Ruptured focal nodular hyperplasia observed during follow-up: a case report

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Abstract

Background: Focal nodular hyperplasia (FNH) is the second most common benign hepatic tumor and is very rarely complicated by hemorrhage or rupture. Although thought to be extremely rare, there have been several reports of hemorrhage caused by ruptured FNH. Herein, we report the case of a patient with ruptured FNH, who subsequently developed hemorrhage during follow-up.

Case presentation: A 32-year-old man was admitted to our department for an asymptomatic hepatic tumor in segments 4 and 5 (S4/5), which measured 8 cm in diameter and observed to project from the liver. Imaging and pathologic examination of a biopsy specimen confirmed the diagnosis of FNH. Three years after the diagnosis, the patient was readmitted to our hospital because of sudden onset of upper abdominal pain. Dynamic abdominal computed tomography revealed ascites around the tumor with high-density areas that were considered to represent hematoma caused by ruptured FNH. Transcatheter arterial embolization (TAE) was performed to stop the hemorrhage. One month after TAE, S4/5 of the liver was resected; macroscopic findings revealed that a large part of the tumor was composed of necrotic tissue and hematoma. Pathological examination using hematoxylin–eosin staining and immunohistochemical examination indicated a final diagnosis of FNH rupture and hemorrhage.

Conclusion: Although a well-established diagnosis of FNH usually requires no treatment or surveillance, careful examination remains necessary when the FNH is large and projects from the liver because of the possibility of rupture and hemorrhage.

Keywords: Focal nodular hyperplasia, Rupture, Hemorrhage

Background

Focal nodular hyperplasia (FNH) is the second most common benign hepatic tumor after cavernous hemangioma [1–3]. Although a large FNH is often associated with significant symptoms, almost all tumors remain stable in size and do not develop complications, such as hemorrhage and rupture. Therefore, FNH usually requires no treatment or surveillance if the diagnosis is well established [4, 5]. However, hemorrhage caused by ruptured FNH may develop [5–13], although such instances appear to be extremely rare. Here, we reported the case of a patient with ruptured FNH that caused hemorrhage during follow-up.

Case presentation

A 32-year-old man was admitted to our department because of a hepatic tumor. Although the patient was asymptomatic, his previous medical history included chronic alcohol consumption for the past 8 years. Dynamic abdominal computed tomography (CT) scan revealed an 8-cm mass that projected from segments 4–5 (S4/5) of the liver. The tumor exhibited contrast enhancement, mainly on the border, from the early phase until the late phase. The tumor contained a low-density area that was considered as a central stellate scar (Fig. 1a, b). Dynamic abdominal magnetic resonance imaging (MRI) showed a mass with contrast enhancement during the early phase until the hepatobiliary phase (Fig. 1c, d). Pathologic examination of a percutaneous biopsy sample from the tumor showed fibrous connective tissue and a bile ductule without a normal portal vein (Fig. 2a, b). The tumor was diagnosed...
as FNH. The patient was advised regular follow-up with no treatment.

Three years after diagnosis, he was readmitted to our hospital because of sudden onset of upper abdominal pain without any preceding traumatic events. His hemodynamic status on admission was nearly stable, except for tachycardia (117 beats per minute). Further physical examination revealed a palpable induration with tenderness and peritoneal signs on the epigastrium. Laboratory test results on admission revealed no anemia (hemoglobin, 15.7 g/dl, and hematocrit, 45.2%) and an increased white blood cell count (17,700 cells/μl). The serum levels of C-reactive protein (30.2 mg/dl), aspartate aminotransferase (256 U/l), and alanine aminotransferase (491 U/l) were also elevated. Dynamic abdominal CT scan showed a small amount of ascites around the tumor. Most of the tumor was observed as a low-density area, but there were high-density areas, which were considered as hematoma around the tumor (Fig. 3a). These findings indicated that the abdominal pain was due to a ruptured FNH.

Although extravasation was not obvious on dynamic CT and the hemodynamic status of the patient was almost stable, the possibility of continuous hemorrhage could not be ruled out because of the presence of hematoma around the tumor, severe abdominal pain, and tachycardia. Although the tumor had been initially diagnosed as FNH, we deemed that hepatic angiography was necessary for reassessment and accurate diagnosis of the hepatic lesion because of the extreme rarity of a ruptured FNH. Hepatic angiography showed patent arterial branches of

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**Fig. 1** Diagnostic imaging findings upon first admission. Dynamic abdominal CT imaging reveals an 8-cm mass projecting from the liver. Contrast enhancement is mainly on the border, and it is observed in the early phase (a) until the late phase (b). In the early phase, a low-density area in the tumor is considered as a central stellate scar (arrow). Dynamic abdominal MRI shows contrast enhancement in the early phase (c) until the hepatobiliary phase (d).

