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Case Report

Aggressive renal myxoid liposarcoma with co-existing bilateral benign angiomyolipoma: A rare case report

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Abstract

This report describes a 71-year-old male with Primary renal myxoid liposarcoma (MLPS), who presented with left loin pain and mass per abdomen. Computed Tomography (CT) revealed a complex mass in the left kidney with a right renal angiomyolipoma. There were two distinct lesions on gross examination. Histopathology, Immunohistochemistry (IHC) and Fluorescence in situ hybridization (FISH) of larger tumour were consistent with Myxoid Liposarcoma, while the smaller tumour was Angiomyolipoma. The patient decided to forgo chemotherapy, and died of disseminated metastasis. This case underscores the diagnostic challenges of rare renal neoplasms, with fewer than five Primary renal MLPS documented in literature.

Keywords: Angiomyolipoma, Bilateral, Multicentric, Myxoid liposarcoma, Renal, Retroperitoneum.

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1. Introduction

Myxoid liposarcomas (MLPS) are mesodermal in origin and constitute <1% of malignant tumours. Retroperitoneal myxoid liposarcomas are rare soft tissue sarcomas, often regarded as metastatic sites rather than primary sites for tumour origin.[1] Sometimes, well-differentiated/ dedifferentiated liposarcoma exhibits a similar morphology to MLPS, leading to diagnostic confusion.[2] Additionally, earlier reported cases of retroperitoneal myxoid liposarcomas were reclassified based on molecular studies into well-differentiated and dedifferentiated liposarcoma.[3] Here, we report a rare case of Aggressive Primary Renal Myxoid Liposarcoma with co-existing multicentric Benign Angiomyolipoma, highlighting its occurrence in an elderly male, unusual association, rare site of involvement, and aggressive clinical course.

2. Case History

A 71-year-old male presented to the urology outpatient clinic with complaints of pain in his left loin for one week. On palpation, a large mass was palpable in the left hypochondrium and lumbar region. Computed Tomography revealed a large, well-defined, heterogeneously enhancing solid cystic lesion measuring 14*13*12cms, arising from the upper pole of the left kidney, with suspicious infiltration of the pancreas and spleen. Also noted was a small right renal angiomyolipoma. On clinical and radiological examination, no other tumoural masses were identified in the body. Intra-operatively, the tumour was reaching close to the pancreas and spleen. The patient underwent left radical nephrectomy with distal pancreatectomy and splenectomy.

On gross examination, a grey-tan, fleshy, and myxoid lesion measuring 15*14*12cms was noted in the upper pole and interpolar region of the kidney (**Figure 1**). Areas of necrosis were present. The lesion reached close to pancreatic, splenic, and adrenal parenchyma, but infiltration was not

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evident. Also noted was a distinct grey-tan circumscribed nodule in the lower pole measuring 1.2*1*0.8cms, which was not identified in the imaging evaluation.

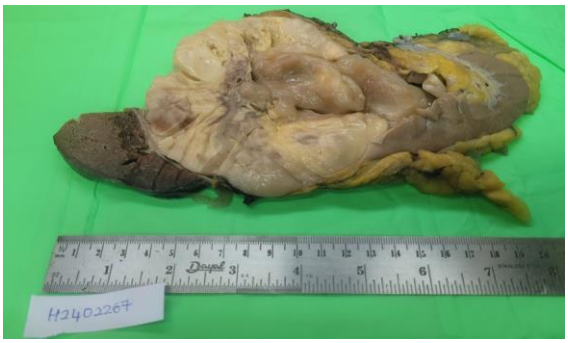

Figure 1: Left nephrectomy specimen with spleen showing large myxoid lesion involving upper and interpolar region

On light microscopy, the lesion in the upper pole showed a cellular tumour with myxoid stroma composed of prominent signet ring lipoblasts, interspersed irregularly dilated vascular spaces with atypical epithelioid cells radiating from the vessel wall (**Figure 2**A-C). Brisk mitosis was noted with a mitotic count of 30 per 10 high-power fields (**Figure 2**D). The tumour showed foci of necrosis (<50%) (**Figure 2**E). Tumour infiltration into adjacent renal parenchyma (**Figure 2**F) and periadrenal fat was present but confined within Gerota's fascia. There was no infiltration into the pancreas and spleen. Renal hilar, peripancreatic and splenic lymph nodes were free of tumour involvement. The differential diagnoses considered were sarcomatoid renal cell carcinoma, sarcomatoid urothelial carcinoma, primary renal dedifferentiated liposarcoma, and primary renal angiomyolipoma with malignant transformation of the lipomatous component.

