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Case Report

Hepatic Adenomatosis: A Rare but Important Liver Disease With Severe Clinical Implications

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A 56-year-old white female presented to the emergency room (ER) with acute onset of right upper quadrant abdominal pain, nausea, and vomiting, and she was found to have a sudden drop in hemoglobin. Abdominal computed tomography (CT) with and without intravenous contrast revealed multiple bilobar focal hepatic hypervascular lesions, one of them demonstrating spontaneous rupture with active intraperitoneal bleeding. A moderate hemoperitoneum was present. The patient underwent exploratory laparotomy for right hepatic posterior segmentectomy (right posterior sectionectomy) and peritoneal lavage. The histopathology evaluation revealed multiple liver adenomas. Hepatic adenomatosis is a clinical entity characterized by 10 or more hepatic adenomas. It must be distinguished from isolated hepatic adenoma as it bears a much higher risk of complications, such as spontaneous rupture, hemorrhage and malignant transformation. Here we discuss the radiologic and histopathologic findings of the current case along with a review of the English language medical literature.

Key words: Liver – Computed Tomography – Adenomatosis – Hemoperitoneum – Hemorrhage – Mass

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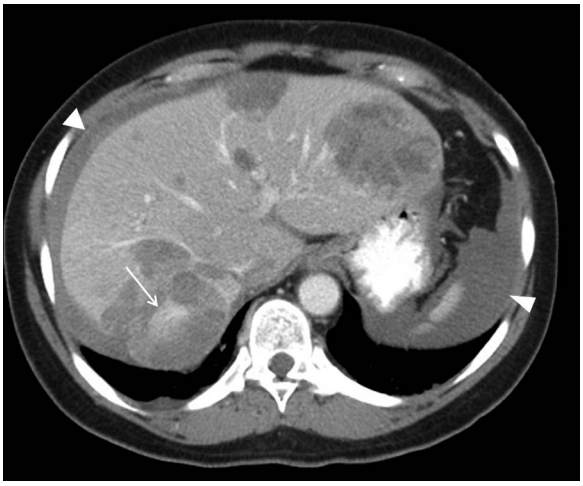

Fig. 1 A contrast-enhanced axial MDCT image that demonstrates multifocal bilobar hepatic adenomas. The largest mass (segment 7) shows spontaneous intralesional bleeding (arrow). Hemoperitoneum is noted (arrowhead).

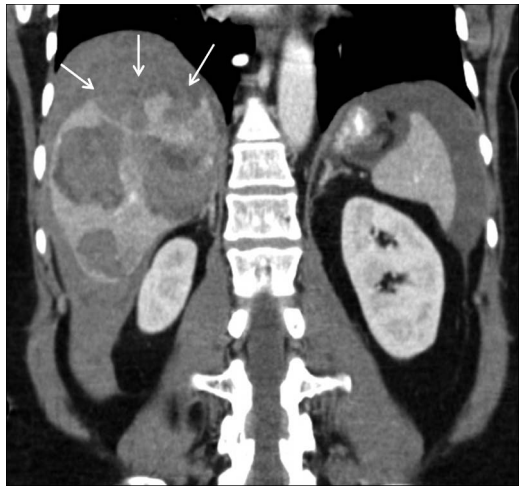

Fig. 2 A coronal multiplanar reconstruction (MPR) image that demonstrates contour irregularity of the hepatic dome (arrows) with adjacent subphrenic, perihepatic, and perisplenic hemorrhage.

Isolated hepatic adenomas are benign neoplasms that commonly occur in young women with a history of oral contraceptive pills or anabolic steroids use and type I glycogen storage disease. Most patients are asymptomatic with a normal liver function test.[1]

Hepatic adenomatosis (HA) was first described as a separate entity in 1985 by Flejou *et al*.[2] He defined this disease as when at least 10 adenomas were present in a background of normal looking hepatic parenchyma. Contrarily to isolated hepatic adenomas, HA shows no relation with oral contraceptive use; an increase of serum alkaline phosphatase and gamma-glutamyl transpeptidase is a common biochemical finding in HA.[2] Although HA is considered a benign disease, some patients may develop potential fatal complications, i.e., hypovolemic shock due to rupture of the liver lesions with intraperitoneal hemorrhage. The overall spontaneous bleeding and hemorrhagic complication rate reaches 62.5%.[2] Malignant transformation to hepatocellular carcinoma occurs in less than 10% of cases.[3,4] We review the English language literature and discuss the radiologic and pathologic findings of this case in comparison with the previously reported cases.

Case Presentation

A 56-year-old white female presented to the emergency room (ER) complaining of sudden onset right upper quadrant abdominal pain, nausea, and vomiting. She denied syncope, lightheadedness, palpitations, or dizziness. Laboratory results showed increased levels of AST (230 U/L), ALT (280 U/L), and alkaline phosphatase (210 U/L) and a drop in hemoglobin level from 12.6 to 10.2 gm/dL.

