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[Case Report]

A CASE OF RAPIDLY EXPANDING AND INCREASING FOCAL NODULAR HYPERPLASIA

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Abstract: We report a case of 14-year-old male patient who underwent bile-duct-to-jejunum anastomosis because of congenital biliary atresia at the age of 2 months. A 15 mm hypervascular nodule was detected for the first time in the S1 region of the liver at the age of 9 years. Two years later, 6 hypervascular nodules were found in the liver. A tumor biopsy was performed. It was diagnosed as a focal nodular hyperplasia (FNH). However, the number of nodules increased from 6 to 12 and those diameters were enlarged two to seven times one year later; the tumor biopsy was performed again. Histologically, the findings were consistent with those obtained previously, which indicated FNH. We consider that this is a very rare case of FNH in which both the number of nodules and the size were increased in a short period of time. We present it here as a valuable case report.

Key words: Congenital biliary atresia, cirrhosis, FNH

INTRODUCTION

Although focal nodular hyperplasia (FNH) is a benign disorder that frequently involves a problem of discrimination with regard to well-differentiated hepatocel-

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lular carcinoma, one exhibiting multiple lesions and an increasing tendency has been reported[1]. We report a case encountered recently in which the patient was diagnosed with FNH using tumor biopsy, performed twice. The number of nodules increased along with their size.

CASE REPORTS

A 14-year-old male was admitted to this department in May 2005 with the chief complaint of right hypochondrium pain.

This patient underwent bile-duct-to-jejunum anastomosis because of congenital biliary atresia at the age of 0 years and was diagnosed with cirrhosis using liver biopsy performed at that time. Endoscopic sclerotherapy was performed for gastric varices at the age of 5 years (1996) and 13 years (2004).

In 2002, a 15-mm-diameter nodule that was identifiable by contrast imaging was pointed out for the first time in the S1 region of the liver by abdominal CT examination. Although no change was found by CT performed the following year, similar multiple nodules were found by CT performed in July 2004 (Fig. 1). Hepatocellular carcinoma also could not be ruled out. Findings obtained by percutaneous tumor biopsy suggested no histological malignancy and were supportive of FNH. The patient was clinically monitored.

According to examination obtained at the time of hospitalization, blood tests showed WBC 2,500/μL, Hb 9.4 g/dL, and PLT $1.23\times10^4/\mu$L. Results of biochemical examination were AST 114 IU/L, ALT 75 IU/L, LDH 249 IU/L, ALP 1,508 IU/L, ALP 1,508 IU/L, γGTP 214 IU/L, and TB 1.9 mg/dL, indicating pancytopenia and hepatic function disorder. In addition, AFP 0.9 ng/mL, PIVKA-II 72 mAU/mL, CEA 1.0 ng/mL, CA 19-9$<$0.1 U/mL, and these tumor markers were at normal level, respectively. The CRP was 1.0 mg/dL, indicating a mild inflammatory reaction. Although the patient has a history of blood transfusion, hepatitis C and hepatitis B virus markers were both negative. The small bowel enema was performed to detect possible causes for abdominal pain revealed contracted or poorly dilated sites with afferent loop which were judged to be the causes of abdominal pain. Abdominal pain itself was relieved after fasting for several days; no symptoms recurred.

Many nodules of approximately 8-30 mm diameter that were densely stained from the early phase of contrast imaging CT were recognized. With some nodules, a slight contrast imaging effect was noticed at the central area, which was considered to reflect central scarring of FNH, although nodules without central scarring were visible. Compared with those obtained in 2004, the number of nodules had nearly doubled in 1 year from approximately 6 locations to approximately 12 locations, and their diameter had increased approximately 2-7 times as a result of lesions or nodules that were not recognized at all, which had subsequently emerged as new nodules (Figs. 1 and 2).

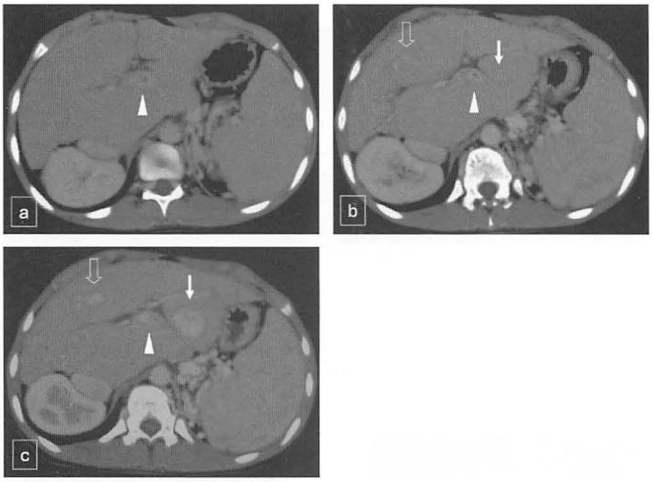

Fig. 1. CT image (Portal phase)
a. In August 2003, a 15-mm imaging effect is found in the S1 region of the liver and a nodule with a low-density central portion is visible (arrow head).
b. In August 2004, changes in the nodule in the liver S1 region are only slightly visible (arrow head). Small lesions with an imaging effect have newly emerged (arrow and open arrow).
c. In June 2005, the nodule in the liver S1 region showed changes in imaging effects, which are considered to represent some shrinkage. Lesions viewed in August 2004 had increased approximately two times and seven times, respectively (same arrow indicates the same lesion).

