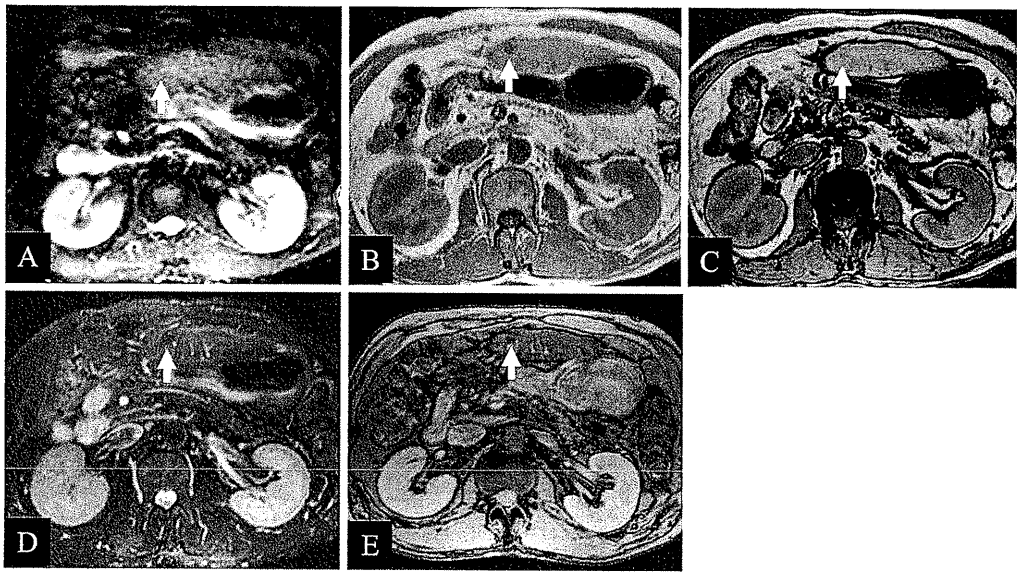

Figure 2. Images of the FNH-like nodule in segment 3 in Gd-EOB-DTPA-enhanced MRI. Arrows indicate the 9mm FNH-like nodule. (A) No detection of nodule in diffusion-weighted MRI, (B) Low signal intensity on in-phase T1-weighted MRI, (C) Isosignal intensity on opposed-phase T1-weighted MRI, (D) Slightly low signal intensity in T2-weighted MRI, (E) Slightly low signal intensity in SPIO-enhanced MRI.

low signal intensity (Fig. 2D), respectively. Although this nodule was detected as slightly low signal intensity (Fig. 2E) in superparamagnetic iron oxide (SPIO)-enhanced MRI, it was uncertain if Kupffer cells took up SPIO because of the slightly low signal intensity on T2-weighted MRI before SPIO injection.

The imaging findings mentioned above were suggestive of HCC, even though several findings, such as low signal intensity on in-phase and isosignal intensity on opposed-phase T1-weighted MRI, low signal intensity in T2-weighted MRI and no detection in diffusion-weighted MRI, were not consistent with typical HCC. We could not histologically assess this hepatic nodule by liver biopsy because of its undetectability by ultrasonography, and we could not ignore the possibility of HCC as the diagnosis of this nodule. Therefore, this nodule was surgically resected after obtaining informed consent from the patient. The nodule of interest was not encapsulated and its margin was difficult to distinguish from the surrounding cirrhotic tissue (Fig. 3A and 3B). Intranodular fibrous septa were present but central fibrous scarring and portal tracts were absent (Fig. 3C). The fibrous septa contained unpaired small arteries accompanied by reactive bile ductules radiating into the parenchyma (Fig. 3D). This nodule showed varying degrees of increased cellularity (Fig. 4A) and marked iron deposits in the hepatocyte and/or Kupffer cells (Fig. 4B) compared to the surrounding cirrhotic tissue. Immunohistochemical analysis using an anti-CD34 antibody (anti-CD34) revealed marked sinusoidal capillarization (Fig. 4C). Thus, the histological diagnosis of this nodule was an FNH-like nodule. Finally, we immunohistochemically assessed the expression of organic anion transporter (OATP) 1B3 in hepatocytes, using an anti-OATP1B3 antibody (anti-OATP1B3) to examine why this nodule exhibited low signal intensity during the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI. Immunohistochemically, OATP1B3 was diffusely and strongly positive for the cell membrane of the hepatocytes in the surrounding cirrhotic tissue, but was nearly absent in the FNH-like nodule (Fig. 5A-C). Thus far neither recurrence of the FNH-like nodule nor the development of HCC has been found in this patient who has stopped drinking alcohol since he was admitted to our hospital.

