

# Evaluation of the characteristics of hepatic focal nodular hyperplasia: correlation between dynamic contrast-enhanced multislice computed tomography and pathological findings

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**Objective:** To evaluate the characteristics of enhancement of focal nodular hyperplasia (FNH) of the liver by analyzing the dynamic contrast-enhanced multislice computed tomography (MSCT) features and correlating them with pathological findings.

**Patients and methods:** Nine males and 16 females with pathologically confirmed FNH and complete preoperative contrast-enhanced MSCT data were recruited for this study. The imaging features of FNH on the pre- and postcontrast MSCT were analyzed by two experienced radiologists by consensus.

**Results:** Pathology showed central scars and abnormal blood vessels in 17 and 21 of 25 lesions, respectively, while MSCT with multiphase enhancement showed central scars in eight of the 17 lesions (47.1%) and abnormal arteries or draining veins in 13 of the 21 lesions (61.9%). Furthermore, abnormal draining veins in five lesions were found to be diagnostic, which is another important finding.

**Conclusion:** Multiphase scanning can provide the panorama of FNH lesions and reveal their enhancement patterns and pathological characteristics. Abnormal blood vessels within or around the lesion are demonstrated more often than central scar, and both should be observed for FNH diagnosis.

**Keywords:** liver, focal nodular hyperplasia, multislice computed tomography, pathological findings, contrast enhancement, abnormal vein

## Introduction

Focal nodular hyperplasia (FNH) is a benign tumor-like liver lesion with a rich blood supply. After hemangiomas, FNH is the second most common benign solid lesion of the liver.<sup>1</sup> It is generally accepted that FNH can be conservatively treated because of its benign nature and minimal risk of complications.<sup>2</sup> Without specific clinical symptoms, most FNH lesions are found during routine examinations. Although some researchers<sup>3</sup> believe that FNH is the result of proliferation of the liver parenchyma in response to vascular malformations or vascular injury, its pathogenesis remained debatable. In addition, some researchers believe that arterial hyperperfusion of the lesions can contribute to the increased expression of vascular endothelial and somatic growth factors along with increased activation of the hepatic stellate cells, which may play an important role in the formation of the typical central scar observed in FNH.<sup>4,5</sup> A group of studies revealed that contraceptives can promote FNH growth.<sup>6</sup> Consistent with the literature, there were more females than males in this database, and the average age

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was 36 years. In addition, vascular malformations such as hereditary hemorrhagic telangiectasia may also be relevant to FNH.<sup>7</sup> Even though lesions can locate in any part of the liver, under most circumstances, the space beneath the capsule is the most frequently involved. There are clear boundaries between the lesion and the normal liver tissues, although a capsule is not present. FNH occurring on the surface of the liver can cause umbilication. Currently, FNH is divided into two types: classic and nonclassic. The nonclassic type contains three subtypes: 1) telangiectatic FNH, 2) FNH with cytologic atypia, and 3) mixed hyperplastic and adenomatous FNH. Classic FNH is characterized by the presence of 1) abnormal nodular architecture, 2) malformed vessels, and 3) cholangiolar proliferation. Nonclassic FNH lesions lack one of the following classic features – nodular abnormal architecture or malformed vessels – but always show bile ductular proliferation.<sup>8</sup>

The detection rate of FNH increased by year. One logical reason may be an annual increase in the prevalence of FNH. Another reason that sounds more meaningful is the increase in use of computed tomography (CT) and magnetic resonance imaging along with an increased understanding of the characteristic features of FNH by radiologists. On the one hand, in clinical practice, it is still necessary to distinguish FNH from liver cell adenoma, hepatocellular carcinoma (HCC), and fibrous lamellar liver cancer.

Multislice CT (MSCT) with multiphase enhancement is currently widely used in abdominal examination, especially for differentiating between benign and malignant hepatic tumors. The advantage of using this modality will be an objective demonstration of the blood supply and pathological characteristics of FNH. Therefore, we conducted this study to evaluate the features of FNH on MSCT in correlation with pathological findings. The findings of plain CT and CT with multiphase enhancement were analyzed and correlated with pathological findings to determine the role of MSCT in FNH diagnosis.