**Fig. 2** Pathologic examination of a percutaneous liver biopsy sample. Fibrous connective tissue, including a bile ductule (b, arrow), and absence of a normal portal vein in the specimen are shown. a Hematoxylin–eosin staining (×100) and b Azan staining (×200).
the S4 and S5 without a spoke-wheel pattern, but with extravasation.

Transcatheter arterial embolization (TAE) of the arterial branches of S4 and S5 was performed to stop the bleeding (Fig. 3b, c). One month after TAE, his condition improved by conservative treatment and elective surgery was performed. On laparotomy, a large S4/5 hepatic tumor adherent to the omentum, minimal ascites, and an old hematocoele were observed. Partial resection of the S4/5 was performed. Macroscopic findings of the surgical specimen showed that most of the tumor was composed of necrotic tissue and hematoma (Fig. 4a). Pathologic examination of the hematoxylin–eosin-stained biopsy sample showed no atypical cells, hepatocyte proliferation, and expanded blood vessels. An area with normal portal vein was not observed (Fig. 4b). Immunohistochemical analyses revealed inactivation of β-catenin and no attenuation of liver fatty acid-binding protein (Fig. 4c, d). The expression of glutamine synthetase (GS) in the tumor region demonstrated the so-called “map-like” pattern (Fig. 4e). From these findings, a final diagnosis of ruptured FNH was made. Postoperatively, the patient was stable and has survived symptom free for 2 years.

**Discussion**

FNH accounts for approximately 8% of all primary hepatic tumors, with an estimated prevalence of 0.9% in the general population [2]. FNH occurs in all age groups in both men and women, but it is more frequent in women aged 20–50 years (i.e., in the reproductive age) [14], especially in those using oral contraceptives [15, 16]. In fact, an association between female hormones, such as estrogen or progesterone, and the occurrence and increasing size of FNH have been suspected; however, this remains to be established [17, 18]. Although the etiology of FNH remains undefined, it may represent a tissue-specific ischemic response to congenital vascular anomalies [19]. Alternatively, this lesion may result from an arteriovenous malformation exerting abnormal pressure on the surrounding sinusoids and portal vein branches [20]. An anomalous arterial supply in FNH has been demonstrated by arteriography [21].

Most FNHs are incidentally discovered with few clinical clues [3]. Only 20% of patients reported signs and symptoms secondary to a liver mass [1, 16, 21, 22]. The presence of a central stellate scar in the tumor is a characteristic finding on abdominal ultrasonography, CT, and MRI [14, 23].
Compared with abdominal gray-scale ultrasonography or CT, MRI has a high diagnostic yield for FNH, with sensitivity of 68–70% and specificity of 98–100% [14, 24, 25]. Particularly, MRI with hepatobiliary-specific contrast agents, such as gadoxetic acid and gadobenate dimeglumine, is very useful in diagnosing FNH, and it has been reported to have 96–97% specificity and 96% positive predictive value [25, 26]. In the hepatobiliary phase of gadoxetate disodium-enhanced MRI (Gd-EOB-MRI), FNH usually appears as an iso- or hyperintense lesion [27], compared with malignant tumors and hepatocellular adenoma (HCA), majority of which demonstrate hypointensity [28]. Similarly, contrast-enhanced ultrasonography (CEUS) can contribute to accurate diagnosis of FNH by real-time evaluation of vascularization and detection of the characteristic spoke-wheel pattern. FNH can present on CEUS as a hyper- or isointense lesion in the Kupffer phase because of the presence of Kupffer cells; in addition, CEUS can differentiate between benign and malignant focal hepatic lesions [29–31]. In this present case, tumor was recognized in the hepatobiliary phase of Gd-EOB-MRI as a hyperintense mass that contained a low-density area, which was a central stellate scar. However, we assessed that an accurate diagnosis by pathologic examination of a liver biopsy specimen should be performed because of some atypical features, such as male gender and an equivocal finding of a central scar. Although CEUS was not performed in our present case, evaluation of real-time dynamism and the Kupffer phase on CEUS should be considered for non-invasive diagnosis of FNH before biopsy.

Microscopically, FNH is a confluent mass of several small nodules of benign-appearing hepatocytes, partially or surrounded by fine bands of fibrous tissue containing proliferating bile ductules and vessels. It lacks a capsule and grows in an expansive manner to compress the adjacent hepatic parenchyma, which may exhibit a pattern of sinusoidal congestion [32–34]. The value of immunohistochemistry in diagnosis of FNH has been recently explored. GS is an enzyme involved in detoxification of ammonia by combining it with glutamate to produce the amino acid glutamine. In the normal liver, GS expression is limited to a narrow rim of hepatocytes around the central vein [35, 36]. This zonation is thought to be the result of β-catenin activation in centrizonal hepatocytes, which may be the result of Wnt signaling from the central vein [35, 36]. In FNH, there is expansion of the β-catenin-activated centrizonal region, which leads to overexpression in a characteristic “geographic map-like” pattern [37, 38], as in the present case. A small subset of β-catenin-activated HCAs may present with diffuse cytoplasmic expression of GS, but the map-like pattern typical of FNH is not observed. GS can provide strong evidence to differentiate between FNH and β-catenin-activated HCA [38, 39].

