Diagnostic Dilemma of Hepatocellular Carcinoma Presenting as Hepatic Angiomyolipoma

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Although this patient's initial imaging and laboratory test results suggested hepatic angiomyolipoma, repeat pathologic analysis finally confirmed a diagnosis of hepatocellular carcinoma.

Hepatocellular carcinoma (HCC) usually develops in patients who have a history of chronic liver disease. In fact, 77% of HCC cases are associated with chronic viral hepatitis, and 62% are associated with liver cirrhosis; only 7% of liver cancers are found to emanate from a normal liver bed.[1] Clear-cell HCC is a rare type of liver cancer, accounting for 7% to 12% of all liver cancer cases.[2] Although clear or fatty cellular changes may be seen frequently in early HCC cases, they are relatively uncommon in larger cancers.[3]

Angiomyolipoma is a benign mesenchymal tumor usually found in the kidney, and rarely in the liver. Hepatic angiomyolipoma (HAML) sometimes can be confused with HCC, particularly the clear-cell variant, because of similar radiologic and pathologic features. Differentiating HAML from HCC is crucial, however, because the treatment pathways for these 2 conditions are diametrically opposed. In HAML, management involves close monitoring with delay of surgical intervention. In HCC, surgical resection or transplantation, if possible, is required.

To emphasize the importance of exactly and expeditiously distinguishing HAML from HCC—clinically, radiologically, and, above all, histologically—we present the case of our patient. Although he displayed the hallmarks of HAML, his pathology tested positive for HCC, thus mandating further radiologic and histologic testing until we isolated a large liver lesion and, with it, a definitive diagnosis of HCC.

INITIAL EXAM

Our patient, an 81-year-old man, initially presented to the VA medical center in Providence, Rhode Island, reporting intermittent, brief, right upper quadrant discomfort. He had no history of alcohol dependence or viral hepatitis. On physical examination, he appeared in good health with no jaundice. His abdomen was soft, nondistended, and nontender. He had no edema. Routine blood work revealed mildly elevated liver function test (LFT) results: alkaline phosphatase level, 67 U/L (reference, 30 U/L to 120 U/L); alanine aminotransferase level, 43 U/L (reference, 10 U/L to 40 U/L); and aspartate aminotransferase level, 40 U/L (reference, 10 U/L to 30 U/L). Serum alpha-fetoprotein (AFP) level was normal at 1.3 mcg/L.

The patient underwent ultrasound of the liver, which showed a large mass with hyperechoic foci (Figure 1). Subsequently, we performed dynamic contrast-enhanced computed tomography (CT) of the abdomen, which revealed the presence of a 7.1 cm × 6.6 cm, heterogeneous mass involving the left lobe of the liver (Figure 2). The lesion enhanced in the periphery, with multiple areas of low attenuation noted within the tumor—consistent with a fat-containing tumor—thus a presumptive radiologic diagnosis of HAML was made. HCC was deemed unlikely be-

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cause of the lesion's high fat content, which rarely is seen in large HCCs. Moreover, our patient was noncirrhotic on physical examination; had no history of alcohol dependence, hepatitis B, or hepatitis C; and had normal-to-mildly elevated LFT results with a normal AFP level.

At this point, our patient underwent CT-guided biopsy of the liver lesion. On initial analysis, the specimen revealed clusters of atypical hepatocytes, with increased nuclear-to-cytoplasmic ratio in the trabecular architecture. Adjacent necrosis and hemorrhage were present. The tumor cells tested positive for polyclonal carcinoembryonic (pCEA) antigen, CD34 antigen, and hepatocyte antigen (Hep Par 1 antibody), suggestive of HCC. The surrounding parenchyma, however, was noncirrhotic. Although the pathology results strongly indicated HCC, the previous CT results, combined with a normal AFP level in a noncirrhotic liver, made definitive diagnosis difficult.

Chemical shift magnetic resonance imaging (MRI) of the liver was obtained to better visualize the lesion (Figure 3). The MRI revealed a tumor with high fat, hyperechoic areas, consistent with HAML. Because doubt regarding the diagnosis persisted, a repeat CT-guided biopsy of the liver mass was performed to obtain another specimen. A battery of stains was performed to establish the diagnosis. The specimen again tested positive for Hep Par 1 antibody and CD34 antigen (for neoplastic liver). The specimen tested negative for MOC-31 antigen (for primary or metastatic adenocarcinoma) and Melan-A antigen (for HAML and melanoma). Therefore, the conclusive diagnosis was HCC.