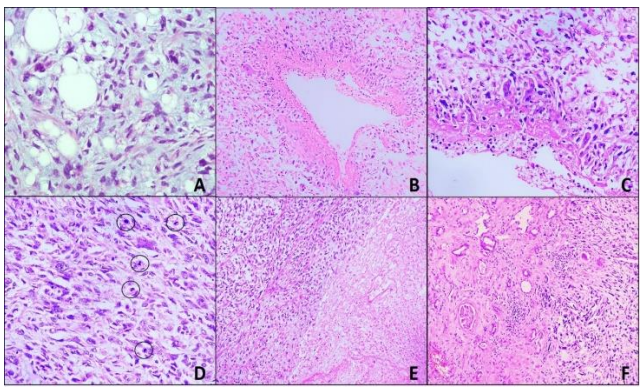

Figure 2: Histopathology images of Large Myxoid neoplasm in the upper and interpolar region of the Left kidney. **A)**: Atypical small spindle cells with admixed lipoblasts in a myxoid background (200x). **B)**: Medium-sized vessel with atypical epithelioid cells radiating from the wall (100x). **C**): Multinucleation and pleomorphism of perivascular atypical cells (200x). **D):** Brisk mitotic activity within the tumour (100x). **E):** Regions of necrosis (100x). **F**): Tumour infiltration into the renal parenchyma (100x)

On immunohistochemistry, the neoplastic cells in the sarcomatous area were negative for MDM2 and CDK4, which was supportive of Myxoid Liposarcoma, High grade, rather than Dedifferentiated liposarcoma. There was focal expression of SMA, p16, HMB45 and Melan A (**Figure 3** A-C). The Ki67 proliferation index was 25-30%. Cytokeratin, PAX8, p63 and GATA3 were negative, which rules out sarcomatoid renal cell carcinoma and sarcomatoid urothelial carcinoma, respectively. MDM2 amplification by FISH was performed on the sarcomatous tumour, and the result showed no amplification (**Figure 3** D). AJCC 8th edition staging for Myxoid Liposarcoma was pT1N0Mx.

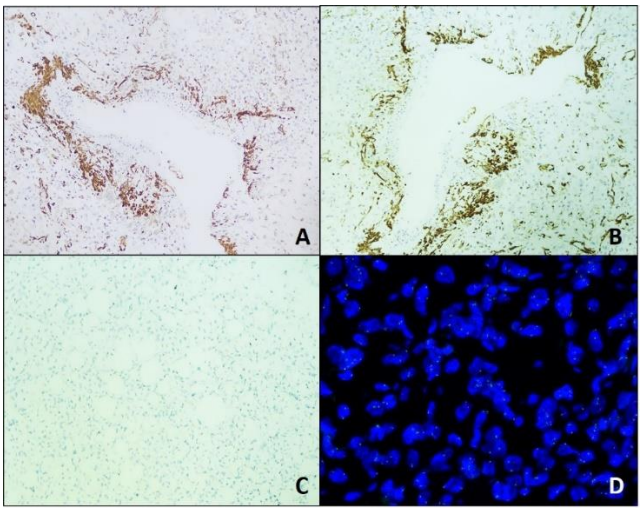

Figure 3: Immunohistochemistry images of large myxoid neoplasm in the upper and interpolar region of the Left kidney. **A**): (100X) Cytoplasmic Smooth muscle antigen expression in perivascular atypical cells. **B):** (100X) Focal HMB45 expression. **C):** (100X) Absent MDM2 expression. **D**): Fluorescence in situ hybridization using dual colour break apart probe from sarcomatous tumour shows an absence of MDM2 amplification

The lesion in the lower pole showed classic histomorphology of Angiomyolipoma with a variable mixture of adipocytic lobules, cellular fascicles of smooth muscle cells, and vascular proliferation (**Figure 4**: A-C). The neoplastic cells in classic AML foci in the lower pole were positive for SMA (**Figure 4**D), HMB45, MART-1, S100, and p16.

