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Primary hepatic leiomyosarcoma - A case report with review of literature

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ABSTRACT

Primary hepatic leiomyosarcoma are very rare tumours with less than 50 cases reported. Due to nonspecific presentations, diagnosis is often delayed until they reach a large size. The rarity of these tumours has precluded our understanding of them and therefore the standard of care has not been well defined. We report a 45-year-old lady who presented with loss of appetite, abdominal distension and bilateral lower limb swelling and hepatomegaly. CT abdomen revealed nodular hepatomegaly with a hypodense lesion on plain scans, heterogenous enhancing lesion on arterial phase and delayed washout on portal venous phase occupying segments VII and VIII and involving right hepatic vein and infiltrating into inferior vena cava (IVC). The pathology report confirmed the diagnosis of leiomyosarcoma. IHC was positive for SMA, vimentin and weakly positive for desmin stain. Due to extensive nature and involvement of IVC, patient was planned for upfront neo-adjuvant chemotherapy (NACT) (Ifosfamide, and doxorubicin with MESNA. The patient has completed 6 cycles NACT and had stable disease. The patient was then switched to oral Pazopanib and is on follow up.

Keywords: *Primary hepatic leiomyosarcoma, neoadjuvant chemotherapy, unresectable cases*

Primary hepatic leiomyosarcoma are rare tumours with less than 50 cases reported in the English literature. Due to non-specific presentation, diagnosis is often delayed until they reach a large size with poor response to therapy often leading to a dismal prognosis. The rarity of these tumours has precluded our understanding of them and therefore, the standard of care has not been well defined. We, herein, report a case of primary hepatic leiomyosarcoma, which was treated with chemotherapy and review the English literature with an emphasis on management outcomes.

CASE REPORT

A 45-year-old lady was referred to our department with loss of appetite for past 9 months, abdominal distension and bilateral lower limb swelling for past 6 months. She had no history of liver disease or alcohol abuse. Her past medical history and family history were unremarkable. Physical examination revealed a marked hepatomegaly extending 13 cm below the right costal margin and extending and occupying whole of the epigastrium. The hepatomegaly was tender and hard. There was no evidence of any other palpable abdominal lump or lymphadenopathy. Bilateral pitting pedal edema was also present.

Laboratory analysis revealed normal liver function tests including serum albumin level and prothrombin time. White blood cell count, platelets, serum α-fetoprotein, CA 19-9 and carcinoembryonic antigen (CEA) were normal. Antibody to hepatitis C virus, human immunodeficiency virus (HIV), ebstein barr virus (EBV) and hepatitis B surface antigen were negative. Impedance cardiogram (ICG) clearance at 15 min was 10%. Abdominal

ultrasonography revealed a hypoechoic mass, measuring 11.9X10.6X9.8 cm, in segment VII and VIII of liver without any evidence of intrahepatic biliary radical dilatation. Lesion was extending into inferior vena cava (IVC) at confluence with significant luminal narrowing.

Abdominal computed tomography (CT) showed nodular hepatomegaly with a hypodense lesion on plain scans, heterogeneous enhancing lesion on arterial phase and delayed washout on portal venous phase occupying segments VII and VIII (**Fig. 1**) measuring approximately 115×84×114 mm. It was seen to be involving right hepatic vein and infiltrating into IVC causing partial luminal compromise. Chest CT, 2D-ECHO and gastrointestinal endoscopy were normal. Pretreatment diagnosis was unconfirmed; so, biopsy was undertaken after obtaining written informed consent.

The histopathology report confirmed the diagnosis of leiomyosarcoma. Light microscopy demonstrated the typical pattern of growth of leiomyosarcoma, predominantly fascicular, with tumour bundles intersecting each other at wide angles and merging of tumour cells with blood vessel walls (**Fig. 2**). The individual cells had elongated, blunted nuclei and acidophilic fibrillary cytoplasm. Numerous mitoses were present. On immunohistochemistry, tumour cells were positive for smooth muscle actin (SMA), and vimentin and weakly positive for desmin stain (**Fig. 3**). It was negative for pancytokeratin, S-100, HMB-15, CD31, CD117, CD10, D2-40 and factor VIII.

Due to the extensive nature and involvement of IVC, patient was planned for upfront neoadjuvant chemotherapy (NACT) for 6 cycles (Ifosfamide 1500mg/m^2 D1-4 + Doxorubicin 20mg/m^2 D1-3 with MESNA 225 mg/m^2 1 hour before ifosfamide and at 4 and 8 hrs after ifosfamide). After 3 cycles of NACT, MRI abdomen was done which revealed a large ill defined soft tissue lesion (approx 10 x11x11 cm) in right lobe of liver involving segment V, VI, VII and VIII displaying heterogenous signal intensity alterations (**Fig. 4**).

