Multiple liver lesions in a patient with Budd-Chiari syndrome secondary to polycythemia vera

Juan Putra,* Arifa Toor,** Todd A. Noce,*** Swan N. Thung,**** Arief A. Suriawinata,* Mikhail Lisovsky*

Department of *Pathology and **Gastroenterology and Hepatology, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA.
***Department of Radiology, Dartmouth-Hitchcock Manchester, Manchester, NH, USA.
****Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, NY, USA.

ABSTRACT

Focal nodular hyperplasia and nodular regenerative hyperplasia are occasionally seen in patients with hepatic venous outflow obstruction as a consequence of circulatory stress in the liver. In addition, neoplastic processes such as hepatic adenoma, hepatocellular carcinoma, and metastatic disease may arise in these patients. Histologic evaluation is necessary when imaging modalities are unable to distinguish these lesions. We present a case of multiple hepatic lesions, suspicious for metastases, in a patient with Budd-Chiari syndrome secondary to polycythemia vera. However, the biopsy findings were consistent with focal nodular hyperplasia. Budd-Chiari syndrome may be associated with multiple nodules of focal nodular hyperplasia, which may be difficult to diagnose radiologically.

Key words. Focal nodular hyperplasia. Nodular regenerative hyperplasia. Hepatic vein thrombosis. Benign hepatic lesion.

CASE REPORT

A 51 year old female was diagnosed with polycythemia vera (JAK2 V617F) during her initial presentation with acute Budd-Chiari syndrome (BCS). Attempts to stent the occluded hepatic vein were unsuccessful and the patient underwent a transjugular intrahepatic porto-systemic shunt procedure which allowed for control of her ascites. A magnetic resonance imaging (MRI) was performed approximately one month after the presentation to follow up a 1.7 cm subcapsular heterogeneous lesion found on liver ultrasound. A 1.6 cm subcapsular lesion in segment 5 (Figure 1A) was suggestive of a regenerative or dysplastic nodule and, less likely, of a well differentiated hepatocellular carcinoma (HCC). A follow-up MRI in 6 months showed numerous nodular lesions scattered throughout the liver. The original lesion had grown to 2.9 cm. An MRI in another 11 months (19 months since the diagnosis of BCS) showed an interval increase in size and extent of what were now innumerable hypervascular liver lesions (Figure 1B) These features were worrisome for metastatic process of a hypervascular primary tumor, such as carcinoid, breast carcinoma or melanoma and, less likely, primary hepatic malignancy. One of the liver nodules was biopsied.

The liver biopsy showed architectural distortion, with lack of portal tracts, 1-2 cell thick plates with hyperplastic hepatocytes, cholestatic rosettes, and focal lymphocytic aggregates (Figure 2A). The nuclei were round, isochromatic and without prominent nucleoli. A focal area of atrophic hepatocytes with adjacent sinusoidal dilatation was also noted (Figure 2B). In addition, fibrous septae containing bile ductules were present (Figure 2C). The hepatocellular lesion was negative for glypican-3, serum amyloid A, C-reactive protein, and β-catenin immunohistochemistry. Immunohistochemical study for glutamine synthetase was unsuccessful due to exhausted tissue. The histologic findings were consistent with focal nodular hyperplasia (FNH). No further treatment was recommended. The patient is followed at regular intervals and is well 2 years after the liver biopsy.

Correspondence and reprint request: Juan Putra, M.D.
Department of Pathology. Dartmouth-Hitchcock Medical Center. One Medical Center Drive. Lebanon, NH 03756, USA.
Ph.: 1 (603) 443-7161
E-mail: Juan.Putra@Hitchcock.org

