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CASE REPORT

Frontiers in Gastroenterology & Hepatology

Case Report: Hepatic angiomyolipoma with an incidental septate gall bladder: A pathologist's perspective

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Abstract

Hepatic angiomyolipoma, a rare and commonly asymptomatic hepatic mesenchymal tumor, is often misdiagnosed preoperatively, on radiology. In this case report, we present a male patient whose only symptom was vague upper abdominal pain. After biochemical, haematological and radiological investigations, he underwent an extended right hepatectomy with a working diagnosis of hepatocellular carcinoma. Histology of the resected specimen confirmed the lesion to be a benign angiomyolipoma, which was completely resected. An incidental septate gall bladder was also seen. The interesting features in this particular case were the radiological suspicion for hepatocellular carcinoma, an oft suspected differential, and the rare HMB45 negativity on immunostaining. The small renal angiomyolipoma in radiology suggests multifocality of these benign lesions, but in this case there was no background tuberous sclerosis. Overall, this indicates that hepatic angiomyolipoma is a rare lesion, which remains diagnostically challenging. Even though the initial working diagnosis was erroneous, the treatment plan was satisfactory and follow-up, unremarkable.

Keywords: *hepatic angiomyolipoma; pathology and immunostains; septate gall bladder*

Introduction

Angiomyolipomas are rare benign tumours, most commonly seen in kidneys, with the liver being the second most common site. There is a slight female preponderance and an association with tuberous sclerosis [1].

In 2002, in the classification of soft tissue tumors, World Health Organization (WHO) classified Hepatic Angiomyolipomas (HAML) as perivascular epithelioid cell tumors (PEComas), the cell of origin of which has not been ascertained with certainty [2]. The radiological diagnosis of angiomyolipoma can be difficult, especially if one component is predominant [3]. The radiological detection of fat in liver lesions is not specific and can also occur in other entities that are eligible for differential diagnosis, such as hepatocellular adenoma or hepatocellular carcinoma. Histologically, AMLs show a triphasic architecture, comprised of smooth muscle, adipose and vascular components [2]. On immunohistochemistry, the tumours are positive for melanocytic markers [4] and at the molecular level, these group of tumors harbour TSC1 or TSC2 alterations [5].

Overall, for the reasons outlined above, HAML proves to be a diagnostic challenge, with the main differential diagnosis being hepatocellular carcinoma, as in the case we report.

Clinical case summary

Initial presentation and referral

37 year old male, with tablet controlled Type 2 diabetes, hypertension and eczema, presented with vague upper abdominal pain at a district hospital and was referred to our specialist hepatobiliary centre, following discovery of a suspicious liver lesion on his CT scan (see subsequent review). There was no history of previous hepatitis or other medical liver disease.

Blood tests

At our centre, initial blood workup showed AST 357 U/L (ref range: 0-45), AST/ALT ratio 0.9, Total bilirubin 23umol/l (ref range: 0-21) and ALP 78 U/L (reference range: 40-130), Albumin varied between 29-33g/l (reference range 35-52 g/l) in regular checks and AFP level was normal.

Kidney function tests

Urea and electrolytes and glomerular filtration rate were all within normal limits.

Radiology

The PET-CT image was reviewed at the multi-disciplinary team meeting (Figure 1) and confirmed a large solitary mass, 97x83mm, within the right lobe of the liver. It was heterogeneous in appearance with some areas of fat density and soft tissue. There was a central area of increased FDG uptake which extended to the lesion edge superiorly. In the inferior portion, the FDG uptake was similar to background hepatic activity, within physiological limits.

Small pulmonary lesions were seen but were below the resolution of PET and hence deemed indeterminate.

A small fat density lesion arising from the lower pole of the right kidney was in keeping with a renal angiomyolipoma.

Diffuse bowel activity was attributed to the patient's oral hypoglycaemic medication.