Adjuvant chemotherapy was recommended, but he chose to proceed with observation. He was initially asymptomatic, but the whole-body MRI imaging on 4-month follow-up showed disease progression to an advanced stage with the development of multiple liver and peritoneal metastasis, and he passed away within 6 months of diagnosis.

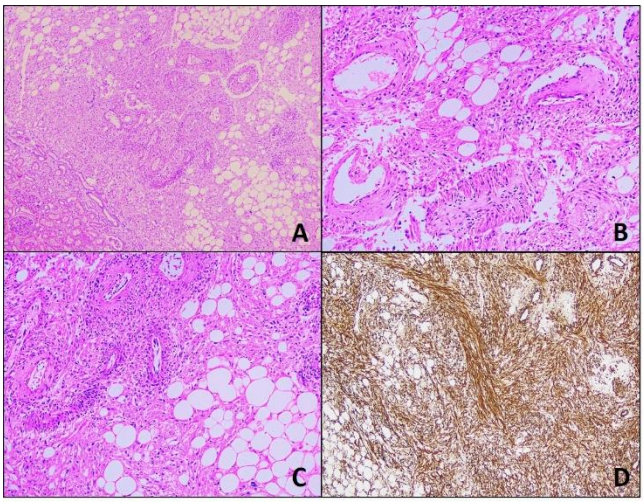

Figure 4: Lesion in the lower pole of left kidney. **A-C):** (H&E stain): Admixture of lobules of mature adipocytes, dysmorphic blood vessels and smooth muscle cells (100X). **D)**: (IHC stain): Strong and Diffuse SMA expression (100x)

3. Discussion

Myxoid liposarcoma is a malignant adipocytic tumour and accounts for 20-30% of liposarcomas. MLPS typically arises in the lower proximal extremities and affects both men and women equally. It has a peak incidence in the fourth to fifth decades of life. Previously known round-cell liposarcoma is considered the high-grade hypercellular counterpart of myxoid liposarcoma.[4] Retroperitoneal myxoid liposarcomas are rare and represent metastasis from extremities. Primary retroperitoneal MLPS usually arise from retroperitoneal fat or peri-renal fat within Gerota's fascia and compress and displace the kidney with a progressive increase in size.[5] Crisan et al. reported two cases of retroperitoneal myxoid liposarcomas.[6]

Imaging modalities such as ultrasonography, CT, Magnetic resonance imaging and Positron emission tomography (PET) scans are invaluable for tumour detection, but there is no standardized imaging for surveillance of MLPS.[7] In our case, a CT scan was initially performed to detect the lesion and assess the extent of tumour spread. A follow-up MRI scan revealed widespread metastasis; however, complete imaging details were not available.

MLPS contains the pathognomonic chromosomal translocation t (12;16) (q13; p11), which results in oncogenic FUS: DDIT3 fusion proteins. FUS is an RNA-binding protein involved in the regulation of transcription and RNA splicing and inhibits RNA polymerase III. DDIT3 gene encodes a protein of the CCAAT/enhancer-binding protein family of transcription factors, which is involved in proliferative control and cellular differentiation, particularly adipogenesis and arrest of lipoblast maturation.[8] The oncogenic fusion transcript drives the development of MLPS.

A minority of cases exhibit t (12;22) (q13; q12), forming EWSR1:DDIT3 fusion oncoproteins. The diagnostic FUS: DDIT3 fusion can be identified using IHC, FISH, Polymerase Chain Reaction (PCR), Classic Cytogenetics and Sequencing. In IHC, the monoclonal antibody targeting the N-terminus of DDIT3 has demonstrated high sensitivity and specificity for high-grade MLPS with nuclear expression of DDIT3 in over 5% of tumour cells considered positive.[9] The MDM2 gene is most frequently amplified in WDLPS/DDLPS, leading to IHC overexpression of MDM2 and CDK4, both of which are consistently negative in Myxoid liposarcoma.