Discussion

FNH-like nodules occurring in cirrhotic livers are reported to have the pathological features such as encapsulation, hepatocyte hyperplasia, fibrous septa containing unpaired small arteries accompanied by reactive bile ductules, iron deposits and/or sinusoidal capillarization (1, 2). It has been suggested that the artery-dominant condition derived from disturbed portal circulation in the cirrhotic liver (10) or the congenital vascular anomaly (11, 12) causes localized hyperplastic changes of the hepatocytes, and generates nodular lesions such as FNH. The increased unpaired arteries, diffuse capillarization, and iron deposits in the nodule would be attributable to a similar mechanism in nodular formation. The FNH-like nodule in this study had these pathological features except for encapsulation. One possible explanation for the lack of encapsulation is that hepatocytic hyperplasia had not expanded sufficiently to be encapsulated because it was the early stage in the development of the hyperplastic nod-

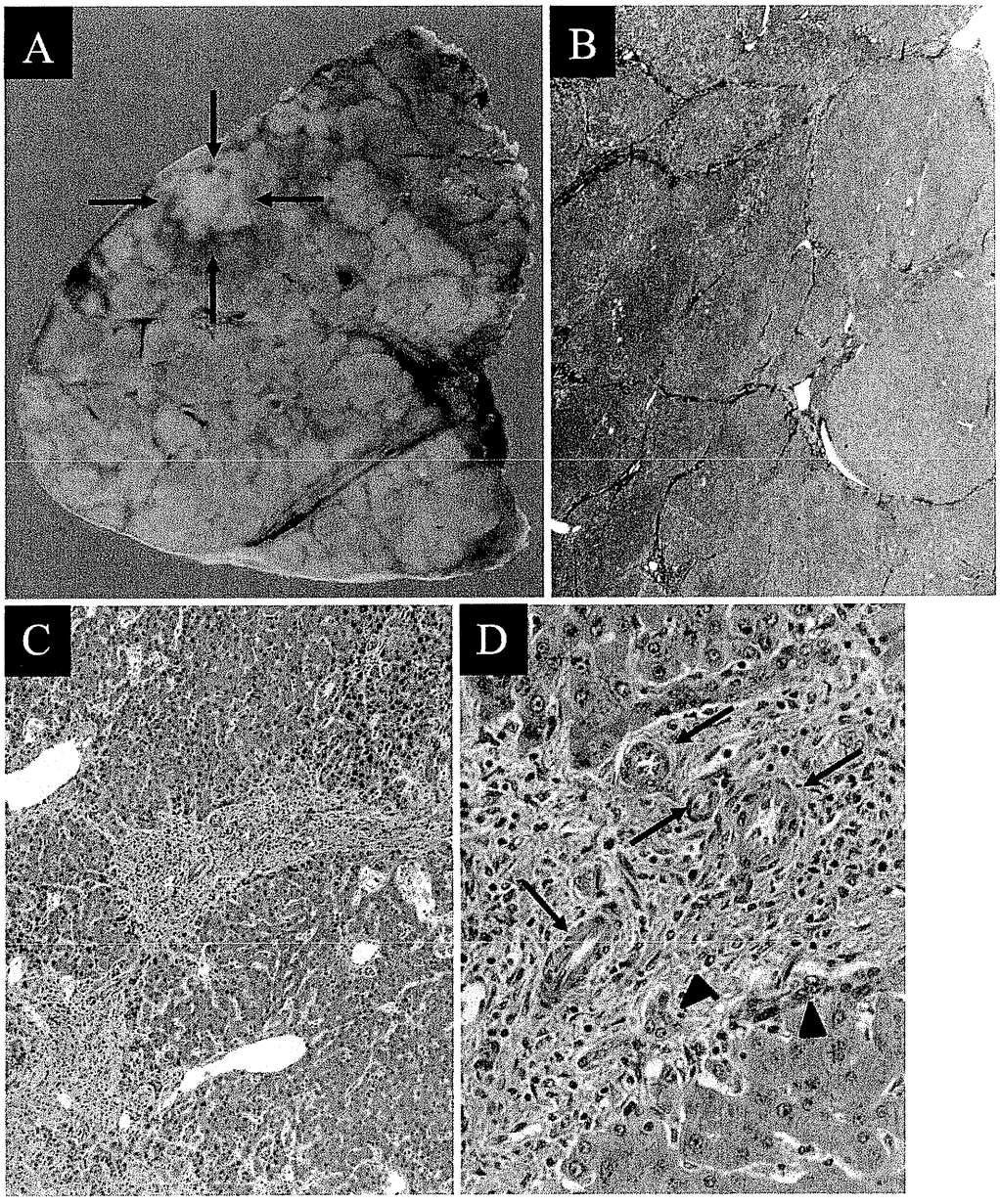

Figure 3. Surgically resected specimen and histology of the FNH-like nodule. (A) Arrows indicate the FNH-like nodule (15mm). The nodule is not encapsulated and its margin is difficult to distinguish from the surrounding tissue. (B) The surrounding tissue shows liver cirrhosis (Masson trichrome ×40). (C) Fibrovascular septa with mild lymphocyte infiltrate within the FNH-like nodule (Hematoxylin and Eosin staining ×100), (D) Unpaired small arteries (arrows) and reactive bile ductules radiating into the parenchyma (arrowheads) within a fibrovascular septum in the FNH-like nodule (Hematoxylin and Eosin staining ×400).