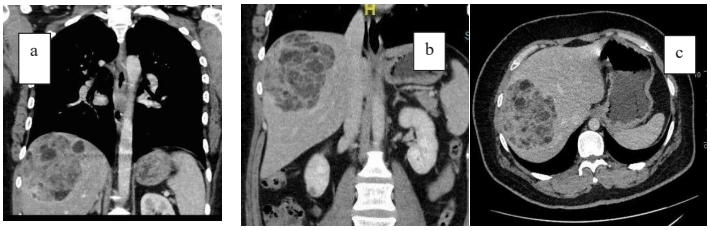

Figure 1: *Radiological image of the lesion showing variegated appearance of the lesion in the right lobe of the liver lesion (a, b, c)*

MDT decision and surgery

Given these findings, the multi-disciplinary team reached a consensus for surgical excision, as the radiology was deemed suspicious of a hepatocellular carcinoma, though in a non-cirrhotic liver. The patient underwent open extended right hemi-hepatectomy with cholecystectomy, following which he made good post-operative recovery without any complications and was discharged home.

Post-operative histology

Histology (Figure 2) showed a tumour morphologically presenting with a triphasic morphology: a mixture of adipocytic elements, proliferating blood vessels and a proliferation of spindle cells with eosinophilic cytoplasm and cytoplasmic clotting, in keeping with immature smooth muscle cells. Some pleomorphism was present but no significant atypia to suggest malignancy was identified, nor was there necrosis or any mitotic activity.

On immunostains (Figure 3) tumour cells stained positive for CD34 and SMA and were negative for S100, PAX8, HMB45, Melan A, hepatocyte antigen, glypican 3, CK7, CEA, CD10, RCC. Ki67 showed a proliferation index of <1%.

The tumour appeared completely excised, with a margin of 1.3mm and no definite evidence of vascular invasion is seen. There was no breach of the liver capsule.

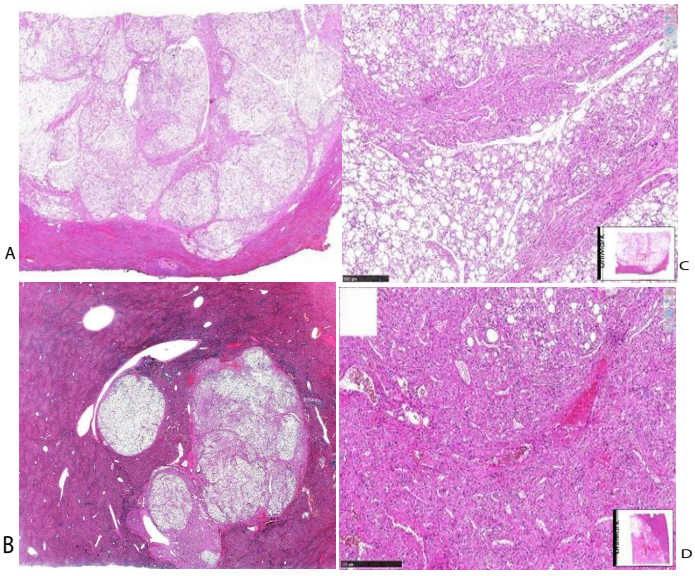

Figure 2: *Haematoxylin and Eosin stained sections of the lesion (a) and its periphery (b) at low magnification (x2). High magnification (x4 magnification) highlighting the mix of adipocytic (c), myoid (c, d) and vascular (d) areas.*