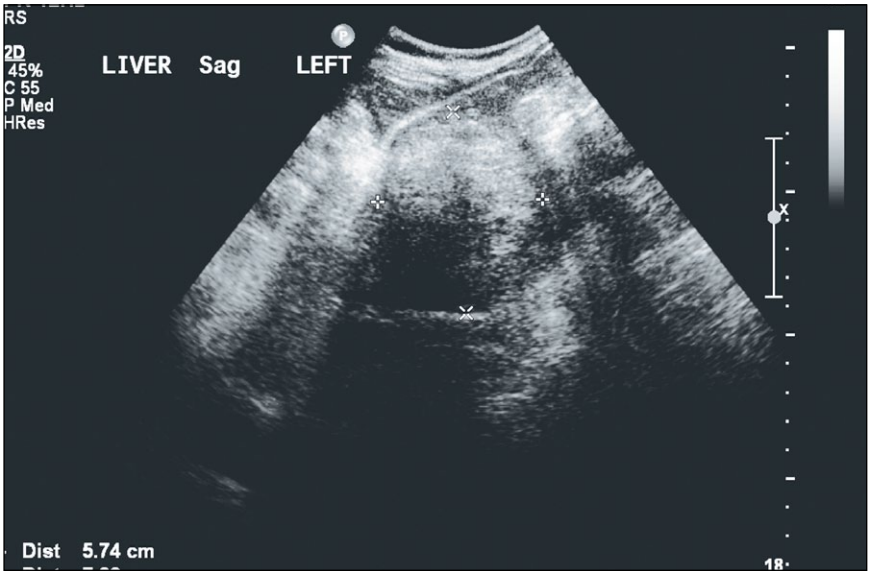

Figure 1. Ultrasound of the liver, showing a large mass with hyperechoic foci.

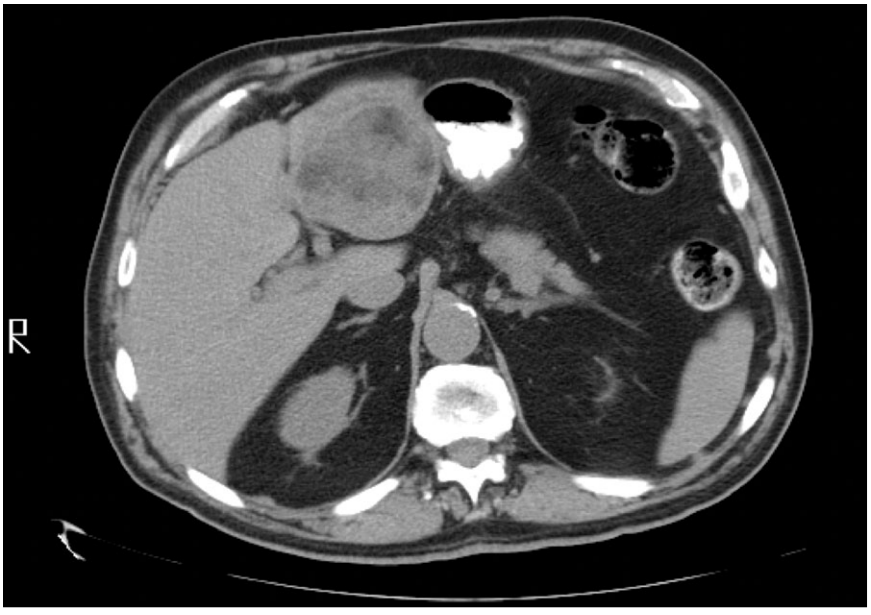

Figure 2. Dynamic contrast-enhanced computed tomography scan, revealing a heterogeneous mass in the left lobe of the liver.

TREATMENT COURSE

Our patient underwent left liver lobectomy. On gross appearance, the tumor was tan, pink, yellow, and green, with variable areas of apparent hemorrhage and necrosis (Figure 4). The final diagnosis was HCC (7.2 cm in maximum dimension), clear/fatty-cell type, with solid, trabecular, and tubular growth patterns (Figure 5). There was no vascular invasion, and the margins were clear of malignancy.