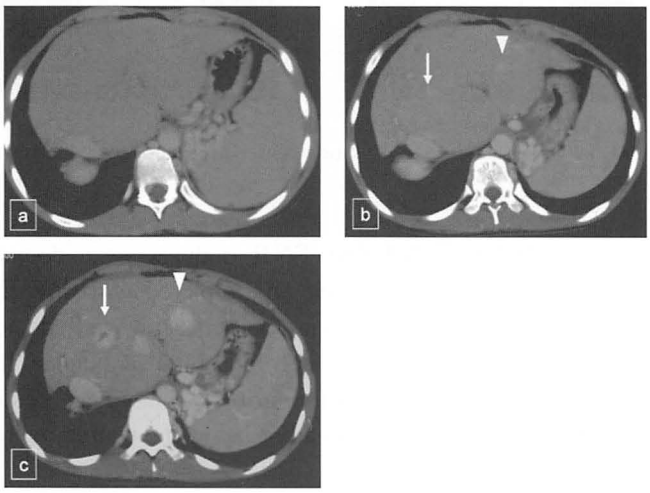

Fig. 2. CT image (Delayed phase)
a. In August 2003, no lesion is visible.
b. In August 2004, small lesions with imaging effects are visible (arrow, arrow head).
c. In June 2005, three 30-mm-diameter masses, each with a low-density area at their center, are visible. The lesion in the S4 region at the center had newly appeared. Lesions in the S5 and S3 region are increased three-fold compared with those observed in 2004 (arrow head corresponds to lesion sites noticed in 2004).

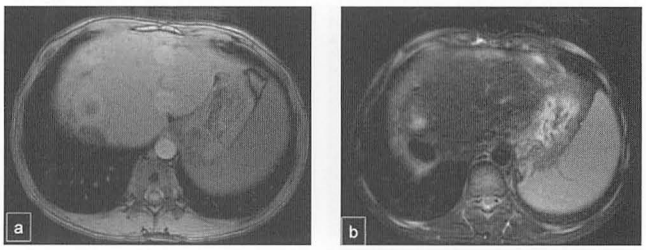

Fig. 3. SPIO-MRI image (June 2005)
a. T1WI image: Nodules with higher periphery portion and a low-density central scar are visible in the liver S8 region.
b. T2WI image: Nodules with a lower periphery portion and high-density central scar are visible in the liver S8 region.

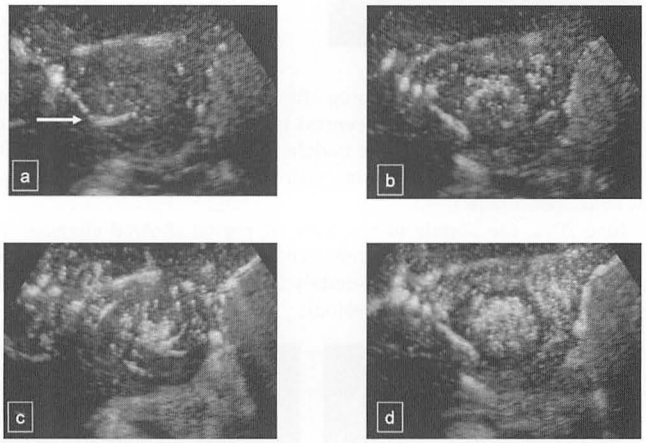

Fig. 4. Ultrasound contrast photograph
The contrast agent entered the tumor's center area and spread from there in a wheel pattern.

Investigation by MRI revealed that FNH nodules were depicted with high intensity under T1WI after SPIO imaging and depicted with low intensity under T2WI. Of the FNH nodules, those having central scar were depicted with low intensity under T1WI and were depicted with high intensity under T2WI (Fig. 3).

By contrast imaging ultrasound examination by Levovist performed for S4 lesions, vascular flows were observed spreading from the center to the periphery in a wheel pattern (Fig. 4).

Compared with those obtained in 2004, the number of nodules and their diameter were increased. Therefore, tumor biopsy was performed again (biopsy sites of 2004 and 2005 were different). Pathologic findings revealed increased central scar and cholangiole-like structures; the obtained findings were not suggestive of any malignancy and are consistent with those for FNH (Fig. 5).

The patient is currently under observation through the outpatient department.

