

## Case Report

# Idiopathic portal hypertension presenting with hepatic nodular regenerative hyperplasia after splenectomy: a case report

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**Abstract:** Idiopathic portal hypertension (IPH) is a rare disease, and its etiology and pathogenesis have not yet been fully clarified. The main clinical manifestations are non-cirrhotic intrahepatic portal hypertension, accompanied by splenomegaly, thrombocytopenia, and recurrent upper gastrointestinal bleeding. The liver histopathologic changes are diverse. Splenectomy is considered an effective treatment for hypersplenism. We report a patient who presented with splenomegaly, then underwent splenectomy to relieve thrombocytopenia based on routine treatment strategies. However, multiple space-occupying lesions were found in the liver about one year later. Thereafter, the lesions were confirmed as nodular regenerative hyperplasia (NRH) by liver biopsy, the patient was finally diagnosed with IPH. We consider that although splenectomy is generally recommended for IPH, under certain circumstances splenectomy may disturb blood flow in the liver, leading to the formation of NRH. Therefore, splenectomy in IPH patients should be chosen carefully.

**Keywords:** Idiopathic portal hypertension, nodular regenerative hyperplasia, splenectomy

## Introduction

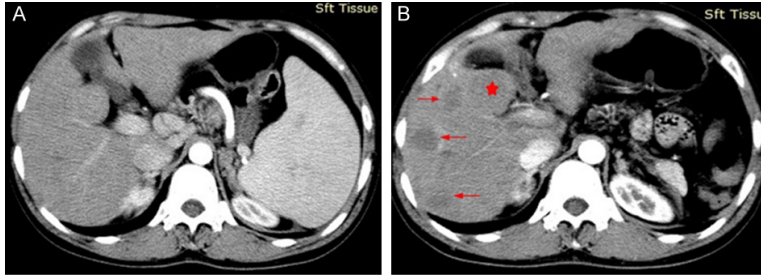
Idiopathic portal hypertension (IPH) is a vascular disease characterized by non-cirrhotic portal hypertension. The cause of IPH is not yet fully understood. Current studies suggest that multiple factors, such as infections, drugs and toxins, prothrombotic states, and immunological/immunogenetic disorders are related to IPH [1-7].

The current clinical treatment strategy for portal hypertension complications is the management of esophageal/gastric varices and hypersplenism. Splenectomy is widely accepted as an effective treatment for alleviating portal hypertension [8-10]. However, the long-term consequences of splenectomy deserve attention. Here, we report a case of IPH manifesting as splenomegaly and pancytopenia. After receiving splenectomy one year later, a number of nodules developed in the liver.

## Case presentation

A 34-year-old female patient was admitted to Beijing YouAn Hospital, Capital Medical University on February 3, 2016, with multiple liver-occupying lesions identified during a regular hospital visit.

The patient herself accidentally found a mass in her upper left abdomen and did not have any discomfort in March, 2014. She went to the local hospital (The 5th Anyang Hospital, Henan Province). The laboratory examinations indicated pancytopenia and a slight increase in transaminases. Hepatitis B, C and other viral infections and autoimmune liver diseases were excluded. Abdominal dynamic contrast-enhanced CT showed obvious splenomegaly, and liver cirrhosis was not observed (**Figure 1A**). Therefore, liver biopsy was performed on March 11, 2014. However, the cause of portal hypertension was not identified. Splenectomy was per-



**Figure 1.** Axial contrast-enhanced CT. A. Pre-splenectomy. The size and shape of the liver were normal, with no obvious liver cirrhosis, and accompanied by splenomegaly. B. Post-splenectomy (January 22, 2016). A proportion of the liver lobe is disordered and a focal nodule bulges (asterisk). There are multiple low-density nodules in the liver without obvious enhancement (arrow).

formed for the treatment of hypersplenism on April 1, 2014. The patient recovered well and her complete blood count gradually returned to normal after surgery. However, in the second postoperative year, abdominal ultrasonography revealed multiple slightly hypoechoic nodules with heterogeneity in the liver. These low-density nodules were confirmed by dynamic contrast-enhanced CT (January 25, 2016). The maximum nodule diameter was 34 mm (**Figure 1B**). In order to identify the cause of the lesions, the patient was transferred to our hospital.