ule. In this respect the state of the present FNH-like nodule may suggest its early stage. The present case clearly indicated the existence of an FNH-like nodule with reduced OATP1B3 expression. Hepatocytic disorder derived from disturbed portal circulation in cirrhotic liver may have suppressed the expression of OATP1B3. We cannot necessarily exclude a possibility of malignant potential of this nodule in terms of nearly absent expression of OATP1B3. Otherwise, unknown mechanisms may have been related to the reduced expression of OATP1B3.

FNH-like nodules also are clinically important lesions in terms of difficulty in distinguishing them from well-differentiated HCC in image diagnosis. There were at least two reasons why we had diagnosed this patient as having probable HCC in imaging. First, the present FNH-like nodule exhibited hypervascularity during the hepatic arterial phase and a washout pattern during the equilibrium phase in contrast-enhanced MRI. Second, the Gd-EOB-DTPA-enhanced MRI revealed this nodule to have low signal intensity during the hepatobiliary phase, which implied re-

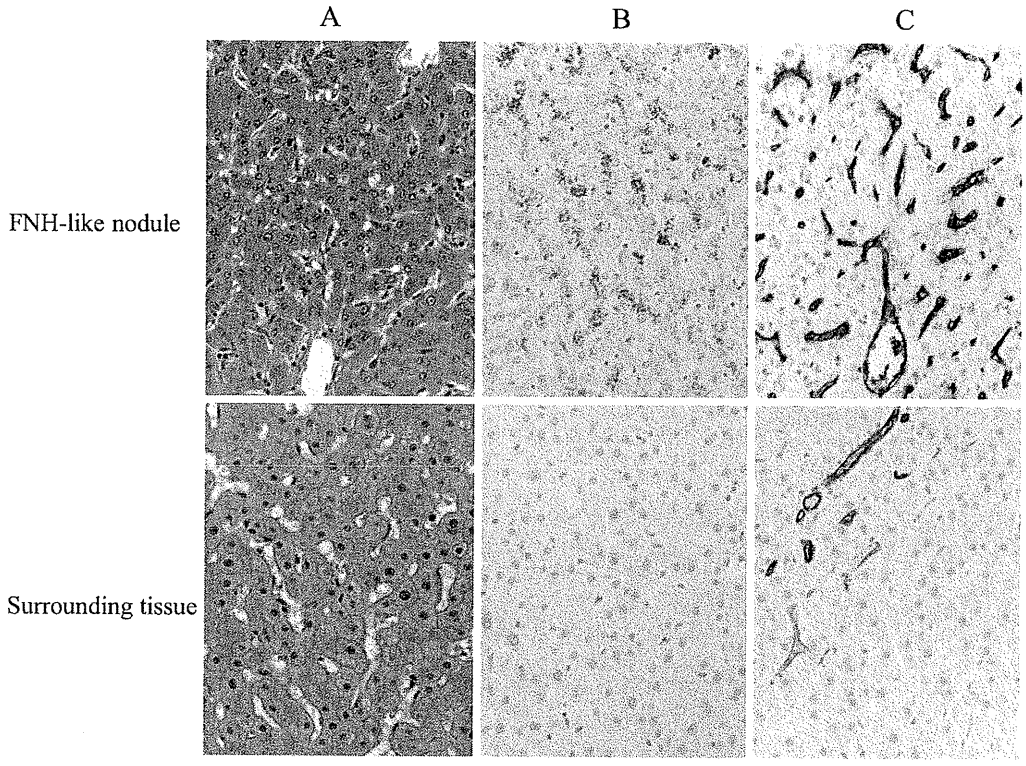

Figure 4. Cell density, iron deposits and sinusoidal capillarization in the FNH-like nodule and the surrounding tissue. The FNH-like nodule shows increased cell density (A, Hematoxylin and Eosin staining ×400), remarkable iron deposits in the hepatocyte and/or Kupffer cells (B, Berlin blue ×400) and marked sinusoidal capillarization (C, immunohistochemical staining using anti-CD34 ×400), compared to the surrounding tissue.

duced uptake of Gd-EOB-DTPA by hepatocytes. Reduced Gd-EOB-DTPA uptake by hepatocytes was reported to suggest an early event of hepatocarcinogenesis in a recent study (13). In contrast, FNH is demonstrated to be enhanced during the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI (5, 14). With respect to this point, it should be noted that the present FNH-like nodule may have had an exceptionally low signal intensity during the hepatobiliary phase. The present results were consistent with the recent report that uptake of Gd-EOB-DTPA is determined by OATP1B3 expression rather than by tumor differentiation or bile production in HCC (15), and suggested the difficulty in discriminating between FNH-like nodules and HCC by assessing the Gd-EOB-DTPA uptake by hepatocytes.