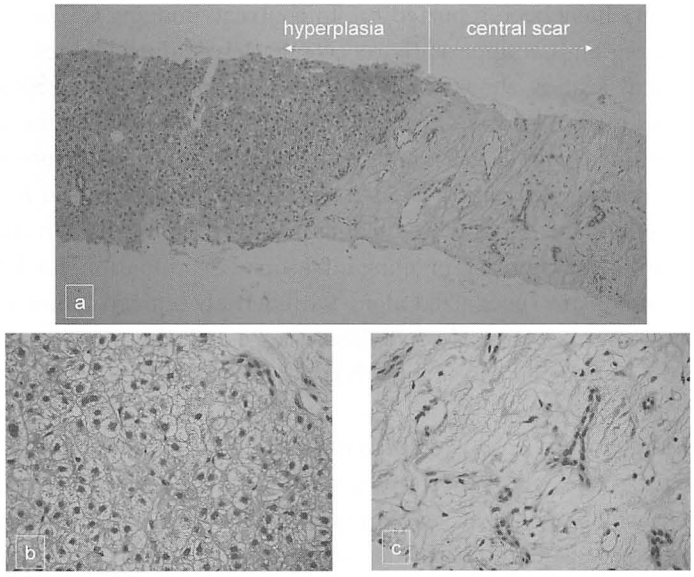

Fig. 5. Biopsy tissue image of the nodule portion
a. Central scar and hepatic cell are visible (HE staining, ×100).
b. Hyperplasia of hepatic cells. Fine structures composed of cells with a normal N/C ratio are visible (HE staining, ×400).
c. Abnormal cholangiolar growth is apparent within the central scar (HE staining, ×400).

DISCUSSION

Proposed by Edmondson in 1958, FNH is a non-neoplastic hyperplastic lesion. Although some reports show that it is frequently found in sexually mature females[2-4], no difference is apparent in the rate of occurrence in males and females. Some reports indicate that cases among comparatively younger subjects, less than 15 years old, are as frequent as 33.3%[5].

Development of FNH and mechanism of proliferation have not been clarified. Although cases attributable to involvement of oral contraceptives have been reported[6-8], some are unrelated, as typically represented by the current case[6-8]. Reportedly, vascular abnormality is responsible for this disorder, which has come to be viewed as the dominant cause.

Many cases are asymptomatic and the number of lesions reported is 1-2: Isak *et al.* report that multiple cases with more than two nodules are as frequent as 32.5%[3]; Wanless *et al.* report 19%[9]; and Okudaira *et al.* report 4.5%[10]. It has also been reported that the number of nodules is 2-5 at most and that FNH with more numerous nodules is rare[1,6].

Because of remarkable developments made recently in image diagnoses, the usefulness of CT, MRI, SPIO-MRI, scintigraphy, contrast imaging ultrasound exam-

ination and others have been reported[11]. In contrast-imaging CT, an asteroid-like low-absorption region that apparently reflects densely stained images from the early phase and central scar is shown as a typical example. Because SPIO-MRI is a useful examination that shows existence of Kupffer cells in the tumor[12], positive findings are obtained with FNH where Kupffer cells are equally present or more numerous than normal hepatic tissue at the periphery, which is used for discrimination from hepatocellular carcinoma yielding negative findings[11]. In the meantime, in a typical example of contrast-imaging ultrasound examination, for FNH, arteries flowing into a tumor are recognized along with densely stained tumor images and a wheel-like angioarchitecture. It has been suggested that angiography will be unnecessary for future diagnosis of FNH[13]; this finding was confirmed in the current case in real time.

Although the current case is consistent with FNH from image and histological perspectives, compared with reports presented so far, the current case is very rare in that the number of tumors increased rapidly in a short period of time along with increased diameter. Kurachi *et al.* describe a case in which the 10 mm diameter tumor increases to 27×22 mm in 10 months and claim that this is comparable with the time for doubling hepatocellular carcinoma of less than 3 cm[8]; in the current case, it is 2-7 times, which is considered to represent far faster growth than that of hepatocellular carcinoma.

In the current case, an examination performed in 1996 yielded no finding that was suggestive of FNH in the liver, but a rapid increase was recognized at recurrence of gastric varices. Therefore, association between manifestation of FNH and growth of FNH, and portal hypertension can not be ruled out. Furthermore, an additional increase in the number of tumors was recognized after treatment of varices during 2004-2005. Kaiji *et al.* pointed out that vasodilation of arteries and increased vascular flow attributable to vascular malformation[14] are responsible for the rapid increase. Furthermore, the possibility exists that progress of cirrhosis and changes in hemodynamics caused by treatment of varices are associated with the rapid progress of FNH in the current case.

Chronological observation of lesions of S1 that existed from the early phase showed a difference of lesions' stainability, although the time phase of photography is slightly deviated. Apparently, the tumor diameter is somewhat reduced. Reports of lesions of FNH have not described changes other than unchanged or increased lesions. It is probable that, if FNH is attributable to increased hepatic perfusion, and if hemodynamics are changed because of progression of cirrhosis or treatment of varices, then the blood flow volume to the FNH is also changed, thereby engendering considerable changes in their imaging effects and size.

In the current case, FNH lesions continue to increase, even though the patient is asymptomatic. The possibility exists that if FNH progresses, but remains benign per se, progression of cirrhosis caused by original biliary atresia might be badly affected. It is therefore considered that presence of FNH might hasten the need for

liver transplantation. Careful follow-up, including consideration of possible development of a malignant tumor, will be necessary.

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