## Patients and methods

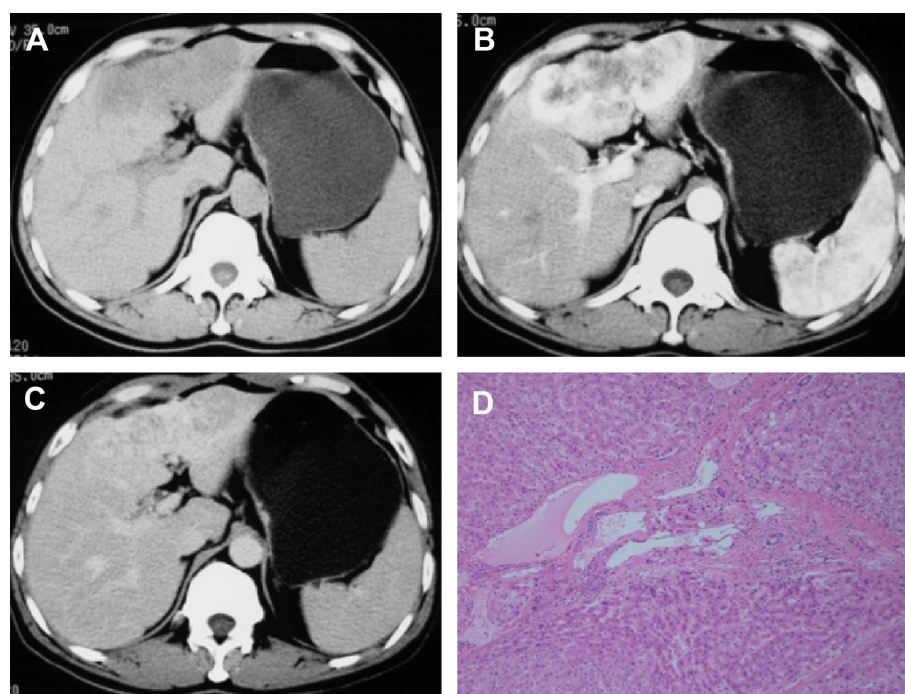
From February 2011 to March 2014, nine males and 16 females with pathologically confirmed FNH and complete preoperative contrast-enhanced MSCT data were recruited for this study from Shanghai Jiangwan Hospital and Zhejiang Province Cancer Hospital. Among these, eight patients visited the hospital because of epigastric pain. The remaining 17 patients were asymptomatic and were diagnosed during routine physical examinations. None of the patients exhibited a history of hepatitis or alpha fetoprotein positivity.

Two experienced radiologists who were unaware of the patient's clinical data and pathological results retrospectively reviewed the imaging features of FNH on pre- and postcontrast MSCT by consensus, including the size and density of FNH, presence of central scars and their density, and presence of feeding arteries and draining veins. All these findings were then correlated with pathological findings of scars and abnormal blood vessels. Contrast-enhanced MSCT was performed using a 16-section spiral CT scanner (Aquilion 16; TOSHIBA, Tokyo, Japan and lightspeed; GE Healthcare Bio-Sciences Corp., Piscataway, NJ, USA). The scanning parameters were as follows: 5–9 mm thickness, 3–5 mm slice space, 250–350 mA, 120 kV, and a 1:1 pitch. The nonionic contrast agent iopamidol (370 mgI/mL; Bracco, Milan, Italy) was injected at a dose of 1.5 mL/kg through the elbow vein using a power injector at the speed of 2–3 mL/s. All patients underwent plain MSCT before contrast injection. The scan times were 28–33 s, 65–70 s, and 250–300 s for the arterial, portal venous, and delayed phases, respectively. The study protocols were approved by the Huashan Hospital Ethical Committee, Shanghai. All patients provided written informed consent.