Angiomyolipoma is a benign neoplasm derived from proximal renal tubular epithelial cells (10), which belongs to the family of lesions with proliferation of perivascular epithelioid cells (PEC). PECs are epithelioid-type cells with perivascular distribution, and they exhibit immunoreactivity for melanocytic markers.[11] AMLPS are usually located in the renal cortex or medulla and retroperitoneal soft tissue, but the involvement of other solid organs, such as the liver, has also been reported.[12] AML has a female predominance and presents with flank pain, haematuria, and a palpable mass. The involvement of regional lymph nodes is considered as multicentricity of the tumour rather than metastasis. Malignancy associated with AML includes malignant epithelioid AML, co-occurring renal cell carcinoma, oncocytoma and sarcomas arising from the components of AML, most commonly Leiomyosarcoma.[13-15] Sarcomatous changes in AML have been reported in the head and neck region, in addition to the kidney.[16]

In 2004, Chandrasoma et al. reported the first case of renal AML with round-cell liposarcoma.[17] (**Table 1**). In contrast to classic AML, malignant AML with myxoid liposarcomatous component was noted in the male population, and the patients were symptomatic for a short duration of one to two weeks, presenting with increasing abdominal girth and discomfort. Patients ranged from 26 years to 57 years of age. The tumour size was between 4 to 8 cm. Immunohistochemically, tumour cells were positive for Vimentin and negative for CK, SMA and HMB45. Initial management involved tumour resection, including radical nephrectomy. One patient had local recurrence and died of disease,[17] while the other patient had extensive peritoneal metastasis and died of cardiac complications.[7] Our patient represents the oldest reported case of renal MLPS, with the tumour measuring 15 cm and showing distant metastasis within a 4-month duration. These characteristics highlight the aggressive natural course of renal MLPS.

Table 1: Clinicopathological characteristics and outcomes in Sarcomas arising from renal angiomyolipoma

Characteristics	Pingali et al.[13]	Al-Hadidy et al.[14]	Chandrasoma et al.[17]	Hwang W et al.[7]	Current report
Age	55	54	26	57	71
Gender	Female	Male	Male	Male	Male
Clinical Symptoms	Retrosternal discomfort and dyspnoea for 1 year	Gross haematuria, loss of appetite and weight	Increased abdomen pain and girth for 2 weeks	Abdominal distension and vomiting	Left loin pain for one week
Laterality	Left renal mass with aorto-caval extension.	Multiple tumours involving both kidneys.	Right renal mass	Left renal mass	Upper pole of the left kidney
Primary intervention	Left radical nephrectomy	Bilateral renal biopsies	Radical nephrectomy	Surgical resection	Left radical nephrectomy with distal pancreatectomy and splenectomy
Tumour size	10.2cms	-	4cms	8cms	15cms
Histology	AML with leiomyosarcoma	AML with pleomorphic sarcoma	AML with round-cell liposarcoma	Primary renal myxoid liposarcoma	Myxoid liposarcoma with co-existing angiomyolipoma
Immuno-histochemistry	Sarcomatous tumour cells – HMB45, SMA, Desmin, and EMA.	-	Sarcomatous tumour cells – vimentin was positive; CK, HMB45, S100 were negative.	Sarcomatous tumour cells - vimentin, S100, MDM2, STAT6 were positive	MDM2 and CD4 negative. SMA and HMB45 focal expression.
Local recurrence	-	-	-	present	-
Distant metastasis	-	Lung	Extensive peritoneal metastasis	-	Liver and peritoneal metastasis
Outcome	-	Died of disease	Died of disease	Died of cardiovascular complications	Died of disease

In this case, the potential origin of myxoid liposarcoma arising from AML was considered based on histomorphology, which revealed atypical perivascular cells radiating from medium-sized blood vessels, along with focal expression of SMA and HMB45 in Immunohistochemistry. Additionally, there was co-existing histologically proven benign AML within the same kidney and radiological evidence of angiomyolipoma in the other kidney. Notably, there was no definitive classic AML component with the sarcomatous tumour despite extensive sampling, and the tumour exhibited very focal expression of myomelanocytic markers on immunohistochemistry.

