Immunohistochemical Staining on an Excision Biopsy Specimen as a Diagnostic Modality for Rare Idiopathic Hepatocellular Adenoma: A Case Report

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ABSTRAK

Adenoma hepatoselular merupakan tumor jinak hati yang sangat jarang, dengan predominasi pada wanita usia muda. Estimasi insidens 3-4 kasus per 1.000.000 populasi setiap tahunnya menjadikan kondisi ini memiliki tantangan diagnostik tersendiri. Melalui naskah ini kami melaporkan seorang wanita berusia 30 tahun dengan adenoma hepatoselular tanpa faktor risiko klasik. Rangkaian metode diagnostik telah dikerjakan untuk dapat menegakkan diagnosis dan hanya biopsi eksisi dari reseksi segmental yang menunjukkan kemaknaan nilai diagnostik. Kasus ini mengilustrasikan peran dari pulasan imunohistokimia pada biopsi eksisi sebagai modalitas diagnostik terbaik untuk adenoma hepatoselular, sekaligus sebagai modalitas terapeutik untuk mencegah transformasi keganasan.

Kata kunci: *adenoma hati, tumor jinak hati, diagnosis, penanda imunohistokimia, reseksi.*

ABSTRACT

Hepatocellular adenoma is an extremely rare benign tumor of the liver which predominantly in young women. Its rare incidence with estimated 3-4 cases per 1.000.000 annually makes it a diagnostic challenge. Here we present a 30-year-old female patient with hepatocellular adenoma without classic risk factors. A series of work up tools have been performed in order to diagnose the condition. None but excision biopsy from segmental resection had been showed to increase diagnostic confidence. This case illustrates the role of immunohistochemical staining from excision biopsy as the best diagnostic modality of hepatocellular adenoma as well as therapeutic modality to prevent malignant transformation.

Keywords: *liver adenoma, benign liver tumor, diagnosis, immunohistochemical marker, resection.*

INTRODUCTION

Hepatocellular adenoma (HCA), also known as hepatic adenoma, are rare, benign, hormonal induced hepatic tumors. Commonly found in childbearing-aged women, HCA has been strongly correlated with the use of oral contraceptives.[1] Incidence of HCA is approximately 1/1.000.000 in women without history of oral contraceptives compare to 30-40/1.000.000 in long-term users.[2,3] Nevertheless, the mechanism of estrogen-induced HCA is not completely understood. Other etiologies inducing the development of HCA include long-term use of anabolic androgenic steroids and glycogen storage diseases.[4]

The clinical presentation of hepatic adenomas varies widely. About 25-50% patients with hepatic adenomas reported with pain in the right upper quadrant or epigastric region. Lesions may be palpable or incidentally found during abdominal imaging study for other study. Bordeaux classification of hepatic adenomas is currently being evaluated. The classification consists of hepatocyte nuclear factor 1α-inactivated HCA (HNF1α HCA 30-35%), β cateninmutated HCA (β-cat HCA 10-15%), inflammatory HCA (50%), and a subgroup of less than 10% that remains unclassified.[5]

Basically, HCA is diagnosis made by excluding other differential diagnosis. Serological test are performed to exclude other possible diagnosis. Serum aminotransferase levels may be mildly elevated due to the mass effect of the tumor. Most patients with hepatic adenoma have normal range of serum alpha-fetoprotein (AFP). An elevation in AFP levels is correlated with primary carcinoma or malignant transformation of adenoma. Radiologic findings are nondiagnostic because the mass commonly found in solitary and well demarcated lesion. Advances in contrast-enhanced MRI and contrast-enhanced ultrasonography may be helpful to distinguish hepatic adenoma and possibly determined Bordeaux classification subtypes.[6] Immunohistochemistry may be performed to further characterize lesion under the new Bordeaux classification while results of histologic evaluation with liver biopsy are nondiagnostic and insensitive.[5] The prognostic for hepatic adenoma is not well established. While complete resolution is uncommon, the risk of malignant transformation still remains even after oral contraceptive or steroid use has been discontinued. All symptomatic tumors should be resected. Asymptomatic adenomas smaller than 5 cm in size may be managed with close monitoring.[7]

