

Hepatic Adrenal Rest Tumour (HART): A Case Report

Dear Editor,

A 47-year-old Chinese woman was found to have mild transaminitis and a hepatic mass detected on ultrasound sonography (US) at a routine medical check-up. She was subsequently referred to our institution for further investigations. She was asymptomatic and general physical examination was unremarkable. Hepatitis viral markers were negative and serum tumour markers, in particular alpha-fetoprotein (AFP), were normal. Magnetic resonance imaging (MRI), with primovist, revealed a slightly protuberant mass, measuring 3.4 cm in maximum dimension, arising from segment VII of the liver. It was hypointense on T1, isointense on T2 and demonstrated peripheral rim enhancement and minimal internal enhancement on the post-contrast phase. The radiologic features were suggestive of a fat-containing lesion with the differential diagnoses of hepatic adenoma, hepatocellular carcinoma (HCC) and angiomyolipoma. Given the concern for malignancy, a wedge resection was performed. At surgery, a well-defined subcapsular hepatic nodule was identified. There was no involvement of the adjacent organs or peritoneal disease. The right adrenal gland was distinctly demarcated from the liver. The specimen was sent for intraoperative frozen section examination. The surgery was uneventful and the patient was well 3 months postoperatively.

Pathologic Findings

The hepatic wedge resection specimen featured a well-demarcated subcapsular mass with a firm, yellow cut surface. No areas of haemorrhage or necrosis were present. The adjacent liver parenchyma did not appear cirrhotic. Both a hepatocellular adenoma and a well-differentiated HCC were considered on frozen section examination. However, in view of the limited sampling, the diagnosis was deferred to permanent sections.

The specimen was subsequently fixed in 10% formalin and routinely processed for light microscopy. Review of the paraffin embedded permanent sections showed a partially encapsulated nodular lesion, composed of polygonal clear cells, arranged in small clusters which occasionally merged into trabeculae. The cells demonstrated distinct cell membranes and moderate amounts of vacuolated cytoplasm.

The nuclei were uniform, small and round. Mitotic figures were extremely scarce.

The lesional cells showed strong cytoplasmic staining for α -inhibin and Melan-A as well as strong nuclear, cytoplasmic and membranous staining for calretinin. CD56 and synaptophysin showed patchy and weak membranous and cytoplasmic positivity; chromogranin was negative. No immunoreactivity was observed for HepPar-1, glypican-3, epithelial membrane antigen (EMA), CD10, renal cell carcinoma (RCC) marker and HMB-45. The Ki-67 proliferation index was less than 1%. Electron microscopic examination was not performed.

Based on the morphology, immunohistochemical profile and corroborative intraoperative and radiologic findings, the diagnosis of a hepatic adrenal rest tumour (HART) was rendered. In view of the tumour's relative small size, lack of cytological atypia, low proliferative activity and absence of invasion, it was postulated to behave in a benign fashion.

Discussion

Adrenal rest tumours are rare tumours derived from heterotopic adrenal cortical tissue. As the adrenocortical primordium develops in close association with the emerging gonad, some nests of adrenocortical cells may eventually be anchored alongside the gonad, or, when not sequestered by the adrenal capsule, be located in the adjacent retroperitoneal fat.¹ The liver is a rare site for accessory adrenal tissue, as is the pancreas, lung and brain. These aberrant nests may undergo marked hyperplasia in patients with increased adrenocorticotrophic hormone production, for instance in congenital adrenal cortical hyperplasia. Occasionally, these rests may give rise to ectopic adrenal cortical adenomas and even carcinomas.

HARTs are relatively rare compared to their gonadal and retroperitoneal counterparts. Only 6 cases were reported in the literature over the past 30 years (Table 1).²⁻⁷ The patients' ages ranged from 21 to 67 years with no gender predisposition. These tumours are frequently non-functional, presenting as an incidental finding. They are generally less than 5 cm in maximum dimension and demonstrate benign histological features. Our case reflects the aforementioned features. Two cases were described to be associated with

endocrine abnormalities.^{6,7} Both occurred in young female patients with relatively large lesions which demonstrated malignant histological features.