An abdominal multidetector computed tomography (MDCT) with and without contrast showed multiple, vascularized focal bilobar hepatic lesions and moderate hemoperitoneum (Fig. 1). The largest mass located in hepatic segment 7 showed intralesional high-density foci consistent with active arterial bleeding (Fig. 2). The patient underwent emergency right hepatic posterior segmentectomy (right posterior sectionectomy; segments 6 and 7) and abdominal washout. Gross pathology showed multiple well-circumscribed hepatic nodules with areas of intralesional hemorrhage (Fig. 3). Microscopic histopathology evaluation revealed multiple liver adenomas (areas of hepatocytes without portal tracts). No cellular atypia was seen (Fig. 4). The patient showed no postoperative complications and was discharged 5 days after the surgical procedure. Patient reported no further episodes of abdominal pain and tolerated diet without difficulty.

Discussion

Hepatocellular adenoma is an uncommon primary benign liver tumor, commonly presenting as a well-

Fig. 3 A gross pathology image that shows multiple yellow-tan nodules located throughout the liver parenchyma. Some nodules were well-circumscribed with a subcapsular location while others were ill-/well-defined with areas of hemorrhage.

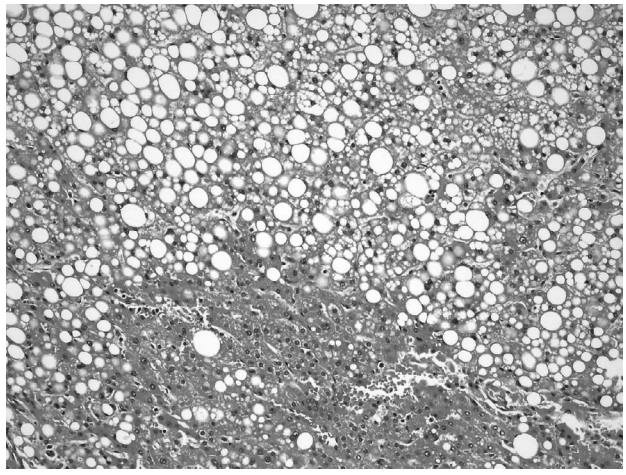

Fig. 4 A microscopic photograph that demonstrates a representative section taken from one of the nodular lesions. Hepatocytes without portal tracts are seen within the nodular proliferations. There is no cellular atypia, and severe or diffuse hepatic steatosis is seen.

defined solitary mass. Histologically, is composed of cords of hepatocytes containing an increased amount of glycogen and fat and is separated by dilated sinusoids. The extensive sinusoids, feeding arteries, and minimal connective tissue account for its hypervascular behavior and tendency to develop intralesional hemorrhage; this complication can spread into the liver or peritoneum when an absent or incomplete capsule is present (two-thirds of the cases).[5,6] The origin of hepatic adenomas has not been well established yet, but the use of estrogen and androgen-anabolic steroids increases their prevalence, number, and size.[7,8] Isolated hepatic adenoma commonly shows regression with cessation of exogenous steroid use. Other at-risk groups are patients with type I glycogen storage disease.[9] Hepatocellular adenoma is mostly asymptomatic, unless it becomes complicated with internal bleeding. Malignant degeneration to hepatocellular carcinoma (HCC) has been reported but is rare. Hepatocellular adenomas are usually detected with ultrasound (US) examinations as incidentalomas. The US appearance varies from a hypo- to hyperechoic lesion. Hemorrhage can increase internal echogenicity. Color Doppler US evaluation generally demonstrates peri- and intratumoral vessels with flat continuous or, less commonly, triphasic waveform.[10,11] Multiphasic MDCT is an excellent modality for detection and characterization of hepatic adenomas. Most hepatic adenomas are hypo- or isodense lesions in noncontrast images depending on the degree of intracellular fat. In patients with hepatic steatosis, the lesion may appear slightly hyperdense on precontrast phase.[5] Postcontrast arterial and venous phases add a temporal hemodynamic component to the morphologic depiction of the tumor. Hepatocellular adenoma demonstrates homogeneous or nearly homogeneous hypervascular enhancement during the arterial phase in 80% of cases.[5] During the portal venous phase, a "quick washout" is typically seen secondary to intralesional arteriovenous shunting. Larger hepatocellular adenomas tend to be more heterogeneous and their CT appearance is less specific. Delayed-phase images demonstrate the tendency of fibrotic components to enhance and retain contrast material producing delineation of the lesion capsule.[5]