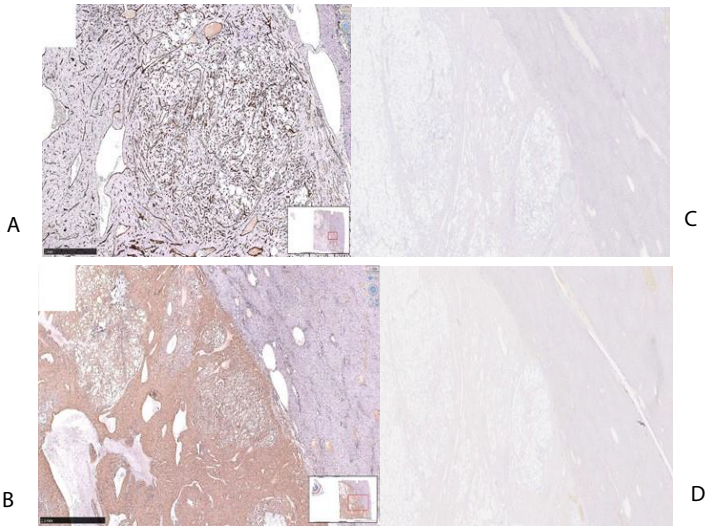

Figure 3*: Immunostaining of the lesion showing positivity for CD34 (a) and SMA (b) but negativity for HMB45 (c) and MelanA (d) (x2 magnification).*

The background liver showed no evidence of fibrosis or cirrhosis. There was mild background steatosis with glycogenated nuclei in keeping with his underlying diabetes. There was no evidence of primary hepatocellular carcinoma.

Morphologically the features were entirely in keeping with a benign hepatic angiomyolipoma. This was agreed both by consultant pathologists with expertise in pancreaticobiliary and soft tissue pathology.

In addition to this, there was also an incidental finding of a septate gallbladder (Figure 4), the histology of which confirmed the gross appearance of a septum at the base of the gallbladder. Two separate chambers were seen, one larger than the other, with a visible communication between the two. The wall of the septum was comprised of all three layers including mucosa, submucosa and muscularis. There was focal chronic inflammation in the gall bladder but none seen in the septum itself.

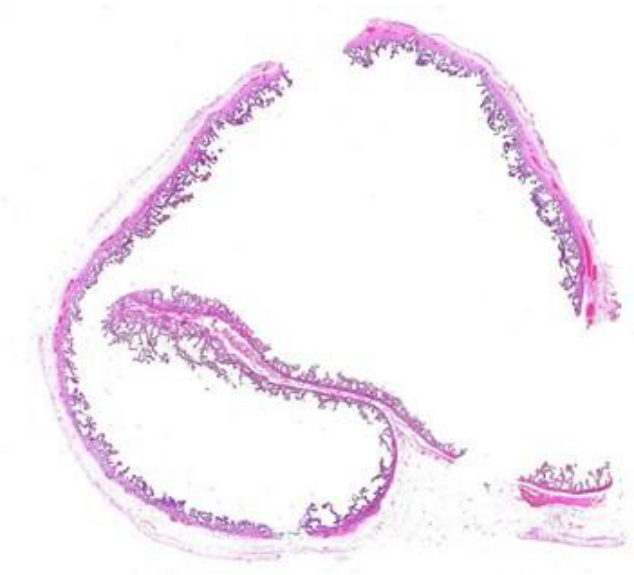

Figure 4: *Haematoxylin and Eosin stained section of septate gallbladder*

Clinical follow up

The patient had an uneventful surveillance follow up at 3 months and 8 months since surgery and has therefore been discharged to the care of his GP. No features to suggest background tuberous sclerosis were noted clinically or in the family history.

Discussion

Originally identified by Ishak and colleagues [6], hepatic angiomyolipomas are rarely encountered by pathologists, radiologists and surgeons alike, unlike lesions of the same name seen more commonly in the kidney [4]. Our case report highlights the rarity of the lesion and some unusual features which may cause diagnostic difficulties.

Compared to the common parameters reported in a retrospective international multi-centre study including all patients with pathologically proven HAML between 1997-2017 at North American and European centres [7], our case had some distinct features. Contrary to the female preponderance depicted (32/38 cases), our patient was of the male sex. In terms of clinical symptoms, usually HAMLs are either asymptomatic or present with vague abdominal pain, which was the presenting symptom in our patient. Nausea and acute liver bleed are very rare in occurrence. There was no history of hepatitis B or C, associations which are sometimes reported in the literature [8,9].