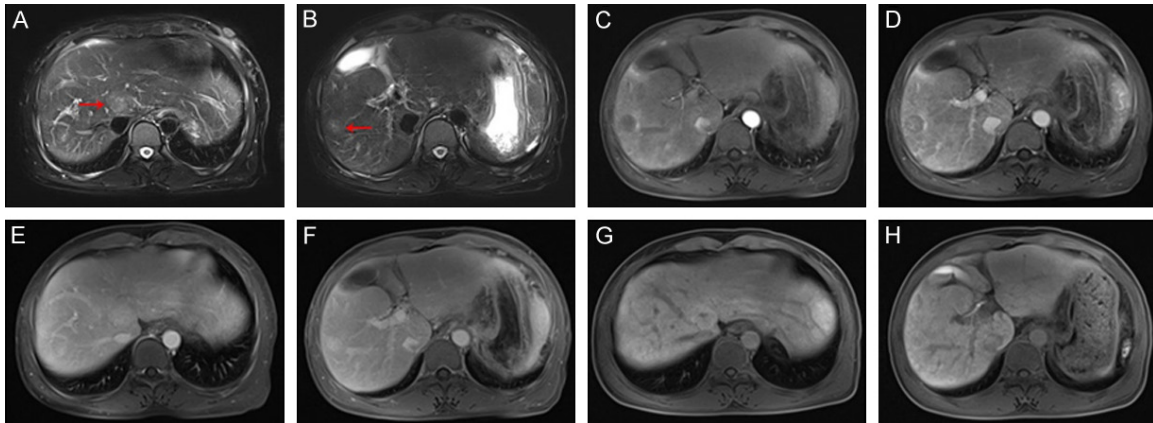
On admission, no obvious abnormalities were found in the laboratory testing including routine whole blood examination, biochemical analyses, coagulation analysis, and other indicators. The tumor biomarker alpha fetoprotein was also within the normal range. Enhanced MRI showed multiple round nodules in the liver (February 3, 2016). The lesions showed an equal or slightly higher signal on T1-weighted images, a slightly higher signal on T2-weighted images, and a slightly higher signal at the diffuse phase. Some of the nodules were significantly enhanced and others were mildly enhanced in the arterial phase. The venous phase showed continuous enhancement of the margin of these intrahepatic nodules and mild enhancement of the lesion center. The signal of the central nodule continued to strengthen on the delayed phase of MRI. The central signal of the intrahepatic nodules was decreased and the edge was an equal-high signal on the hepatobiliary stage of MRI. The distribution and shape of the intrahepatic bile ducts were normal and there was no expansion of the extrahepatic bile ducts (**Figure 2A-H**). According to the

imaging results, the nodules were considered benign lesions. Liver biopsy was recommended in order to exclude the possibility of malignant lesions.

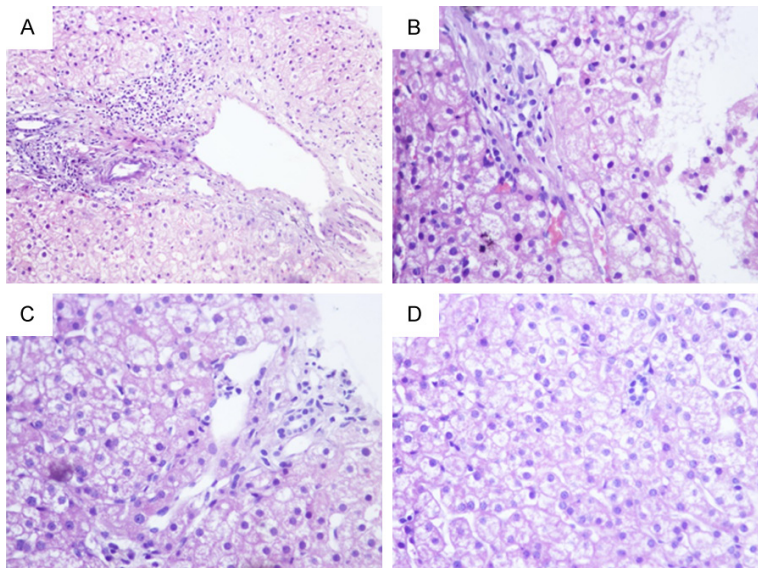
In order to make a definite diagnosis, liver biopsy under CT guidance was performed again. Liver biopsy specimens were taken from nodular and peripheral nodular lesions. The tissue sections were examined by an experienced liver pathologist. In addition,

liver tissue sections from the first biopsy were reviewed again by the same pathologist. For the first liver biopsy, histologic changes showed that normal hepatic lobular structure was preserved. The portal tract showed mild inflammation and fibrosis. The wall of the portal vein branch was thickened in the larger portal tract. In the smaller portal tract, the portal vein branch was inconspicuous with compensatory dilatation of peripheral venules, which appeared to herniate into adjacent parenchyma. Several portal tract remnants could be seen in the parenchyma (**Figure 3A-D**). For the second liver biopsy, the hepatic lobular structure was normal without cirrhosis. The portal tracts showed fibrosis and enlargement with incomplete thin fibrous septa, which were worse than those seen in the first biopsy. Mild inflammatory infiltration was observed in the portal tracts. There were several thin-walled vascular channels in some portal tracts. Sinusoidal dilation was seen in some areas of the parenchyma. The thickened liver cell plates in the periportal tracts were surrounded by atrophic plates in the centrilobular areas, which formed a nodular appearance consistent with nodular regenerative hyperplasia (NRH). Immunostaining with CD34 showed an increased number of draining veins in parenchyma (**Figure 4A-F**). Combined with the above pathologic findings, the patient was diagnosed with IPH.