Several studies reported that FNH does not have an aggressive or malignant course [4, 19, 22]. Therefore, FNH usually requires no treatment or surveillance if the diagnosis is well established. However, although extremely rare, FNH associated with intraperitoneal hemorrhage has been reported in ten cases, including the present case, based on review of English literature since 1974 (Table 1) [5–13]. All cases, except this patient, were women; fatal hemorrhage occurred in one patient in late pregnancy [13]. The maximum tumor diameter ranged from 1 to 10 cm (median, 7 cm). Among the cases in which the location could be estimated, the tumors were located at...
or near the liver surface. Li et al. recommended surgical resection over observation for large FNH (>5 cm), irrespective of the presence of symptoms, because surgery was associated with less mortality and it can estimate the possibility of rupture or hemorrhage [12]. Surgical resection was performed in nine patients because one patient was diagnosed during autopsy [13]; in three patients, including this patient, preoperative TAE was performed.

Spontaneous rupture occurs in 3–26% of hepatocellular carcinoma (HCC) cases, and it is regarded as a life-threatening condition [40–45]. Some studies reported that TAE is effective in controlling bleeding from a ruptured HCC in the acute phase [46–48]. Hsueh et al. reported that the prognosis of a ruptured HCC after TAE was better than that after conservative treatment and that TAE achieved successful hemostasis in 99% of patients [49]. For patients with ruptured FNH, TAE may be also effective in controlling bleeding in the acute phase. In the present case, extravasation was revealed on hepatic angiography and TAE was performed. Staged resection after TAE should be considered for selected patients based on the presentation of repeated hemorrhage and extensive tumor necrosis, as observed in the present case. TAE and staged resection should be considered a standard treatment for ruptured FNH.

Conclusions
In conclusion, although majority of FNH cases are asymptomatic and require no treatment, spontaneous rupture may occur in some patients during the follow-up period. Although ruptured FNH is extremely rare, careful examination is necessary for a large FNH that projects from the liver because of the risk of spontaneous rupture, which can present as sudden onset of abdominal pain.

Table 1 Documented patients of hemorrhage caused by FNH

| Patients | Author | Publication year | Age (years) | Gender (M/F) | Maximum diameter of tumor (cm) | Number of tumor | Location | Treatment | Preoperative TAE |
|----------|--------|------------------|-------------|--------------|-------------------------------|-----------------|----------|-----------|-----------------|
| 1        | Mays ET| 1974             | 26          | F            | 10                            | 1               | Anterior segment | Surgery   | No              |
| 2        | Becker YJ| 1995            | 18          | F            | 4.5                           | 2               | Anterior and medial segment | Surgery   | No              |
| 3        | Hardwigesen J| 2001  | 37          | F            | 5                             | 1               | Segment 7        | Surgery   | Yes             |
| 4        | Bathe OF| 2003             | 27          | F            | 6                             | 1               | Right lobe       | Surgery   | No              |
| 5        | Rahili A| 2005             | 35          | F            | 9.8                           | 1               | Lobus caudatus   | Surgery   | No              |
| 6        | Chang SK| 2005             | 42          | F            | 10                            | 1               | Segment 7/8      | Surgery   | No              |
| 7        | Demarco MP| 2006         | 37          | F            | 5.2                           | 4               | Lateral segment (2 tumors), segment 4B, and posterior segment (hemorrhagic lesion) | Surgery   | No              |
| 8        | Li T    | 2006             | 26          | F            | 15                            | ND              | Left robe         | Surgery   | Yes             |
| 9        | Yajima D| 2013             | 23          | F            | 1                             | 1               | Right lobe       | Revealed at autopsy |                |
| 10       | Kinoshita M| 2016        | 35          | M            | 8                             | 1               | Segment 4A/5      | Surgery   | Yes             |

M male, F female, ND not described in the report, TAE transcatheter arterial embolization

Abbreviations
CEUS: Contrast-enhanced ultrasonography; CT: Computed tomography; FNH: Focal nodular hyperplasia; Gd-EOB-MRI: Gadoxetate disodium-enhanced MRI; GS: Glutamine synthetase; HCA: Hepatocellular adenoma; HCC: Hepatocellular carcinoma; LFABP: Liver fatty acid-binding protein; MRI: Magnetic resonance imaging; TAE: Transcatheter arterial embolization

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Authors' contributions
All authors conceived the study, participated in its design and coordination, and helped in drafting the manuscript. All authors read and approved the final version of the manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and its accompanying images.

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