## Results

### MSCT findings

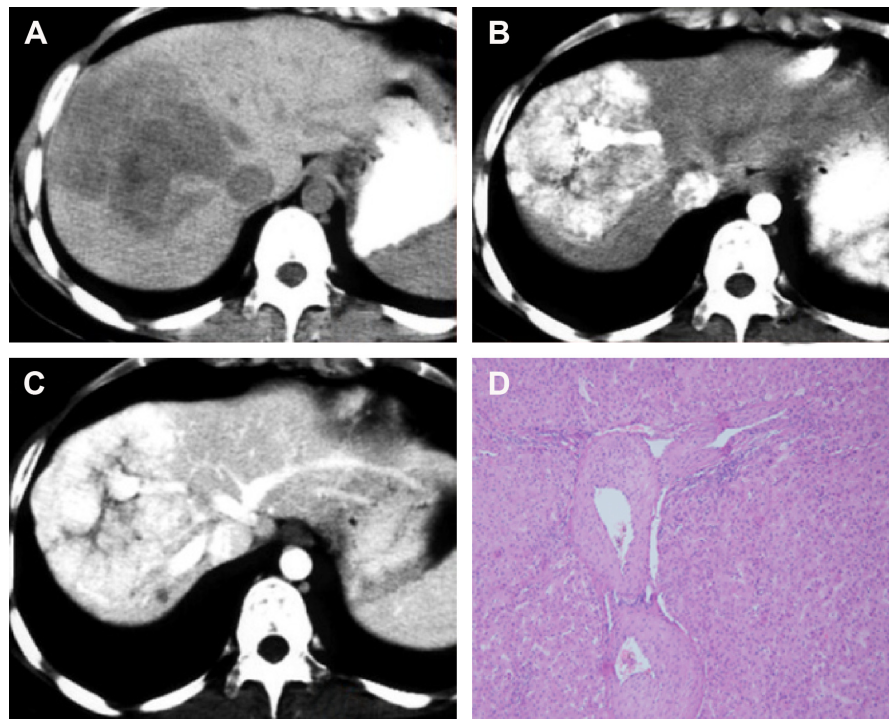
In total, 25 lesions in 25 patients were analyzed. Figures 1–3 show the imaging and pathological findings of representative cases. The lesion size ranged from 2.1 cm to 9.0 cm. Ten and 15 lesions were situated in the right and left lobes, respectively. Except for six irregular lesions, 19 displayed a circular or a circular-type shape. On plain MSCT, 21 lesions showed hypodensity (Figure 1A) and four showed slightly low density. Central scars with hypodensity were presented in eight lesions. There were no calcifications in any lesion. In the arterial phase, all lesions were evidently enhanced (except the central scars; Figures 1B, 2B, and 3B), with CT values ranging from 85 HU to 120 HU (mean,  $103 \pm 15$  HU), which were almost equivalent to the value for the aorta abdominis. All lesions exhibited clear margins. The central scars remained hypodense compared with the surrounding lesion tissues. Meanwhile, tortuous feeding arteries were observed at the center or the periphery of eight lesions (Figure 1B). In the portal venous phase, the enhancement type varied as follows: hyperdensity ( $n=15$ ; Figure 2C), isodensity ( $n=12$ ), and hypodensity ( $n=1$ ; Figure 1C). Dilated draining veins were observed in five lesions. In the delayed phase, only five lesions showed hyperdensity (Figure 3C), whereas 19 and one showed isodensity (Figure 3C) and hypodensity,



**Figure 1** Representative MSCT images of focal nodular hyperplasia misdiagnosed as a malignancy in a 49-year-old woman (case 15).

**Notes:** (A) Plain computed tomography showing a hypodense mass with a clear margin in the left lobe of the liver. (B) In the arterial phase, the mass is with a clear margin, heterogeneously enhanced with an internal hypodense area and a dilated artery. Tortuous feeding arteries show up. (C) In the portal venous phase, the mass shows heterogeneous peripheral enhancement. (D) Photomicrography of the resected specimen shows a central scar with malformed blood vessels and the bile duct (hematoxylin–eosin; original magnification,  $\times 200$ ).