CASE ILLUSTRATION

A 30-year-old female was referred with abdominal pain in the right upper quadrant over the preceding one year. The pain was described as localized, episodic, and non-triggered by food or activity. She had not complained of nausea, vomit, dark-colored stool urine, black stool, abdominal enlargement, bloating or weight loss. She could still carry on daily activity without restriction. She had no history of jaundice, blood transfusions, hepatitis, excessive alcohol consumption, or long-term oral contraception. Clinical examination revealed no abnormalities, no abdominal palpable mass found.

Laboratory tests were within normal limits. Tests for hepatitis B surface antigen and hepatitis C antibodies were all non-reactive. Serum tumor markers (AFP, CEA, Ca 19-9, Ca 125) were all within normal range. Multiphase abdominal multi slice computed tomography (MSCT) showed a focal mass in right lobe liver, segment 5, with size of 6.3 cm x 5.2 cm x 5 cm. The mass was shown as iso-hypodense lesion with slight enhancement in arterial phase, followed by heterogeneous enhancement in portovenous phase and contrast washed out in delayed phase (**Figure 1**). The CT findings suggested hepatocellular carcinoma with differential diagnosis of adenoma, adenocarcinoma. Liver core biopsy was then performed to ensure the diagnosis. Core biopsy findings suggested liver adenoma with differential diagnosis hepatocellular carcinoma grade 1. Immunohystochemical staining was performed following core biopsy, with findings of positive granular cytoplasm with expression of glypican 3, complete expression of CD 34, positive expression of CD10, and less than 5% of expression of Ki67 (**Figure 2**). The findings suggested hepatocellular carcinoma grade 1.

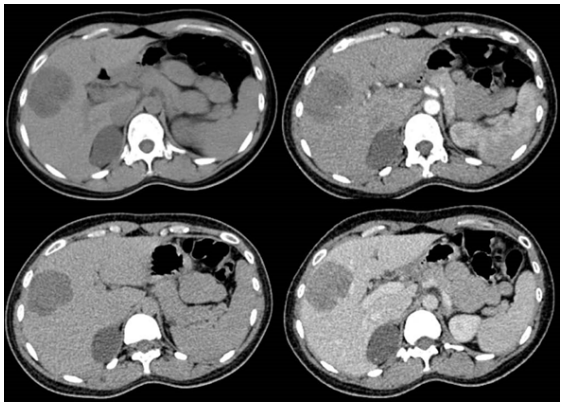

Figure 1. Multiphase abdominal MSCT of the patient (clockwise from top left): non-contrast, arterial phase, venous phase, delayed phase.

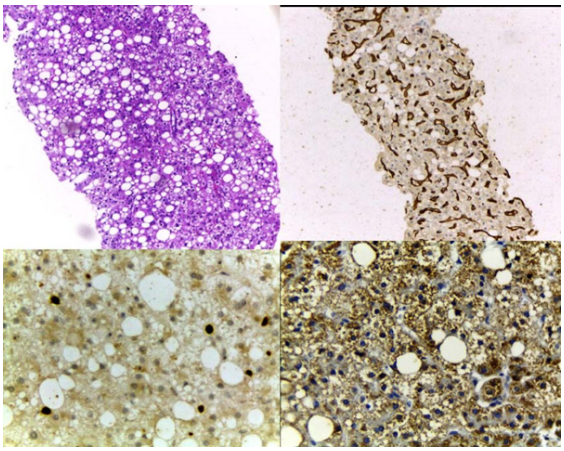

Figure 2. Histopathology finding and immunohistochemical staining on core biopsy specimen (clockwise from top left): stained with Hematoxylin & Eosin (H&E), CD34, glypican-3, and Ki67.