Our patient's postoperative course was uncomplicated and he had a very good outcome. He was discharged

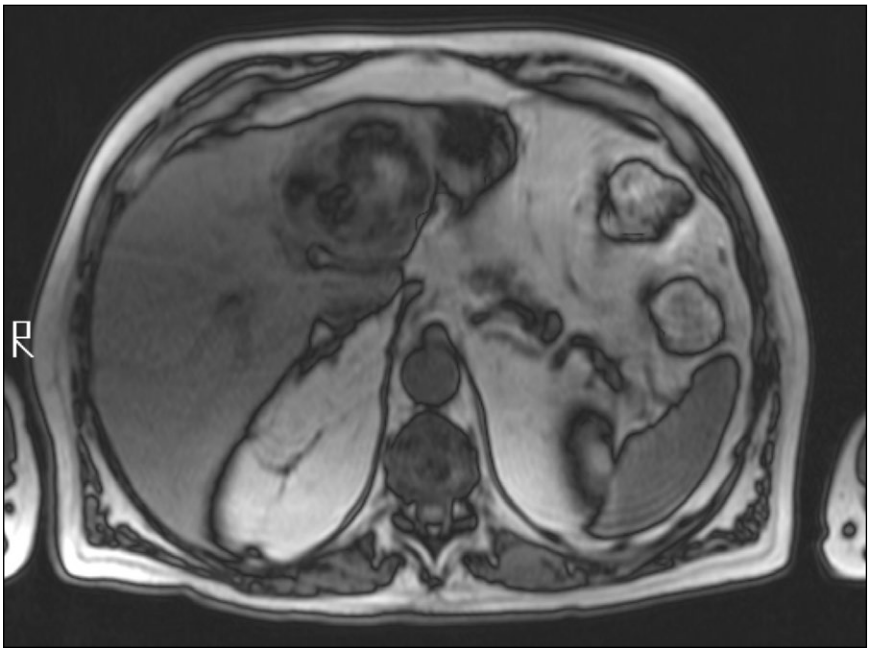

Figure 3. Chemical shift magnetic resonance image, showing a liver mass with fat-containing hyperechoic areas.

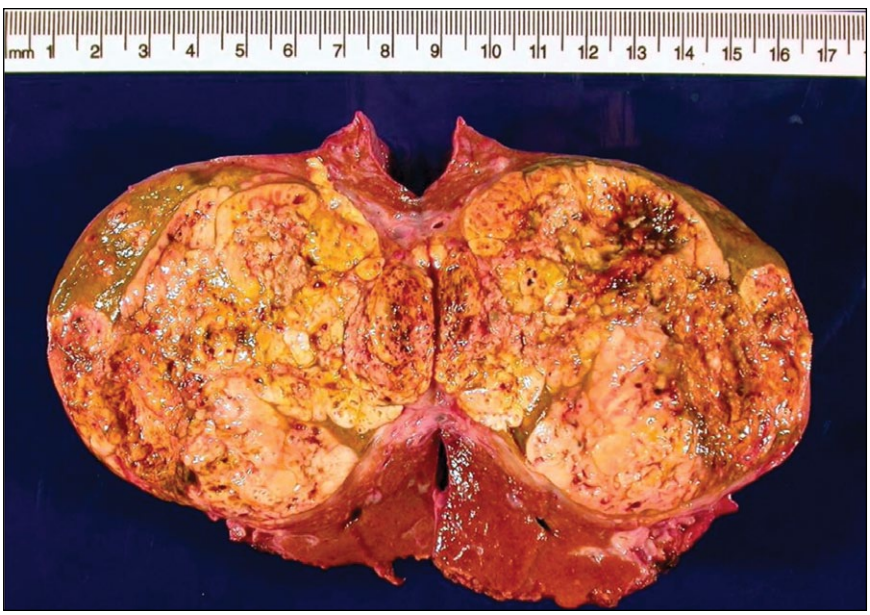

Figure 4. Gross appearance of the liver lesion, displaying tan, pink, yellow, and green colorations, apparent hemorrhage, and necrosis.

and returned to his nursing home on postoperative day 7. Up to the present, our patient has undergone repeat history and physical examinations, CT of the abdomen and pelvis, and AFP testing every 6 months, all of which have been negative for recurrence or metastasis.