Though HART is typically diagnosed on histological grounds, correlating preoperative radiological findings are still imperative. MRI is the most specific imaging technique and the identification of fat, reflecting the intracytoplasmic lipid accumulation of the tumour cells, is the most suggestive feature (Fig. 1).⁸ However, fat-containing tumours of the liver are many, encompassing both benign and malignant lesions, which range from hepatocellular adenoma and angiomyolipoma to HCC with fatty change and metastases.

Hypervascularity is also characteristic of HART but is likewise non-specific.⁸ Likely due to its rarity, HART was not considered in the preoperative radiological assessment of all 6 reported cases.

The histological diagnosis of HART is still a challenging one owing to the wide range of lesions of similar appearance. Morphologically, they are reminiscent of the adrenal cortex, featuring trabeculae, cords and nests of large, polygonal cells with well-defined cell borders and containing clear cytoplasmic vacuoles (Fig. 2). They also exhibit the same immunohistochemical profile staining positively with low molecular weight cytokeratins, α -inhibin, calretinin

Table 1. Hepatic Adrenal Rest Tumours Reported in the Literature

Source	Age/Sex	Size (cm)	Clinically Functional	Radiological Features	Histological Features	Clinical Outcome
Wallace EZ, et al, 1981	23/F	18.0	Yes	Hypervascular	Malignant	Died of pulmonary embolism postarteriography
Contrearras P, et al, 1985	21/F	12.0	Yes	Hypervascular	Malignant	No recurrence 3 months postoperatively
Aria K, et al, 2000	62/M	2.5	No	Hypervascular	Benign	No recurrence 3 years postoperatively
Tajima T, et al, 2001	55/F	2.5	No	Hypervascular, fat-containing	Benign	No documented long-term follow-up
Baba Y, et al, 2008	67/F	1.7	No	Hypervascular, fat-containing	Benign	No documented long-term follow-up
Yong MS, 2010	62/M	3.0	No	Hypervascular	Benign	No documented long-term follow-up

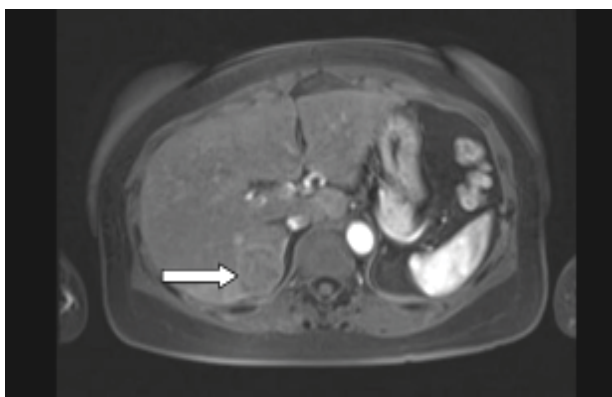


Fig. 1. An MRI image showing the lesion (white arrow) in segment VII of the liver with a distinct peripheral rim and internal enhancement (post-contrast phase, sagittal section).

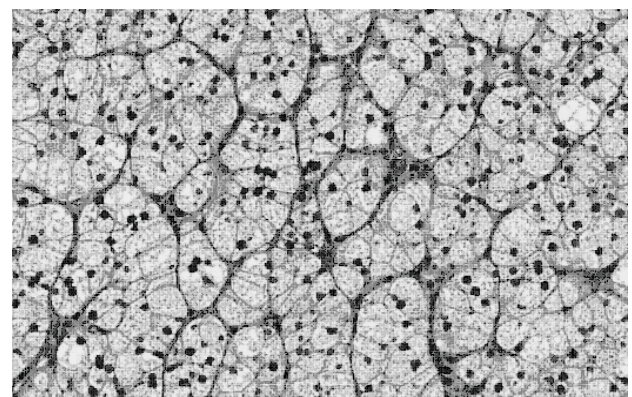


Fig. 2. Polygonal clear cells arranged in nests and trabeculae, reminiscent of the zona fasciculata of the adrenal cortex (Haematoxylin and Eosin, original magnification x200).

and Melan-A. While most reported HARTs show benign histological features, cases of malignant transformation have been documented.^{6,7} This is signified by invasive borders, necrosis, predominantly solid architecture, cytological atypia and increased mitotic activity with atypical forms.