The patient underwent open laparotomy. Medial laparotomy incision from xiphoid process to two fingers below umbilicus, passing through cutis, sub cutis, and linea alba. Intraoperative ultrasonography (USG) was performed and showed solid lesion of 3 x 3 x 3 cm in hepatic segment V. Tumor resection margins were determined with the use of USG guidance. Liver mobilization began by releasing the liver from the falciform ligament, coronary ligament, and triangular ligament. Hepatoduodenal ligament was identified and released from surrounding tissues at right hepatic artery, right portal vein and common bile duct using Pringle maneuver. To treat the lesion, hepatectomy of segment V was performed.

The specimen was brown-black colored, spongy, measuring 10 x 7 x 4.5 cm. The mass itself measured 7 x 6 x 3 cm, yellow-brown colored, firm and tender. A 2.5 x 2 x 1.5 cm hollow with inner irregular surface was shown in division of the mass (**Figure 3**). Microscopic examination showed tumor tissues with partly poor-circumscribed edges. Neovascularization was also seen. Tumor cells showed hepatocytes differentiation consists of trabecular tissue of 2-4 cells/field in depth, common uniform nucleated tumor cells, some with vivid nucleolus, and mitosis was hardly found (**Figure 4**). Microscopic examination showed the lesion was hepatocellular adenoma. The specimen was consulted and sent to Groningen, Netherlands and New York, USA, of which both confirmed the diagnosis was hepatocellular adenoma. Mutation examination revealed it was inactivated hepatocellular adenoma through evaluation of HNF-1α.

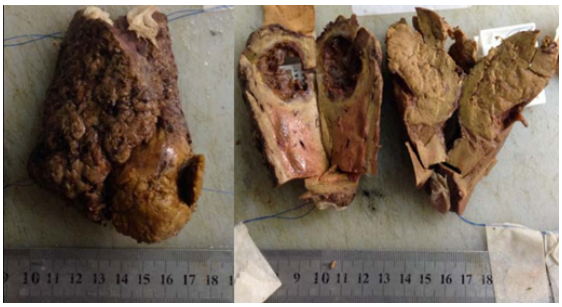

Figure 3. Macroscopic specimen of liver mass.

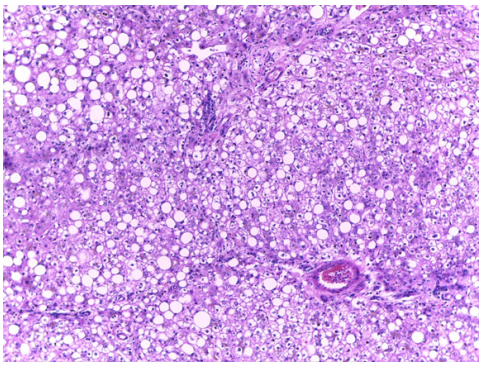

Figure 4. H&E staining on excision biopsy specimen showing hepatocellular adenoma characterized by sinusoidal dilatation and cluster of small arteries surrounded by inflammation.

No signs of liver failure were shown after surgery. The patient was discharged one week

after surgery. The patient was advised for follow-up ultrasound examination six months after the operation.

DISCUSSION

The differential diagnosis of benign liver cell tumors requires understanding of the clinical, radiological, and pathological features of the liver lesions. A detailed history, physical examinations, hepatic tests, imaging, and histopathological studies are necessary for precise diagnosis. There are several points of approach for the lesion which may be beneficial as the clues of establishing HCA diagnosis, differentiating it with focal nodular hyperplasia (FNH) or hepatocellular carcinoma (HCC).

Patients with liver adenomatosis range in age from 12 to 75 years, with a mean age of 34 years.[8] Eighty-eight percent of them are women, as well as those with FNH (80-90%), meanwhile HCC predominates in men.[9] Patients diagnosed with HCA are typically young women with long-standing oral contraceptive use or with history of glycogen storage diseases.[9] In the present case, the diagnosis is difficult to be determined and distinguished from other possible diagnosis due to absence of classic risk factors from neither HCA nor HCC (viral, alcoholic, metabolic syndrome) and FNH (local or systemic vascular anomalies). HCA typically occurs in noncirrhotic livers.8 However, a recent case of HCA was observed in a hepatitis B virus or alcoholic-associated cirrhotic liver.[10]