The patient received no special treatment, but attended regular follow-up visits every six months. As of the last follow up, the patient had no discomfort. Compared with the images seen in 2016, there were no significant changes in the



**Figure 2.** MRI of the upper abdomen after splenectomy (February 3, 2016). A, B. Nodules with a slightly higher, uniform signal on T2-weighted MRI. C. Intrahepatic nodules had slight edge enhancement on the arterial phase. D. The venous phase showed continuous edge enhancement and mild central enhancement of the lesion. E, F. The delayed phase of MRI showed continuous central enhancement of the nodule. G, H. Central signal of intrahepatic nodules decreased and the edge had an equal-high signal on the hepatobiliary stage.



**Figure 3.** Pathologic changes in liver tissue before splenectomy (H&E staining). A. Mild inflammation and fibrosis are seen in the larger portal tract and the wall of the portal vein branch is thickened ( $\times 200$ ). B. Portal vein branch occlusion in the smaller portal tract ( $\times 400$ ). C. The portal vein branch is inconspicuous with compensatory dilatation of peripheral portal vein branches ( $\times 400$ ). D. Portal tract remnants ( $\times 400$ ).

with nodules more than 34 mm in diameter has never been reported before.

The current diagnostic criteria for IPH mainly include the Japanese criteria for IPH, APASL criteria for NCPF/IPH [11], and EASL clinical practice guidelines on vascular diseases of the liver [12]. All these criteria are based on exclusive diagnosis. The patient reported in this case showed splenomegaly, but no liver cirrhosis or liver pathology. Chronic liver disease and other diseases causing non-sclerotic portal hypertension were also excluded. Imaging examination suggested that the portal vein was open. This patient met the above diagnostic criteria for IPH [11, 12].

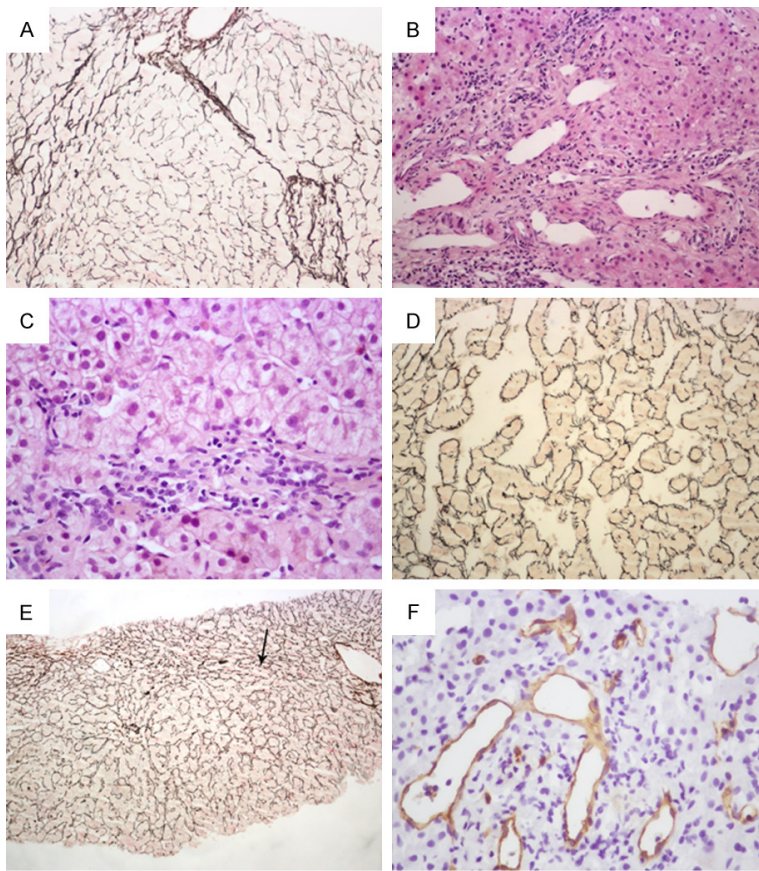
liver lesions on the latest abdominal MRI (March 28, 2018) (Figure 5A, 5B).