548

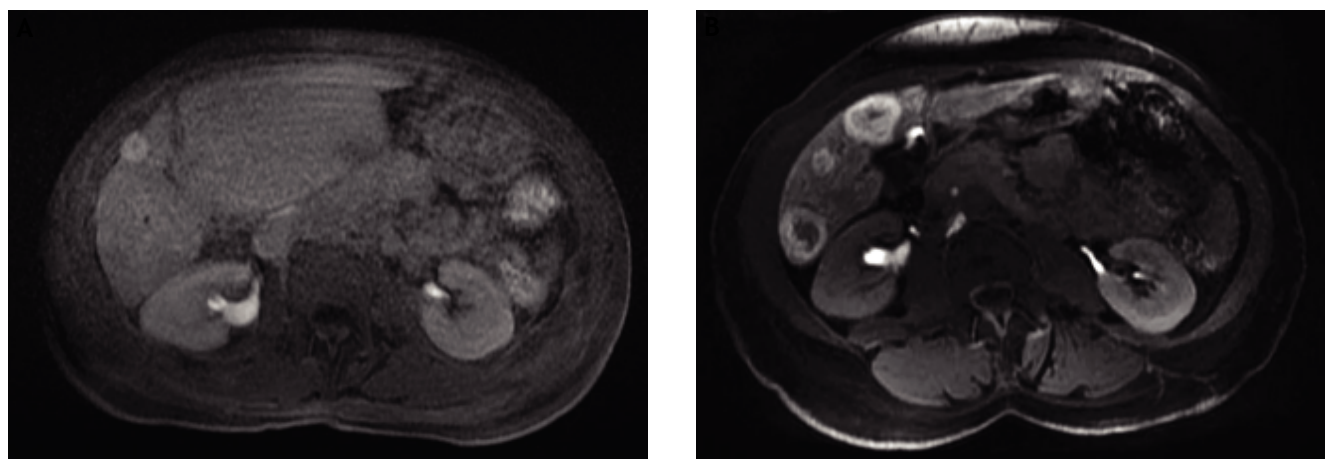Putra J, et al. Annals of Hepatology, 2015; 14 (4): 547-549

Figure 1. *Initial MRI (**A**) showing a 1.6 cm subcapsular lesion in segment 5, suggestive of a benign regenerative or dysplastic nodule. Follow-up MRI after 11 months (**B**) revealed multiple hypervascular lesions which were suspicious for metastases.*
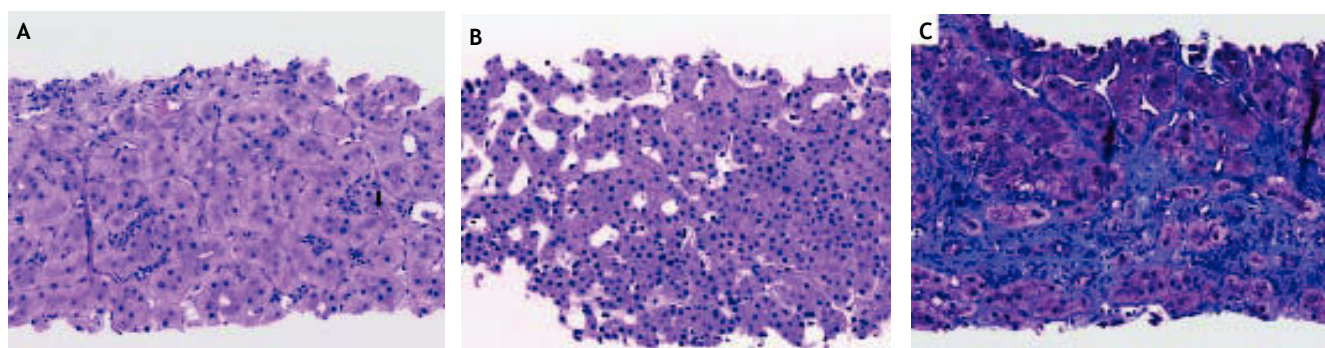

Figure 2. *Liver biopsy with features of focal nodular hyperplasia. The lesion is predominantly composed of regenerative hepatocytes with cholestatic rosettes and focal lymphocytic infiltrates. The arrow shows dilated bile canaliculi (**A**, H&E, 200x). Focal atrophic hepatocytes with adjacent dilated sinusoids (**B**, H&E, 200x) and fibrosis with bile ductular proliferation (**C**, trichrome, 200x) are also identified.*

DISCUSSION

The patient presented with multiple liver nodules, suspicious for metastatic malignancy, in the setting of polycythemia vera and previous BCS. Microsopically, atypical features such as acinar architecture and thickened hepatocyte plates raised the possibility of well differentiated HCC. However, the presence of cholestatic rosettes and lack of more than 2-cell thick hepatocyte plates argued against HCC. The remaining diagnoses to consider were inflammatory hepatocellular adenoma (HA) and FNH, both of which can present as multiple intrahepatic lesions.