Which MRI imaging findings were useful for distinguishing between FNH-like nodules and HCC in this patient? When we analyzed the images of this nodule retrospectively, there seemed to be three important findings for diagnosis. First, the low signal intensity on in-phase and isosignal intensity on opposed-phase T1-weighted MRI may have reflected iron deposits in the FNH-like nodule, since similar phase-shift imaging has been reported to reflect hemosiderin deposits in regenerative nodules in liver cirrhosis (16). In contrast, the isointensity to slightly high intensity on in-phase and the low signal intensity on opposed-phase T1-weighted MRI are known to reflect hepatocellular nodules with fatty degeneration (8). Thus, the combined findings from the in-phase and opposed-phase may facilitate discrimination between FNH-like nodules and well-differentiated HCC, since the former frequently have iron deposits and the latter has fatty degeneration. Second, FNH-like nodules and HCC have been shown to be likely to exhibit iso- to low signal intensity and high signal intensity in T2-weighted MRI, respectively (17), which was consistent with the low signal intensity in the present nodule. Third, the lack of detection in diffusion-weighted MRI may help in distinguishing FNH-like nodules from HCC, since diffusion-weighted MRI imaging has been reported to be useful in differentiating benign hepatocellular nodules including FNH from HCC (18). However, it still may be difficult to distinguish such small FNH-like nodules showing low signal intensity during the hepatobiliary phase in Gd-EOB-DTPA-enhanced MRI from HCC in clinical practice.

In addition, it remains controversial whether FNH-like nodules can be distinguished from HCC based on the presence of Kupffer cells in the nodules. A defect in the Kupffer phase on contrast-enhanced ultrasonography, which implies the absence of Kupffer cells, has been reported in the FNH-like nodule in alcoholic liver cirrhosis (19), whereas the presence of Kupffer cells on SPIO-enhanced MRI has also been shown in FNH-like nodules in alcoholic liver cirrhosis (17). The present FNH-like nodule may have contained

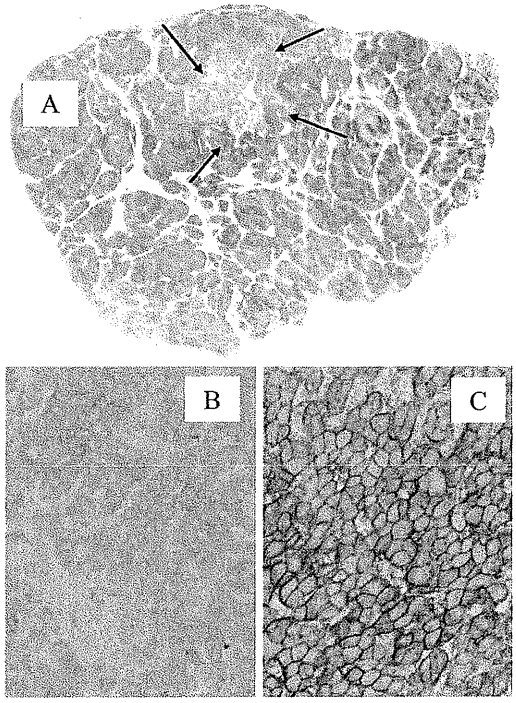

Figure 5. Expression of OATP1B3 in surgically resected specimen. Arrows indicate the FNH-like nodule (A). The expression of OATP1B3 is nearly absent in the nodule (B, ×400), but is diffusely found in the surrounding tissue (C, ×400). OATP1B3 was immunohistochemically detected using anti-OATP1B3.

Kupffer cells, since Sonazoid contrast-enhanced ultrasonography did not detect this nodule. However, we could not precisely assess the uptake of SPIO by Kupffer cells because of the slightly low signal intensity on T2-weighted MRI before SPIO injection. Thus, the present case suggests the importance of pathological diagnosis for hepatic small nodular lesions as well as the difficulty in image diagnosis for such lesions. We also propose that observational follow-up is also an important modality to be chosen when nodules are less than 1.5 cm in diameter, since small nodular lesions associated with chronic liver diseases smaller than 1.5 cm have been reported to have less potential to be early HCC (20).

In conclusion, we found an FNH-like nodule with reduced expression of OATP1B3 in a patient with alcoholic liver cirrhosis, and retrospectively analyzed imaging findings useful for distinguishing FNH-like nodules from HCC.

The authors state that they have no Conflict of Interest (COI).

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