ABOUT THE CONDITION

A few case reports have documented the similarities between clear-cell HCC and HAML. HAML first was described by Ishak in 1976.[4] Since then, more than 200 cases have been reported in the literature.[5] HAML usually presents as a solitary tumor in a noncirrhotic liver. Although HAML most often is asymptomatic, abdominal pain is the most common presenting symptom, followed by abdominal fullness and weight loss.[6] This description fit perfectly with the clinical and radiologic findings in our patient, which is why we initially suspected HAML. On first look, HAML can resemble HCC on imaging because both are heterogeneous liver masses that can contain varying amounts of fatty infiltrate; further work-up is necessary to differentiate one from the other.

Various imaging modalities are used to differentiate HAML from HCC. On ultrasound, HAML most often is a homogeneously hyperechoic mass. Some have heterogeneous echogenicity, depending on the proportion of each tissue component. Whether homogeneous or heterogeneous in nature, it is difficult to distinguish HAMLs from other fatty or hypervascular lesions, such as lipoma, hemangioma, or hyperechoic focus of a malignant lesion.[7,8] On CT, the fatty component usually has an attenuation value of < –20 HU, and the vascular component enhances during the arterial phase. This enhancement is early and intense, and peaks later than the fatty foci of HCC.[8] The fat content of HAML ranges from 5% to 79%, making it difficult to distinguish from HCC with fatty/clear-cell variant.[9,10] However, the presence of fat, combined with early, intense, and

prolonged enhancement, especially of central vessels, may help distinguish HAML from HCC.[11]

On MRI, the fat foci of HAML give it a high-intensity signal on both T_1- and T_2-weighted images. Furthermore, chemical shift MRI allows accurate differentiation between fat-containing hyperechoic liver lesions and hyperechoic lesions without a fatty component, such as old hematomas and lesions that contain melanin or large amounts of accumulated copper.[12] New MRI agents are available for evaluation of hepatocellular lesions, including ferumoxides and mangafodipir, as well as dynamic contrast-enhanced MRI; however, each has its drawbacks. Ferumoxides and mangafodipir lack dynamic enhancement information,[13] while dynamic contrast-enhanced MRI is cumbersome and not widely used.[14] In 2008, gadoxetic acid disodium was approved by the FDA for intravenous use in T_1-weighted MRI of the liver. MRI using this promising new agent—which has selective hepatocyte uptake—was found to be superior in characterizing liver lesions, when compared with unenhanced MRI and CT imaging.[15] Although combining ultrasound, CT, and MRI increases the likelihood of a correct diagnosis, the imaging features are so varied and nonspecific that accurate preoperative diagnosis is difficult, reporting to be less than 50%.[16,17]

As such, pathologic analysis is necessary for precise differentiation of HCC from HAML. Again, although HAML and HCC share certain histologic features, such as cellularity, pleomorphism, intranuclear inclusions, prominent nucleoli, and transgressing endothelium, a more detailed analysis with specific stains allows distinction of these 2 entities.[18] Macroscopically, HAML usually is a yellow-to-grayish brown, well-circumscribed, spongy tumor, with no fibrous capsule. Microscopically, it is composed of smooth muscle tissue, thick-walled and tortuous blood vessels, and mature adipose tissue. Depending on the predominance of each tissue component, it is categorized into mixed (most common), lipomatous (≥ 70% fat), myomatous (≤ 10% fat), and angiomatous types. The cells often are irregular with an epithelioid appearance. They may be polygonal and multinucleated, with increased nuclear-to-cytoplasmic ratio, and also may form trabeculae and sinusoid-like structures. These are all characteristics of cells seen in HCC. One difference, however, is that, unlike cells in HCC, cells in HAML exhibit no mitoses.[19-21]