The majority of the tumors are in the size range of 5 to 15 cm at the time diagnosis, but they can be < 0,5 or > 30 cm. Clinical presentation is usually related to the size of the tumors, with size of ≥ 5 cm tend to be more likely simptomatic, presented with acute abdominal pain (43%) and hemorrhagic complications (46%).[8]

Several diagnostic modalities have been performed. Unlike in HCC, both HCA and FNH were usually presented with normal function liver test results and no or minimal elevation in serum tumor markers, such as α-fetoprotein.10 Although the laboratory test results in our case appeared within normal range, hepatocellular carcinoma was suggested from radiologic findings.

Radiological findings for HCA are similar with those in HCC or FNH. Adenomas are sharply marginated (85%), nonlobulated (95%), sometimes encapsulated (30%), and rarely calcified (10%), demonstrated with homogenous or nearly homogenous enhancement in 80% of cases.[11] While most of adenomas were presented in a single mass that may contain area of fat or hemorrhage, we have found none in our case. Also, the accurate differentation of the HCA lesion often can be better interpreted with magnetic resonance imaging (MRI) or contrast enhanced ultrasonography (CEUS).[8,9]

Several primary hepatic tumors, including HCC, FNH and HCA, are classified as hypervascular tumors, on the basis of helical multiphasic CT observations and pathophysiology, and therefore a confident preoperative diagnosis of HCA are difficult based on the radiologic observations.[12,13] FNH usually comes with diagnostic pointer of central scar with centrifugal or eccentric enhancement,8 whereas well-differentiated HCC is usually large, heterogenous, and lobulated, with large, central, or eccentric scars and radiating fibrous septa, calcifications (40-68%), as well as abdominal lymphadenopathy (65%).[11]

Distinction between HCA and HCC are obviously of paramount clinical importance in determining appropriate therapy and assessing prognosis, unless often can usually be achieved only on histologic grounds. We found that the histopathology examination of core biopsy from our patient indicated benign lesion. The later immunohistochemical staining with glypican 3, CD34, CD10 and Ki67 of core biopsy specimen indicated HCC lesion. However, distinguishing HCA from well-differentiated HCC can be extremely challenging when the diagnostic material is a small needle biopsy.8 Nonetheless, the efficacy of percutaneous liver biopsy is limited with preoperative accuracy about 50%.[13,14]

Conservative treatment was the initial treatment for HCA < 5 cm in diameter. A tumor size ≥ 5 cm and abdominal complaints, as found in our case, were major criteria for surgical resection. Among all HCAs, 9% may transform into HCC with risk factors including male sex,

androgen use, size ≥ 5 cm, and ß-catenin-mutated HCA. In these complicated cases, early surgical removal may improve patient outcomes.[15] As an alternative, several reports also demonstrated the efficacy of radiofrequency ablation (RFA), especially in cases not amenable to surgery or in patients who would require major hepatic resection otherwise.[16] Our patient was then decided to undergone surgery with hepatectomy for diagnostic and therapeutic purpose.

Immunohistochemical examination of glutamine synthetase, beta-catenin, serum amyloid A and C-reactive protein, and liver fatty-acid binding protein on surgical specimen determined the lesion as of non-inflammatory HCA or specifically HNF-1α HCA. Among all HCAs, the HNF-1α HCA is the least aggressive subtype with almost no risk for the development of malignancy.

CONCLUSION

As illustrated in this case, similar findings of HCA and well-differentiated HCC as well as FNH in radiologic findings can be a challenge in distinguishing the diagnosis. Because management of these tumors is different, confident preoperative diagnosis is essential. Although documented in low statistic number, HCA could occur in individual without classic risk factor. Atypical features such as heterogeneous enhancement should be evaluated with additional imaging, such as MRI; or biopsy; even surgical resection. In such cases, all possible diagnosis must be excluded. Resection and histopathology examination remains the best modality in diagnosing HCA, as well as therapeutic option to exclude malignant neoplasm.

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