though some patients will have post embolisation complications like postembolisation syndrome and abscess formation needing secondary procedures like pecutaneous drainage or nephrectomy; selective trans arterial embolisation (TAE) is considered effective for tumour shrinkage in most renal angiomyolipomas, with acceptable complication and relapse rates [8].

In patients with sporadic AMLs, selective angioembolisation provides long-term sustained freedom from recurrence. However, patients with TS and multiple AMLs continue to represent a therapeutic challenge for the urologist, with recurrence rates as high as 60%. Nevertheless, selective angioembolisation appears to be safe in this cohort, providing on average long intervals between recurrences [9]. The question remains whether selective angioembolisation maximally preserves normal renal parenchyma when compared with newer percutaneous and laparoscopic ablative techniques such as cryoablation, radiofrequency ablation or partial nephrectomy [10].

Rapamycin (sirolimus) is a commercially available immuno-suppressant, which forms an inhibitory complex with the immunophilin FKBP12, which binds to and inhibits the ability of mTOR to phosphorylate downstream substrates, such as the S6Ks and 4EBPs. It acts by inhibiting the T-cell proliferation, and has been approved for use in angiomyolipoma because of mTOR activation has role in tumour development.

Two derivatives of Rapamycin, Everolimus and Temsirolimus, have similar mechanism of action although their pharmacokinetics, bioavailability, and adverse effect profiles may differ. The usual side effects include aphthous oral ulcers, hypercholesterolemia, thrombocytopenia, acneiform rash, immunosuppression, and impaired wound healing. FDA cleared everolimus in November, 2010 for surgically non treatable subependymal giant cell astrocytomas [11].

Most patients with acute or potentially life-threatening haemorrhage require total nephrectomy if it is explored; in such circumstances, selective embolisation can temporize and in many cases prove definitive. Partial or total nephrectomy if planned should be done within few days of angioembolisation to avoid extensive adhesion [12,13]. If surgical option is not present then everlimus may be considered as alternative therapeutic options.

CONCLUSION

Embolisation is the treatment of choice for acutely bleeding AML. When preventive treatment is considered, in symptomatic or asymptomatic AML, a nephron sparing approach either by TAE or partial nephrectomy, is clearly preferred. However, in patients with Tuberous Sclerosis, angiomyolipomas in both kidneys or in solitary functioning kidneys, renal preservation is mandatory and can salvage the kidneys and avoid need for renal replacement therapy. Medical therapy in form of Everolimus may be considered for patients not suitable for surgery.

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