The maximum diameter of the lesion was higher than the median HAML-diameter (57.5 mm), reported in [7] and was in fact, slightly larger (97mm) than the range reported in this study (38.5–95.3mm) and other series (48±39 cm) [10]. That the initial multidisciplinary team diagnosis was incorrect, is not unusual, reported similarly in upto ~40% of the series. The image characteristics of HAML [3,11] are mostly reported to be solid with only isolated cystic/uncertain lesions reported. On imaging the features are often non-specific, with enhancement in the arterial phase, as in hypervascular tumors [17]. In the portal venous/delayed phase, lesions with profuse central vessels demonstrate a rapid contrast decrease while pauci-vascular lesions show prolonged enhancement [3,11]. Overall, contrast enhancement in the portal venous and delayed phases, is mostly reduced. The variegated image in the current case and the large size were deemed complex features. Along with the altered liver enzymology, it is therefore not surprising that the multi-disciplinary team favoured a preoperative diagnosis of malignancy. Though there were minor areas of fat density and soft tissue radiologically, these may also occur in the common differentials [10] of liver neoplasms such as steatotic hepatic adenomas, focal nodular hyperplasia and hepatocellular carcinoma with steatotic areas, and hence resection was deemed the safest option.

The literature suggests that a preoperative biopsy may be deemed helpful to solve the conundrum in difficult cases. In our example, the sheer size of the lesion would still have justified a resection. Literature [7,10] suggests that a size >5cm warrants excision, but in smaller masses a preoperative tissue diagnosis may offer an opportunity for wait and watch surveillance. Indeed, this should be considered in a non-cirrhotic liver, as malignant transformation is extremely rare in HAMLs. However, preoperative diagnosis is not infallible, some cases still being mis-diagnosed as metastases or gastro-intestinal stromal tumours, depending on tissue composition of areas sampled.

In terms of pathology, the morphology in the current case was triphasic, easing the diagnosis. All three components, smooth muscle fibers, mature adipocytes and thick-walled blood vessels were present. Problems arise when the components are unevenly distributed or variable in appearance. For example, the epithelioid type HAML [12,13] is characterized by predominantly cells varying in appearance from epithelioid to polygonal or spindle-shape with cytoplasmic clearing or central condensation. Vascular/adipocytic components are sparse, and hence, may be mistaken for hepatocellular carcinoma or adenoma. This morphological variant should be carefully identified and followed up, as it has a propensity to recur. Though invasive growth of HAMLs into the adjacent liver is not necessarily a pointer of malignancy, this feature should be examined for carefully alongside parameters of atypia, coagulation necrosis and vascular invasion, loss of CD117 expression as risk factors for relapse/malignant transformation [14]. Presence of portal vein thromboses should also warrant careful follow-up [15].

Histologically, in the differential diagnosis, liver tumours, gastrointestinal stromal tumours, metastatic carcinomas, mesenchymal tumors and malignant melanoma must be considered. Rare variants such as lipoma-like HAML [16] may be misdiagnosed as lipoma or liposarcoma (often more monophasic and mitotically active); while angiomatous like HAML may be difficult to distinguish from hepatic hemangioma. Inflammatory myofibroblastic tumor and follicular dendritic cell tumors are rare but reasonable differentials to exclude for the rare inflammatory HAML [17]. Morphological diagnosis should be supplemented with immunostains and pathologists should not hesitate to use broad immunopanels to confirm diagnosis. The usual positive stains are SMA, CD34 and HMB45/Melan A. We excluded hepatocellular carcinoma with negativity for Hepatocyte antigen and glypican 3. Malignant melanoma was ruled out with S100 negativity, as both HMB45 and MelanA can be positive in both HAMLs and melanomas. The choice of immunostains to rule out metastatic carcinomas is guided by morphology and radiology and given the concomitant renal lesion, a metastatic renal carcinomas was ruled out with negativity for CK7, RCC, CEA and PAX8. For epithelioid HAMLs, gastrointestinal stromal tumours can be excluded by DOG1 negativity (CD117 being non-discriminatory). The pathological peculiarity of the current case is the negativity for HMB45 and MelanA. According to Gunster [18], histological identification of lipomatous, myomatous, and angiomatous tissue with immunohistochemical positivity for HMB-45 provides the most reliable evidence of HAML. However, Klompenhouwer et al. have reported HMB-45 negativity in 8.5% of patients with HAML [7]. Thus morphological assessment remains key, and good clinical practice warrants that such cases be reviewed by both hepatobiliary and soft tissue pathologists for consensus. Another pitfall to be aware especially in females is the rare positivity of HMB-45 in metastatic endometrial stromal sarcomas. In cases of HAML showing brown pigments, a positive Prussian blue can highlight hemosiderin alongside melanoma markers. Hyaline globules may be identified using periodic acid Schiff (PAS)/diastase stains [19].