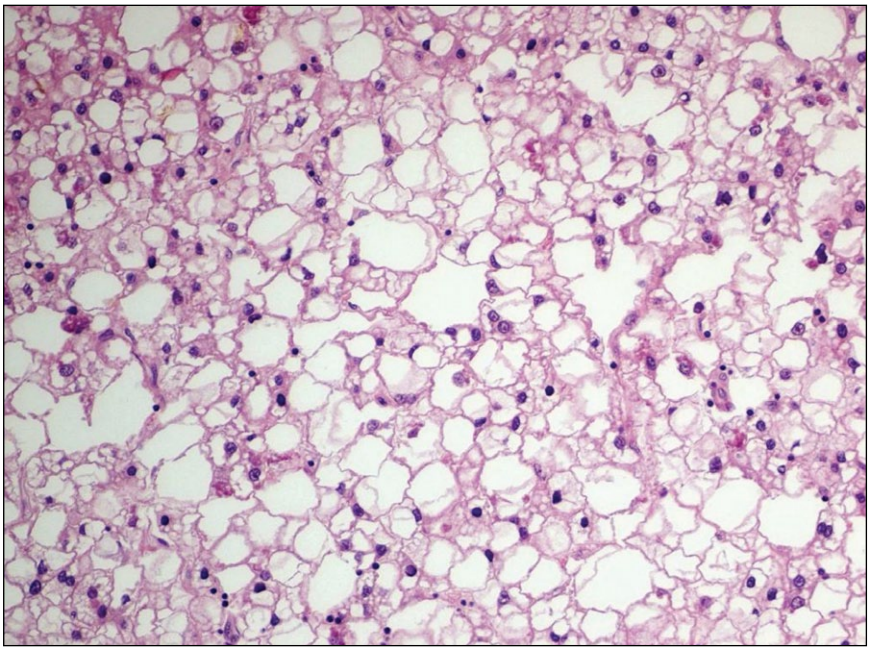

Figure 5. Microscopic analysis, revealing clear cells of hepatocellular carcinoma, which are difficult to differentiate from mature adipose cells found in hepatic angiomyolipoma (magnification ×75).

Immunohistochemistry allows further differentiation. The myoid cells of HAML are positive for HMB-45, a melanoma-specific monoclonal antigen, and smooth muscle actin (SMA) antibody in 100% of cases. They are positive for Melan-A antigen in 93% of cases. These markers are all negative in HCC.[18-20,22] In contrast, CAM 5.2, a keratin-specific antigen, and Hep Par 1 antibody are positive in 92% and 100% of HCC cases, respectively, while they are negative in HAML.[18,20,23,24] CD34 stains blood vessel endothelium in both HAML and HCC.[20,21] pCEA, monoclonal CEA, and MOC-31 antigens are useful in distinguishing HCC from metastatic adenocarcinoma, but they do not play a role in differentiating HCC from HAML.[25]

IN SUMMARY

We conclude that HCC should be included in the differential diagnosis of any liver mass. Radiologic imaging is nonspecific and does not allow for a definitive diagnosis. The high

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fat content of a tumor should not be used to rule out HCC because there are variants of HCC that have a high fat content (for example, clear-cell). Also, the fat content of benign lesions, such as HAML, is variable. HCC may occur in healthy livers, in the absence of cirrhosis, and without elevation of serum AFP level (which is normal in more than 20% of HCC cases).[26] Anytime there is doubt about the diagnosis, the next step should be image-guided biopsy with thorough pathologic analysis. As it relates to HAML and HCC, pathologic analysis combining a hepatocyte-specific stain, like Hep Par 1 (positive in HCC, negative in HAML), with HMB-45 or SMA (positive in HAML, negative in HCC) allows accurate preoperative differentiation of HAML from HCC. In our case, preoperative pathologic diagnosis with the use of these stains allowed resection of a hepatic tumor that we could confidently predict would be HCC.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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REFERENCES