### Discussion

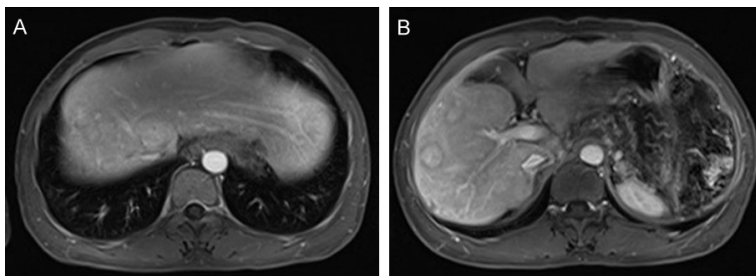
This report describes the 4-year follow-up findings in a female patient with multiple intrahepatic nodules of regenerative hyperplasia which emerged following splenectomy for IPH. To the best of our knowledge, NRH after splenectomy

Splenomegaly can be the primary clinical manifestation of IPH [8]. In addition, complications of portal hypertension such as gastrointestinal bleeding can also appear. Studies have suggested that approximately 20-58% of patients with IPH have no symptoms [13]. Liver function examination usually shows no obvious abnormalities. The clinical manifestations in our patient were splenomegaly and hypersplenism along with mild liver function abnormalities.

## NRH and splenectomy



**Figure 4.** Pathologic manifestations in liver tissue after splenectomy. A. Incomplete septa (reticulin  $\times 200$ ). B. Increased number of portal vessels (H&E  $\times 200$ ). C. No portal vein in the small portal tract (H&E  $\times 400$ ). D. Centrilobular sinusoidal dilatation (reticulin  $\times 400$ ). E. Nodular regenerative hyperplasia: hyperplastic hepatocytes were surrounded by an atrophic hepatocyte plate (arrow, reticulin  $\times 200$ ). F. Increased number of draining veins (immunostaining with CD34,  $\times 400$ ).



**Figure 5.** Contrast-enhanced T1-weighted MRI of the upper abdomen after splenectomy (March 28, 2018). A, B. Compared with the previous MRI (February 3, 2016), the size and number of liver nodules showed no significant changes.

Imaging of IPH demonstrates that non-nodular liver showed enlargement of the tail lobe and atrophy of the right lobe. Patients can also have intrahepatic portal vein occlusion or thrombo-

sis, focal nodular hyperplasia, and perfusion abnormalities. The spleen is often enlarged [14]. During the initial stage in our patient, liver size was normal, the proportion of each lobe was appropriate, and no obvious sclerosis or space-occupying lesions were observed. The spleen was enlarged.

Liver biopsy is particularly important in the diagnosis of IPH. The pathologic manifestations of IPH are diverse. Studies suggest that the typical pathological features of IPH include portal tract remnants, phlebosclerosis and nodular regeneration [15]. This patient underwent liver biopsy before and after splenectomy. Pathologic changes showed occlusion or stenosis of portal vein branches without cirrhosis, which supported the diagnosis of IPH. By comparing the pathologic manifestations after splenectomy with those pre-splenectomy, it was found that there was obvious progression of fibrosis in the portal tract, and sinusoidal dilatation was detected in the second liver biopsy. The newly emerged space-occupying lesions in the liver were unexpected and finally identified as NRH. Although NRH is usually considered a typical sign of IPH [15, 16], neither the liver histological features nor imaging examinations of this patient showed the presence of NRH before splenectomy. It is not clear whether the newly formed NRH was caused by splenectomy or an inevitable stage of IPH progression.

However, due to the apparent spatiotemporal relationship between NRH and splenectomy, it is reasonable to speculate that the development of NRH in this patient was related to sple-

nectomy. A possible mechanism for this is that splenectomy reduced the liver blood supply, consequently causing rearrangement of blood flow. Adapting to this hemodynamic change, the hepatocytes with reduced blood supply appeared to atrophy, while the hepatocytes in the normal blood supply tended to be hyperplastic. When this compensation is re-balanced, over-regeneration of hepatocytes is stopped. However, the exact pathophysiologic changes after splenectomy are unclear and require further investigation.

Previous studies have suggested that abnormalities in spleen blood flow regulation are crucial in the development of IPH. Splenomegaly is often accompanied by hypersplenism. Splenectomy is considered the main treatment option for IPH to relieve portal hypertension [8, 9]. Most studies, however, were short-term observations. The emergence of multiple obvious hepatic lesions of NRH after splenectomy and the accompanying worsened liver fibrosis in this patient illustrate that splenectomy in patients with IPH should be chosen carefully.

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### Disclosure of conflict of interest

None.

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## NRH and splenectomy

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