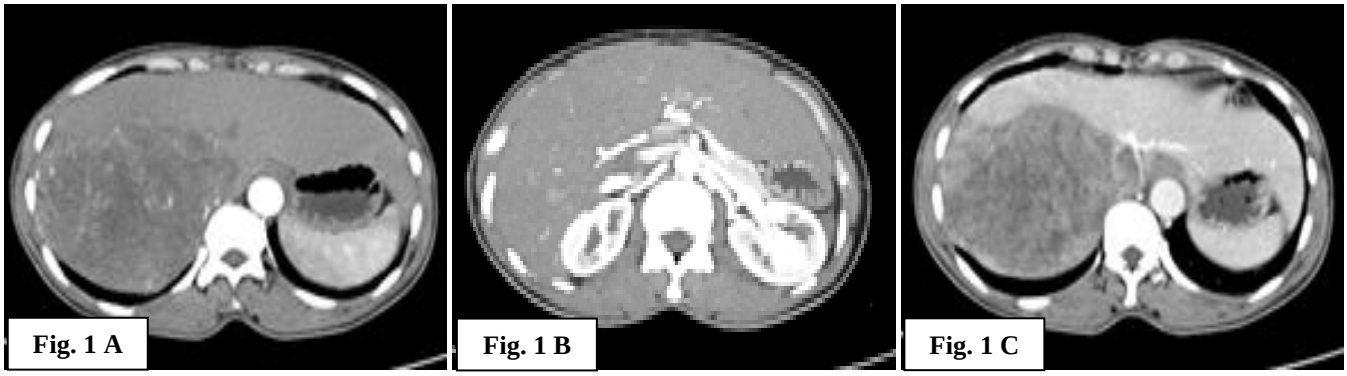
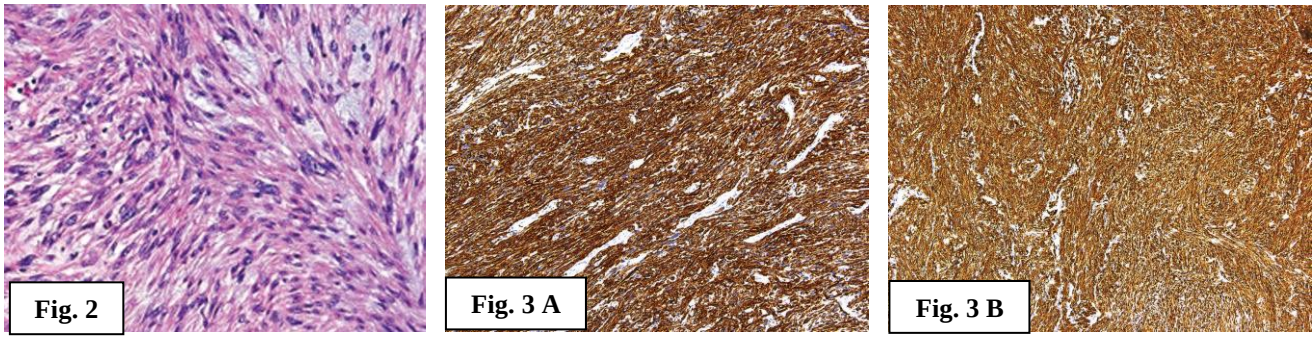


Figure1. Arterial (A), venous (B) and delayed portal venous (C) phases on triple phase CECT of liver showing hepatic mass involving segment VII and VII compressing and infiltrating into intrahepatic IVC showing well encapsulated heterogenous enhancing lesion on arterial phase and delayed washout on venous phase, predominantly supplied by right hepatic artery (1A)



Figures: Fig 2 - light microscopy showing fascicular growth pattern with tumor fascicles intersecting each other at wide angles and merging of tumor cells with blood vessel. Fig 3 - IHC positive for desmin (A) and SMA (B)