Given the concurrent radiologically identified small renal angiomyolipoma in the right kidney, we pondered whether the lesion represents a metastasis of the renal lesion. However, the renal lesion had no malignant features radiologically and the histology of the liver lesion had no features to indicate malignancy and hence, both hepatobiliary and soft tissue pathologists, deemed the liver lesion as primary and benign. Metastases from a benign renal or hepatic angiomyolipoma is extremely rare, though not unheard of [20]. However, given the multifocality of angiomyolipmas in this case, an association with tuberous sclerosis was sought, given the known an association, albeit commoner in renal lesions and females [5]. There were no clinical indicators of tuberous sclerosis

either in the patient or his family members. Nonetheless, patients should be interrogated carefully and examined for epilepsy, learning disabilities, behavioural problems (hyperactivity or an autistic spectrum disorder), patches of light-coloured or thickened skin, or red acne-like spots, breathing difficulties and hydrocephalus to suggest tuberous sclerosis. As we move into the era of molecular pathology, there may be a role of for targeted next generation sequencing analysis to reveal mutations in TSC1 and TSC2 [5]. Concomittant BRAF and NRAS mutation analysis may be requested to distinguish from malignant melanomas.

In patients with the tuberous sclerosis complex, ~15% have been reported to harbor HAMLs [5]. There is a female preponderance and all individuals had mutations in the TSC2 gene and had coexisting renal angiomyolipomas. Within TSC, there are several pathogenic variants for TSC1 and TSC2 inactivating mutations, including deletion, nonsense, and missense mutations. The TSC proteins usually form a complex to constitutively inhibit mechanistic target of rapamycin (mTOR) signaling. Mutations constitutively activate mTOR signaling and increase proliferation and protein synthesis.

The follow-up was unremarkable in the current case, as in most cases the prognosis is favourable (mortality rate: 0.8% and post-surgical recurrence rate ~2.4%) [21].

Incidentally, a septate gall bladder was found in this case. In a septate gallbladder, a septum divides the viscera into two chambers, either longitudinally (bilobed) or transversely (hourglass), as in our case [22]. Most commonly developmental, septation may also arise from post-inflammatory adhesions. Septation may itself predispose to biliary stasis and cholelithiasis, but no stones were seen in the current case. There are however no reported associations of HAML and a septate gall bladder, though an exophytic HAML has been found with gall bladder parietal calcification and lithiasis [23].

Conclusion

HAMLs are rare lesions posing diagnostic challenges. Where in doubt, a pre-operative biopsy may have a role in solving the dilemma. When the three characteristic histological components are present and immunohistochemical expression of HMB45 is seen in addition to smooth muscle actin, the diagnosis process is smooth. But unusual morphology and immunostains, may pose challenges. As the most important differentials include liver tumours, malignant melanoma and mesenchymal neoplasms, it is sometimes prudent to be safe and proceed to excision, where other worrying features such as large size and indeterminate radiological/ pathological features are seen. In the molecular era, testing for mutations in the TSC1 / 2 gene can help firming diagnosis and in multifocal cases tuberous sclerosis should be explored.

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