Malignant transformation of hepatic adenoma complicated by rupture and hemorrhage: An extremely rare clinical entity

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1. Introduction

Hepatic adenomas (HAs) are rare benign tumors of the liver resulting from monoclonal proliferation of liver cells and comprise 2% of all liver tumors with an annual incidence of 3-4/100,000 per year in Europe and North America. Risk factors for the development and progression of HAs include- use of estrogen containing contraceptive pills, androgen or anabolic steroid intake (used primarily for management of Fanconi syndrome, impotence, body building and in transsexuals), conditions leading to impaired glycogenesis and excessive hepatic intracellular glycogen deposits such as glycogen storage diseases (GSD), familial adenomatous polyposis and metabolic syndromes like diabetes mellitus, insulin resistance, dyslipidemia and high blood pressure (1). Two recognized complications for HAs are hemorrhage and malignant transformation to hepatocellular carcinoma (HCC). It has been observed that HAs less than 5 cm tend not to bleed, while the reported risk of a malignant transformation of an HA to HCC is very low (4-5%), and the reported mean size of solitary HA with features of malignant transformation is 10.5 cm (range: 4.5-18 cm) (2).

We present a unique case of a solitary HA in a young woman on the oral contraceptive pill (OCP) that underwent malignant transformation, which subsequently ruptured and presented with intraperitoneal bleed. This article therefore highlights the need to carefully evaluate any liver lesion in a young female on the OCP to be a possible adenoma and if confirmed to be so, to consider the potential risks associated with it as well as the need for follow-up imaging in order to avoid life threatening complications.

Keywords: Hepatic adenoma, inflammatory adenoma, hepatocellular carcinoma, oral contraceptive pill, hemorrhage, malignant transformation
L) and normal Total bilirubin (17 umol/L). She was referred for ultrasound examination of the abdomen for further evaluation.

Ultrasound of the abdomen revealed a 10 cm poorly defined hypoechoic lesion in the right lobe of the liver close to the capsule (Figure 1A). No significant vascularity was noted within the lesion on colour doppler. Additionally, turbid free fluid was noted in the pelvis in the right lower quadrant and in the posterior cul-de-sac (Figure 1B) raising the possibility of intrabdominal hemorrhage. The patient was immediately referred to our University Hospital for further evaluation and management.

The patient was further evaluated by contrast enhanced abdominal and pelvic computed tomography (CT). On non-contrast CT (Figure 2A), the liver appeared non-cirrhotic and demonstrated a 10.4 × 9.5 × 10.7 cm predominantly hyperdense lesion occupying majority of the right lobe of the liver. In addition, subcapsular hematoma involving the right lobe of the liver was noted, as well as adjacent intraperitoneal hemorrhage into the right subphrenic space with extension into the peritoneal cavity, with significant hemoperitoneum in the right lower quadrant and pelvis. On the post contrast image (Figure 2B), the lesion was noted to involve the entire right lobe (segments 5 to 8) and portions of segment 4a of the liver. In addition, peripheral areas of soft tissue enhancement were demonstrated in a patchy distribution. No additional lesions were noted in the liver. No intra or extra-hepatic vessel occlusion were seen. With the combination of these findings on CT along with the background history of OCP usage, the possibility of a ruptured adenoma was raised.

The patient was taken up for immediate surgery and an extended right hepatectomy including portions

Figure 1. Ultrasound of the abdomen revealed a poorly defined non-vascular hypoechoic lesion (A) in the right lobe of the liver close to the liver capsule. Additionally, turbid free fluid was noted in the pelvis in the right lower quadrant (B) in the posterior cul-de-sac raising the possibility of intrabdominal hemorrhage.

Figure 2. Non-contrast coronal reformatted CT image (A), showing non-cirrhotic liver with a 10 cm hyperdense lesion occupying the majority of the right lobe of the liver, in addition, subcapsular hematoma involving the right lobe of the liver as well as adjacent intraperitoneal hemorrhage into the right subphrenic space as well as into the peritoneal cavity was also identified. Post contrast coronal reformatted CT image (B) showing peripheral areas of soft tissue enhancement were demonstrated in a patchy distribution. In addition, a liver capsule defect was clearly visible, confirming lesion rupture and subsequent intraperitoneal hemorrhage.
HAs can be classified into six major molecular subgroups namely: HNF1α inactivated HA, inflammatory HA, b-catenin exon 3 mutated HA, b-catenin exon 7/8 mutated HA, Sonic Hedgehog activated HA and unclassified HA. The b-catenin exon 3 mutated HAs have a greater propensity for malignant transformation, while the Sonic Hedgehog activated HAs are at risk for bleeding (7). The Bordeaux group (8), identified useful immunohistochemical markers for identifying HA subtypes, namely, β-catenin and glutamine synthetase (GS) for β-catenin activated HA, liver-fatty acid binding protein (LFABP) for HNF-1α inactivated adenomas, serum amyloid A (SAA) and C-reactive protein (CRP) for the inflammatory subtype of HA. However, no markers were identified for the unclassified subtype.

Risk factors for malignant transformation of HAs include- large size (˃ 5 cm), multiplicity, β-catenin mutated subtype of HA and the male gender (9).

The commonly used imaging modalities for evaluation of HAs are ultrasound, contrast enhanced CT and magnetic resonance imaging (MRI). Typically, HAs (< 3-5 cm in size) on ultrasound appear isoechoic to background liver parenchyma, but these tumors can appear hypoechoic in patients with steatosis. However, HAs containing glycogen (e.g. in patients with GSD) or fat such as in HNF-1α subtype, generally appear hyperechoic. Large HAs (> 5 cm) tend to be...
heterogenous in appearance because hemorrhage or necrosis. Colour doppler has poor sensitivity and may demonstrate predominantly peripheral vascularity (10). On non-contrast CT, HAs appear as well circumscribed hypodense lesions (because of intra-tumoral fat, chronic hemorrhage or necrosis). In cases of acute hemorrhage, the tumor appears hypodense. Calcifications may be seen in 5-10% of the cases. On post intravenous contrast administration these tumors show enhancement in the arterial phase becoming isodense to background liver parenchyma on the portal venous and delayed phases, although some lesions can show washout on the portal or delayed phases (11). MRI features of HAs can vary depending on the subtype and has been elaborated in detail in Table 1 (3,12).

Management strategies for HAs depend on the underlying risk factors and size. In patients on hormone replacement therapies (including estrogen and androgen) complete cessation is recommended as studies have shown a regression rate of almost 80% and even complete resolution of the tumor in some patients on stopping OCPs (13). In obese patients, weight loss and even bariatric surgery has proved to be beneficial. For patients with GSD, alterations in dietary habits can even bariatric surgery has proved to be beneficial. For patients with OCPs (> 5 cm) in size and those adenomas that don't regress or increases in size following OCP cessation during the 6-month follow-up interval (13). Surgery is also recommended for HAs demonstrating increase in size, belonging to the β-catenin subtype, rising alpha fetoprotein (AFP) levels, those with features of malignant transformation and HAs in males, as the latter are prone to have the β-catenin subtype. The main indications for liver transplantation include multiple HAs not amenable to surgical resection with suspicious or confirmed malignant transformation, and the presence of porto-systemic venous shunt (13).

4. Conclusion

Malignant transformation of HAs is proven and occurs in 4-5% of all cases. Our case is unique, as the HA not only underwent malignant transformation but was further complicated by rupture and intra-abdominal bleed. By identifying the risk factors for HAs and recognizing the imaging characteristics, an early and accurate diagnosis can be reached thereby enabling urgent intervention which could potentially be lifesaving.

References

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