1. Liver Cancer Study Group of Japan. Follow-up Committee. Liver Cancer Study Group of Japan: 16th report of national follow-up study of primary liver cancer (2001-2002), 2003:31-86.
2. Lai CL, Wu PC, Lam KC, Todd D. Histologic prognostic indicators in hepatocellular carcinoma. *Cancer.* 1979;44(5):1677-1683.
3. Emile JF, Lemoine A, Azoulay D, Debuire B, Bismuth H, Reynes M. Histological, genomic and clinical heterogeneity of clear cell hepatocellular carcinoma. *Histopathology.* 2001;38(3):225-231.
4. Ishak KG. Mesenchymal tumors of the liver. In: Okuda K, Petres RL, eds. *Hepatocellular Carcinoma.* New York, NY: Wiley Medical; 1976:247-307.
5. Xu AM, Zhang SH, Zheng JM, Zheng WQ, Wu MC. Pathological and molecular analysis of sporadic hepatic angiomyolipoma. *Hum Pathol.* 2006;37(6):735-741.
6. Yeh CN, Chen MF, Hung CF, Chen TC, Chao TC. Angiomyolipoma of the liver. *J Surg Oncol.* 2001;77(3):195-200.
7. Nonomura A, Mizukami Y, Kadoya M. Angiomyolipoma of the liver: A collective review. *J Gastroenterol.* 1994;29:95-105.
8. Ahmadi T, Itai Y, Takahashi M, et al. Angiomyolipoma of the liver: Significance of CT and MR dynamic study. *Abdom Imaging.* 1998;23(5):520-526.
9. Goodman ZD, Ishak KG. Angiomyolipomas of the liver. *Am J Surg Pathol.* 1984;8(10):745-750.
10. Takayama Y, Moriura S, Nagata J, et al. Hepatic angiomyolipoma: Radiologic and histopathologic correlation. *Abdom Imaging.* 2002;27(2):180-183.
11. Yan F, Zeng M, Zhou K, et al. Hepatic angiomyolipoma: Various appearances on two-phase contrast scanning of spiral CT. *Eur J Radiol.* 2002;41(1):12-18.
12. Martin J, Puig J, Falco J, et al. Hyperechoic liver nodules: Characterization with proton fat-water chemical shift MR imaging. *Radiology.* 1998; 207(2):325-330.
13. Semelka RC, Helmberger TK. Contrast agents for MR imaging of the liver. *Radiology.* 2001;218(1):27-38.
14. Ward J, Guthrie JA, Scott DJ, et al. Hepatocellular carcinoma in the cirrhotic liver: Double-contrast MR imaging for diagnosis. *Radiology.* 2000;216(1):154-162.
15. Raman SS, Leary C, Bluemke DA, et al; United States EOB Study Group. Improved characterization of focal liver lesions with liver-specific gadoxetic acid disodium-enhanced magnetic resonance imaging: A multicenter phase 3 clinical trial. *J Comput Assist Tomogr.* 2010;34(2):163-172.
16. Low SC, Peh WC, Muttarak M, Cheung HS, Ng IO. Imaging features of hepatic angiomyolipomas. *J Med Imaging Radiat Oncol.* 2008;52(2):118-123.
17. Zhong DR, Ji XL. Hepatic angiomyolipoma—misdiagnosis as hepatocellular carcinoma: A report of 14 cases. *World J Gastroenterol.* 2000;6(4):608-612.
18. Cha I, Cartwright D, Guis M, Miller TR, Ferrell LD. Angiomyolipoma of the liver in fine-needle aspiration biopsies: Its distinction from hepatocellular carcinoma. *Cancer.* 1999;87(1):25-30.
19. Tsui WM, Colombari R, Portmann BC, et al. Hepatic angiomyolipoma: A clinicopathologic study of 30 cases and delineation of unusual morphologic variants. *Am J Surg Pathol.* 1999;23(1):34-48.
20. Xu AM, Zhang SH, Zheng JM, Zheng WQ, Wu MC. Pathological and molecular analysis of sporadic hepatic angiomyolipoma. *Hum Pathol.* 2006;37(6):735-741.
21. Székely E, Schaff Z, Madaras L, Kupcsulik P, Zsirka A. Trabecular angiomyolipoma mimicking hepatic cell carcinoma. *Pathol Oncol Res.* 2000;6(3):224-226.
22. Makhlouf HR, Ishak KG, Shekar R, Sesterhenn IA, Young DY, Fanburg-Smith JC. Melanoma markers in angiomyolipoma of the liver and kidney: A comparative study. *Arch Pathol Lab Med.* 2002;126(1):49-55.
23. Chu PG, Ishizawa S, Wu E, Weiss LM. Hepatocyte antigen as a marker of hepatocellular carcinoma: An immunohistochemical comparison to carcinoembryonic antigen, CD10, and alpha-fetoprotein. *Am J Surg Pathol.* 2002;26(8):978-988.
24. Wee A. Diagnostic utility of immunohistochemistry in hepatocellular carcinoma, its variants and their mimics. *Appl Immunohistochem Mol Morphol.* 2006;14(3):266-272.
25. Wang L, Vuolo M, Suhrland MJ, Schlesinger K. HepPar1, MOC-31, pCEA, mCEA and CD10 for distinguishing hepatocellular carcinoma vs. metastatic adenocarcinoma in liver fine needle aspirates. *Acta Cytol.* 2006;50(3):257-262.
26. Burditt LJ, Johnson MM, Johnson PJ, Williams R. Detection of hepatocellular carcinoma-specific alpha-fetoprotein by isoelectric focusing. *Cancer.* 1994;74(1):25-29.