FNH is a reactive mass-forming process secondary to blood perfusion defects, characterized by 1-2 cell thick hepatocyte plates, central stellate scar with large vessels, and fibrous bands with accompanying bile ductular reaction. Periseptal lymphocytic inflammation and dilated sinusoids can also be seen. In our case, it was difficult to distinguish between FNH and inflammatory HA because the latter, similar to FNH, may also demonstrate lymphocytic aggregates, abortive bile ductules, and dilated sinusoids. However, the presence of fibrous bands was consistent with FNH. Immunohistochemical markers helpful in discriminating FNH from HA and identifying HA subtypes include glutamine synthetase, liver-type fatty-acid binding protein, β-catenin and serum amyloid A or C-reactive protein.[1] FNH exhibits a characteristic "map-like" staining pattern of glutamine synthetase. HNF1α-inactivated HA shows loss of LFABP staining, β-catenin activated HA demonstrates diffuse nuclear staining of b-catenin and diffuse positivity of glutamine synthetase, while inflammatory HA shows positivity of serum amyloid A and C reactive protein.[1] In our case, negative immunostaining for serum amyloid A,

C-reactive protein, and beta-catenin supported the diagnosis of FNH.

BCS is a condition characterized by hepatic venous outflow obstruction which may lead to severe congestion, lobular hemorrhage with ensuing fibrosis or cirrhosis.[2] Regenerative nodules, such as FNH and nodular regenerative hyperplasia, have also been described in these patients.[3,4] Neoplastic processes unrelated to BCS, such as HA, HCC or metastatic disease can also occur in these patients.

A recent study using multiphasic helical computed tomography scan and MRI showed that benign hepatic nodules in patients with BCS were typically small, multiple and hypervascular.[5] In addition, the presence of central scar was significantly more prevalent in benign/ reactive nodules compared to HCC.[5] Contrast-enhanced MRI with Gadoxetate disodium, a gadolinium-based contrast agent helps to distinguish FNH from other liver lesions. FNH will appear bright on T1-weighted MRI, while other lesions (e.g. HCC or metastases) will not take up the agent and will appear darker.[6] FNH may sometimes lack central scar, appear hyperintense on both T1 and T2 weighted images and isointense in the hepatobiliary phase.[7] In these instances, tissue biopsy is recommended for accurate diagnosis.

In summary, familiarity with the concept of multiple regenerative or reactive nodules in the liver of patients with previous BCS is important. Tissue biopsy is helpful when these lesions are difficult to distinguish radiologically from a primary neoplastic or metastatic process.[8]

CONFLICT OF INTEREST

All of the authors have nothing to disclose.

REFERENCES

1. Bioulac-Sage P, Cubel G, Taouji S, Scoazec J, Leteurtre E, Paradis V, Sturm N, et al. Immunohistochemical markers on needle biopsies are helpful for the diagnosis of focal nodular hyperplasia and hepatocellular adenoma subtypes. *Am J Surg Pathol* 2012; 36: 1691-9.
2. Pavri TM, Herbst A, Reddy R, Forde KA. Budd-Chiari syndrome: a single-center experience. *World J Gastroenterol* 2014; 20: 16236-44.
3. Tanaka M, Wanless IR. Pathology of the liver in Budd-Chiari syndrome: portal vein thrombosis and the histopathogenesis of veino-centric cirrhosis, veno-portal cirrhosis, and large regenerative nodules. *Hepatology* 1998; 27: 488-96.
4. Ibarrola C, Castellano VM, Colina F. Focal hyperplastic hepatocellular nodules in hepatic venous outflow obstruction: a clinicopathological study of four patients and 24 nodules. *Histopathology* 2004; 44: 172-9.
5. Maetani Y, Itoh K, Egawa H, Haga H, Sakurai T, Nishida N, Ametani F, et al. Benign hepatic nodules in Budd-Chiari syndrome: radiologic-pathologic correlation with emphasis on the central scar. *AJR Am J Roentgenol* 2002; 178: 869-75.
6. Leyendecker JR. Gadoxenate disodium for contrast magnetic resonance imaging of the liver. *Gastroenterol Hepatol (NY)* 2009; 5: 698.
7. Albiin N. MRI of focal liver lesions. *Curr Med Imaging Rev* 2012; 8: 107-16.
8. Choi JY, Lee HC, Yim JH, Shim JH, Lim YS, Shin YM, Yu ES, et al. Focal nodular hyperplasia or focal nodular hyperplasia-like lesions of the liver: a special emphasis on diagnosis. *J Gastroenterol Hepatol* 2011; 26: 1004-9.