The aetiology and pathogenesis of myxoid liposarcoma arising from benign angiomyolipoma remain speculative. According to the literature, multifocal angiomyolipoma is commonly associated with tuberous sclerosis, which usually occurs bilaterally and in the younger age groups. They are histologically indistinct from sporadic tumours.[18] While multifocal angiomyolipoma was observed in this patient, the short clinical history and lack of long-term evidence of the tumour argue against the malignant transformation of preexisting AML. Therefore, a denovo myxoid liposarcoma was favoured over the malignant transformation of preexisting angiomyolipoma.

Even though there is an instance of liposarcoma infiltrating the renal parenchyma,[19] in this case, the tumour was surrounded by a thin fibrous capsule, ruling out extrarenal tumour infiltrating the kidney, and sections from the renal sinus fat, and perinephric fat showed no atypical histomorphology. Other differential diagnoses, including sarcomatoid change in renal cell carcinoma and urothelial carcinoma, were ruled out by the absence of characteristic histo-morphological features and lack of IHC expression of cytokeratin, PAX8, p63 and GATA3. The diagnosis of primary renal myxoid liposarcoma with co-existing bilateral benign angiomyolipoma was confirmed through classical

findings on histomorphology, immunohistochemistry, and molecular and radiological findings. However, confirmation of the diagnostic FUS: DDIT3 fusion by molecular testing represents a significant limitation in this case.

Primary treatment involves en bloc tumour resection, aiming for complete tumour removal and negative margins. Irregular tumour borders and the multifocal nature of the disease render R0 resection impossible.[20] However, studies have shown that surgical resection for low-grade MLPS prolongs survival and decreases the local recurrence rates. At the same time, it does not benefit the high-grade MLPS cases involving retroperitoneum.[21]

Postoperative follow-up with imaging is often required because of the highly recurrent nature of MLPS. ESMO guidelines suggest twice-a-year follow-up for an initial 2 to 3 years, followed by once a year for a minimum of 8 to 10 years. There is no consensus on the follow-up intervals universally for retroperitoneal LPS because the doubling time for tumour cells is shorter with rapid tumour re-growth.[22]

Myxoid/round cell liposarcoma in extremities is radio-/chemosensitive.[10,23] Radiotherapy is an independent prognostic risk factor for MLPS and effectively controls postoperative local recurrence, but its efficacy for tumours localized to retroperitoneum remains controversial. Despite chemotherapy, these patients had accelerated local and distant metastasis with poor prognosis.[17,24] A recent study by Sanflippino et al., demonstrated that a combination of Trabectedin and pre-operative radiotherapy had good tolerability and pathological remission in MLPS.[25] Other potential therapeutics include PPARγ agonists, which are involved in the terminal differentiation of LPS cells; Immune checkpoint inhibitors, adoptive cell therapy, PDL1 Monoclonal antibody and cancer vaccines are under clinical trials; NY-ESO-1, a cancer-testis antigen, is an important target in MLPS. A multidisciplinary team with an individualized treatment plan is required for the management of MLPS.

Poor prognostic factors include elderly age, advanced stage of disease, incomplete tumour resection, and higher grade of the tumour.[26] Hence, primary tumour resection was performed in our patient. Given the elderly age of the patient and the documented poor response to chemotherapy in existing literature, the patient opted for observation instead.

4. Conclusion

Primary Myxoid liposarcoma of the kidney is exceedingly rare, with fewer than five documented cases in the literature. To date, primary retroperitoneal myxoid liposarcomas have shown rapid disease progression despite chemotherapy. Since dedifferentiated liposarcoma can masquerade as many different histology in H&E staining, our case highlights the importance of comprehensive pathological evaluation. It includes thorough tumour sampling, extensive IHC panel, molecular analysis, and radiological examination to rule out the possible primary lesion from another site, ultimately leading to an accurate diagnosis.

5. Highlight of the Report

We report this case of Aggressive Primary Renal Myxoid Liposarcoma with unusual co-existing Bilateral Angiomyolipoma in an adult patient for its rarity and aggressive clinical course.

6. Source of Funding

Nil.

7. Conflict of Interest

There are no conflicts of interest

8. Ethical Approval

Approval was obtained from the Institutional Ethical Committee on 27/07/2024. [AMH-C-S-052/06-24].

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