On magnetic resonance imaging (MRI), hepatocellular adenomas have been described as mildly hyperintense lesions on T1 weighted images and predominantly hyperintense on T2 sequence. Dynamic gadolinium-enhanced MRI imaging can be used to demonstrate early arterial enhancement due to the presence of subcapsular feeding vessels.[12]

Previously considered as multiple liver adenomas, HA was first described by Flejou *et al* as a different clinical entity in 1985. Flejou defined HA as the presence of 10 or more adenomas in a normal liver.[2] The etiology and conditions that predispose a patient to HA are poorly understood, but many authors have described congenital or acquired abnormalities of the hepatic vasculature as predis-

posing factors.[13,14] HA shows no steroid use association or regression with steroid medication cessation.[2] Originally, Flejou described no gender prevalence, but this is no longer accepted, as the majority of reported cases are female (74%).[4,17] The liver function abnormalities are related to the space-occupying nature of tumors. Serum alkaline phosphatase and gamma-glutamyl transferase levels (GGT) are generally elevated. Malignant degeneration to HCC has been reported and may be suspected by elevated serum tumor markers or sudden increased in a tumor size.[1] Hemorrhage is frequent, especially in large and subcapsular adenomas.[15,16] Chiche *et al* have suggested 2 distinct patterns of HA. The "massive type," which presents with gross hepatomegaly, a deformed liver contour, and contains many large tumor nodules, and the "multifocal type," which contains many adenomas, but the liver contour is not distorted; this latter group is unlikely to develop symptoms and appears to have a less aggressive clinical course.[4]

The English-language medical literature search was performed for publications on HA by using the following keywords: "Hepatic Adenomatosis" or "liver Adenomatosis" in the PubMed search engine. Only 40 articles were retrieved and the majority was not directly related to this topic. To the best of our knowledge as reported by Barthelmes *et al* there are approximately 81 cases of HA documented in the literature: 41 (51%) of them presented with stable disease, 34 (42%) patients had disease progression with increased size and/or number of lesions, and 6 (7%) developed malignancy.[17] Fifteen (18%) patients presented with hemorrhagic complications and 2 (2.5%) died on presentation due to hemorrhage.[17] While liver transplantation was chosen by some of the authors (17 cases, 21%), the majority of the cases (64 cases, 79%) were managed with liver resection or conservative managements.[17]

We currently lack a consensus with regard to the best treatment options for this disease. The potential for intraperitoneal hemorrhage or malignant transformation of the tumors is difficult to estimate as are the technical difficulties associated with complete resection. Some authors have recommended resection of large (>5 cm) or symptomatic lesions and follow-up of smaller (<3 cm) asymptomatic lesions.[16] Other authors have offered no systematic proposal for surgery (neither for size nor for imaging criteria). Their indications for surgical removal have included only cases with acute complications such as hemorrhage or sudden necrosis causing asthenia or pain.[18] The glycogen storage disease population has an increased risk of bleeding in liver surgery by presence of a concurrent defect in platelet aggregation, so a preventive protocol concerning hemostasis using systematic corticosteroid and desmopressin (DDAVP) have been proposed.[18] Management with minimally invasive procedures, such as radiofrequency ablation (RFA), are generally associated with a lesser risk of bleeding. This technique destroys tumors up to 3 cm by localized application of heat to produce coagulative necrosis.[19] The only potential cure for HA is liver transplantation. The benefit of liver transplantation to prevent bleeding or cancer has to be balanced against the potential risks of transplantation. Perioperative mortality of liver transplantation is reported as 1%, and 5-year survival is about 66%.[20]

Although one of the initial intentions for consideration of liver transplantation in management of the patients with HA was prevention of future liver malignancies, development of hepatocellular carcinoma in 30% of the patient who underwent liver transplantation for HA (3 out of the 10 cases reported in the literature who have a known follow-up) have raised serious concerns on validity of this option for management of patients with HA.[17]

In the current case, as the lesions were bilobar and scattered in different segments of the liver, it was not feasible to resect all the adenomatous lesions. As suggested by Barthelmes and colleagues, we opted to resect the lesion/s with the greatest risk of hemorrhage (large and or subcapsular lesions may cause intraperitoneal bleeding).[17]

Our patient is going to be followed with a yearly surveillance program, which includes clinical assessment, liver function and tumor marker blood tests, and radiologic evaluations for follow-up of the unresected liver lesions.

Conclusion

HA is an extremely rare disease with multiple adenomas (more than 10), as opposed to an isolated liver adenoma, in a background of a normal-looking liver. There is no association between occurrence of HA and the use of anabolic steroids or oral contraception. These lesions are commonly symptomatic and have an increased risk of intralesional hemorrhage or malignant transformation. Asymptomatic patients should be followed with cross-sectional imaging and tumors makers. In case of

persistent right upper quadrant pain, surgical resection has to be considered. The role of transplantation remains unclear.

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