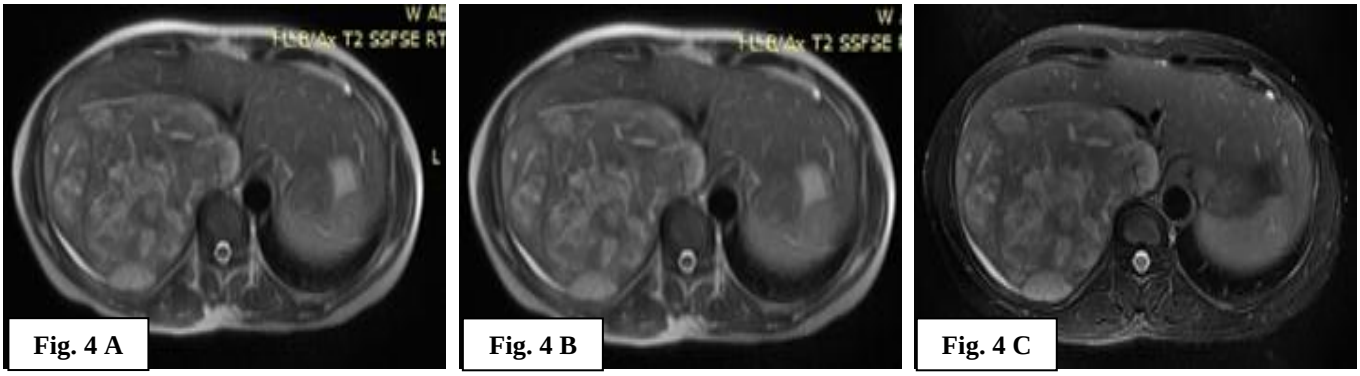


Fig 4 A, B, & C - MRI T2 fat suppressed axial views showing a large ill defined soft tissue lesion in right lobe of liver involving segment V, VI, VII and VIII displaying heterogenous signal intensity alterations and extending upto the capsule posteriorly and laterally. A separate feeder vessel was also noted.

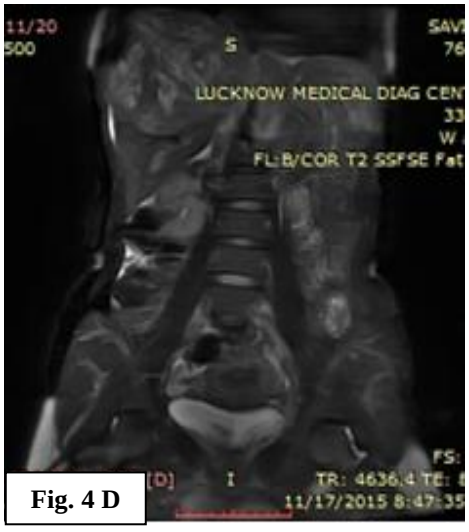


Fig 4 D - MRI T2 coronal view showing a large ill defined lesion in right lobe of liver involving segment V, VI, VII & VIII displaying heterogenous signal intensity alterations and extending up to capsule posteriorly and laterally

It was extending upto the capsule posteriorly and laterally. The lesion was compressing and partially extending into intrahepatic portion of IVC. After completing 6 cycles of NACT, patient had unresectable but stable disease. The patient was then switched to oral Pazopanib 800mg OD and is on regular follow up.

DISCUSSION

Primary leiomyosarcoma of the liver is a recognized, but very rare, malignancy according to the World Health Organisation classification [1]. Sarcomas constitute only 1% to 2% of all primary malignant tumours of the liver with majority being either hepatocellular carcinoma or cholangiocarcinoma. Nearly all primary sarcomas of liver are angiosarcomas, epitheloid hemangioendotheliomas or undifferentiated embryonal sarcoma constituting nearly 70% with leiomyosarcoma constituting only 8-10% of all sarcomas. Most hepatic leiomyosarcoma are metastatic from other sites including gastrointestinal tract, uterus, retroperitoneum and lung. So, exclusion of metastatic leiomyosarcoma in liver is an essential event in diagnosing a primary lesion.

Hepatic leiomyosarcoma may arise from intrahepatic vascular structures, bile ducts or ligamentum teres. Tumours arising from hepatic veins may develop Budd-Chiari syndrome and have worse prognosis while tumours arising from the ligamentum teres have better prognosis due to its increased resectability. No underlying etiologic factors are known; although, Thorotrast, HIV, EBV, prior history of immunosuppression such as post-renal transplant and previously treated Hodgkin's lymphoma and cirrhosis due to hepatitis C have been described [2].