The principle histological differential diagnoses are HCC, metastatic RCC and metastatic adrenocortical carcinoma. HCC can morphologically mimic a HART, especially when the hepatocytes accumulate cytoplasmic glycogen and/or fat, giving them a clear appearance. Histological features more in keeping with a HCC include Mallory-Denk bodies, bile production, cirrhosis in the adjacent liver parenchyma and a canalicular staining pattern demonstrated by CD10 and pCEA. HepPar1 positivity will further affirm the diagnosis. Among metastatic neoplasms with clear cells, RCC is the most likely to be confused with a HART. The presence of a network of small thin-walled blood vessels is a diagnostically helpful characteristic of this tumour. The lesional cells will show RCC antigen, CD10 and EMA positivity.

An intrahepatic malignant adrenocortical lesion can represent either malignant transformation of a HART or metastatic adrenocortical carcinoma. Radiological and intraoperative demonstration of the involvement of the adrenal gland is imperative in the determination of the primary site. Microscopic evidence of residual benign adrenocortical parenchyma can indicate an antecedent HART. Immunohistochemical studies are not discriminatory with regards to the site of origin. In our case, no malignant histological features were discerned. The right adrenal gland was clearly segregated from the liver on intraoperative examination, showing only mild fibrosis on its posterior aspect. The left adrenal gland was unremarkable.

Conclusion

In summary, we describe a case of an incidental HART, occurring in a 47-year-old woman, showing the classic histological and immunohistochemical features. The tumour's relative small size, lack of cytological atypia, low proliferative activity and absence of invasion, portends a benign nature. The lesion was completely excised and the patient was well postoperatively. The diagnosis of HART is both radiologically and histologically challenging with its wide range of differential diagnoses. This emphasises the value of clinical, radiological and histological correlation in guiding and ascertaining the correct diagnosis. On histological examination, it can potentially be misinterpreted as other primary or secondary neoplasms with clear cells if the key histological features are not appreciated and the appropriate immunohistochemical studies not performed. Despite its rarity, it is important to be aware of this entity and consider it in the differential diagnosis of clear cell neoplasms in the liver.

REFERENCES

1. Crowder RE. The development of the adrenal gland in man, with special reference to origin and ultimate location of cell types and evidence in favour of the "cell migration" theory. *Carnegie Inst Contrib Embryol* 1957;26:193-210.
2. Arai K, Muro H, Suzuki M, Oba N, Ito K, Sasano H. Adrenal rest tumour of the liver: a case report with immunohistochemical investigation of steroidogenesis. *Pathol Int* 2000;50:244-8.
3. Tajima T, Funakoshi A, Ikeda Y, Hachitanda Y, Yamaguchi M, Yokota M, et al. Nonfunctioning adrenal rest tumour of the liver: radiologic appearance. *J of Comp Assist Tomogr* 2001;25:98-101.
4. Baba Y, Beppu T, Imai K, Masuda T, Iyama K, Sasano H, et al. A case of adrenal rest tumour of the liver: radiological imaging and immunohistochemical study of steroidogenic enzymes. *Hepatol Res* 2008;38:1154-8.
5. Yong MS. Hepatic adrenal tumour mimicking hepatocellular carcinoma. *Korean J Hepatol* 2010;16:338-41.
6. Wallace EZ, Leonidas JR, Stanek AE, Avramides A. Endocrine studies in a patient with functioning adrenal tumour of the liver. *Am J Med* 1981;70:1122-5.
7. Contreas P, Altieri E, Liberman C, Gac A, Rojas A, Ibarra A, et al. Adrenal rest tumor of the liver causing Cushing's syndrome: treatment with ketoconazole preceding an apparent surgical cure. *J Clin Endocrinol Metab* 1985;60:21-8.
8. Prasad SR, Wang H, Rosas H, Menias CO, Narra VR, Middleton WD, et al. Fat-containing lesions of the liver: radiologic-pathologic correlation. *Radiographics* 2005;25:321-31.

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