The median age of diagnosis is 58 years with sporadic occurrence of tumor in younger age group and male to female ratio is 33 to 34:1 [3]. Primary hepatic leiomyosarcoma presents a clinical dilemma as not only are they rare, but they are often asymptomatic until they become large, when they produce only nonspecific symptoms. Patients may be afflicted with a wide spectrum of symptoms, such as abdominal pain, weight loss, anorexia; vomiting, jaundice and rarely acute intra-abdominal bleeding secondary to tumor rupture [4]. Tenderness of upper abdomen, hepatomegaly, and mass may be the main signs. Some patients may have abnormal liver function tests but essentially the α-fetoprotein and other serological markers are normal.

As with other liver tumours, histological pre-operative diagnosis of hepatic leiomyosarcoma is controversial as most of these tumours are treated presuming to be hepatocellular carcinoma with its inherent propensity for needle track seeding. Histological examination reveals tumor composed of intersecting bundles of spindle-shaped cells. Immunohistochemistry is positive for desmin, vimentin and SMA but negative for keratin, S-100 protein and neuron-specific enolase and FNA biopsy will allow for specific FNA diagnosis in most of the cases [5].

CT findings of primary hepatic leiomyosarcoma have been described as a large, well-defined, heterogeneous hypodensity mass with internal and peripheral enhancement or cystic mass with an enhancing thick wall. Cystic variant of leiomyosarcoma may be misdiagnosed as hydatid cyst or liver abscess [6]. On MR imaging, tumor displays homogenous or heterogeneous hypointensity on Tl-weighted and hyperintensity on T2-weighted images with occasional observation of encapsulation [7]. PET-CT can be applied to sensitively detect primary tumours and metastases.

Due to the rarity of primary hepatic sarcomas in general, and primary hepatic leiomyosarcoma in particular, standard of care has not been defined. However, surgical resection followed by adjuvant chemotherapy is being widely followed in an empirical manner [2]. Hepatic leiomyosarcoma has four different histological types. Types 1, 2, 3, and 4 are defined as well differentiated, moderately differentiated, poorly differentiated, and myxoid leiomyosarcoma, respectively. Type 4 or myxoid leiomyosarcoma has an aggressive growth pattern.

Resection surgery forms the cornerstone of successful management of primary hepatic leiomyosarcoma with an intention of R0 resection. All patients with potentially resectable tumours with adequate remnant liver volume should undergo surgical exploration and liver resection. Criteria for inoperability include extrahepatic spread, diffuse intrahepatic tumor making complete tumor removal unlikely, and impaired liver function. The role of partial resection in multifocal tumours has not been defined. The surgical outcome for R0 resection extrapolated from 2 large series was 67% disease specific survival at 5 years with 0% 3 years survival for patients who underwent R1+ resection [8]. Age was another major prognostic factor with patients less than 50 years achieving better survival.

Role of adjuvant chemotherapy/chemo radiotherapy is not well defined. Adjuvant chemotherapy in the form of doxorubicin and ifosfamide seems to slow the course of disease and may prolong survival in R1 resections but evidence is lacking as data are extrapolated from setting of unresectable or metastatic leiomyosarcoma [9].

Liver transplant has been attempted sporadically in primary hepatic leiomyosarcoma but is not as well defined as in primary hepatic epithelioid hemangioendothelioma [10]. The outcome for liver transplant has been varied with all cases developing recurrent or metastatic disease and only one case showing long term survival after undergoing resection for local chest wall recurrence [11]. Immune status manipulation may play an important role in prolonging survival in post transplant period by preventing recurrence [3].

The efficacy of chemotherapy and radiotherapy for leiomyosarcoma is extremely low. Additionally, postoperative therapy and management of recurrence are not established [12]. Despite being slow growing and having late metastasis, leiomyosarcomas carry poor prognosis and high incidence of local recurrence. Even after complete resection, prognosis is poor and long-term observation is required. They tend to metastasize hematogenously to the lung, but lymphatic metastasis and peritoneal seeding have also been described [13].

Adjuvant chemoradiotherapy had been recommended for eradication of microscopic residual disease. However, its success in achieving local control and prolonged patient survival needs to be further studied as a meta-analysis has shown a small benefit [10]. Postoperative chemo-radiotherapy has been tried without much success. Chemo-embolization of metastatic hepatic sarcomas has been shown to increase the survival [14]. To have a better understanding of these rare tumours, we need to have a global database to analyze and understand the outcomes of different therapies.

CONCLUSION

The rarity of primary hepatic leiomyosarcoma has precluded our understanding of them and therefore, the standard of care has not been well defined. This case helps us to highlight the importance of neoadjuvant chemotherapy management of this rare tumor presenting in an inoperable situation.

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