**Abbreviation:** MSCT, multislice computed tomography.

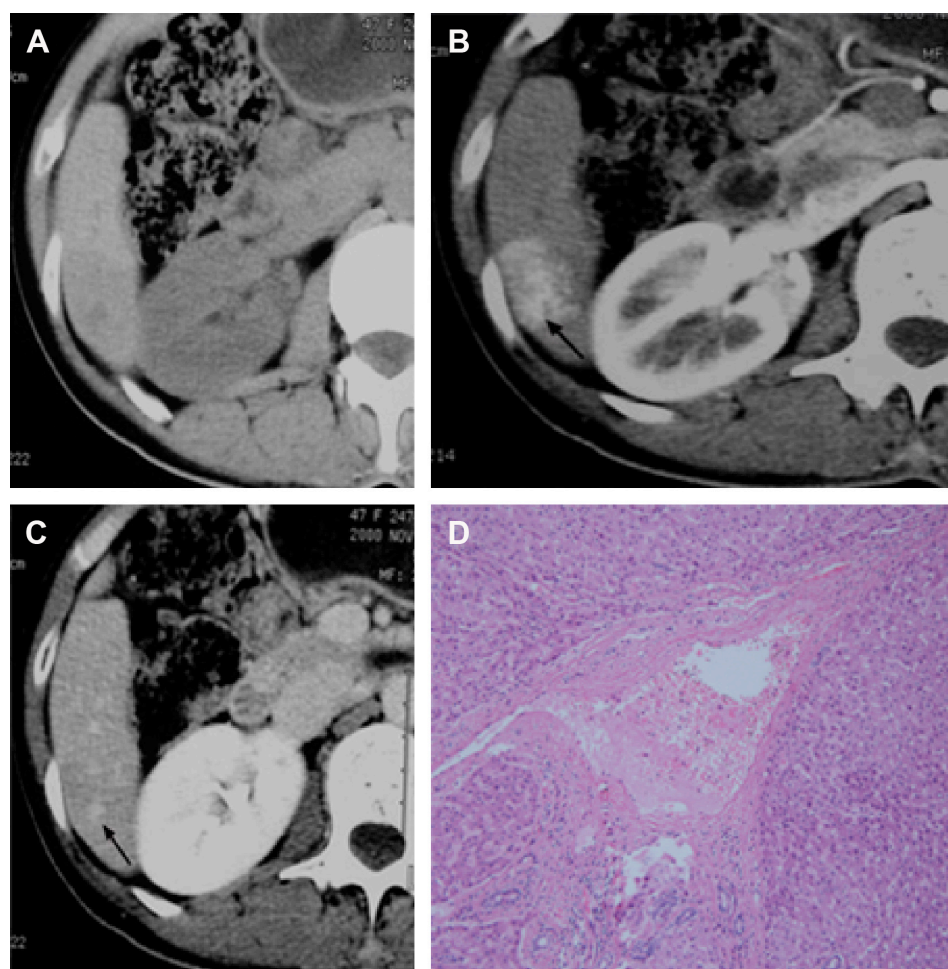


**Figure 2** Representative MSCT images of focal nodular hyperplasia in a 40-year-old man (case 19).

**Notes:** (A) Plain computed tomography showing an isodense mass in the right lobe of the liver. (B) In the artery phase, the mass with clear margin, except the central scar area, is heterogeneously enhanced. (C) In the portal vein phase, the density of the mass is higher than that of the surrounding liver tissue. (D) Photomicrography of resected specimen shows an abnormal dilated artery within the lesion (hematoxylin–eosin; original magnification,  $\times 100$ ).

**Abbreviation:** MSCT, multislice computed tomography.





**Figure 3** Representative MSCT images of focal nodular hyperplasia in a 37-year-old man (case 21).

**Notes:** (A) Plain computed tomography showing a small hypodense mass under the capsule of the right lobe of the liver. (B) In the arterial phase, the mass with clear margin (arrow), except the central scar area, is evidently enhanced. (C) In the delayed phase, the mass demonstrates isodense and the central scar (arrow) appears high density. (D) Photomicrograph of resected specimen shows a central scar with abnormal dilated veins and the bile duct (hematoxylin–eosin; original magnification,  $\times 200$ ).

**Abbreviation:** MSCT, multislice computed tomography.

respectively. Delayed enhancement of the central scars (hyperdensity relative to the surrounding tissues) could be seen only in three lesions (Table 1).

## Pathological findings

All tumor specimens presented a medium texture without any capsules. The color of the gross specimen was generally khaki, although some differences caused by varied tissue composition existed. Lesions rich in fibroplasia demonstrated a gray color, while those with more cell components tended to be taupe. Conventional hematoxylin and eosin staining showed typical radial fibrous proliferation, and the liver tissue was divided into distinguishing nodules. The liver mesenchyma was dotted with proliferated small bile ducts, vessels, Kupffer cells, and lymphocytes. The proliferated liver cells were arranged in masses with no cells showing atypia. Central scars and abnormal blood vessels were

observed under microscopy in 17 and 21 lesions, respectively (Figures 1D, 2D, and 3D).

## Discussion

In the present study, important findings included evident enhancement of the tumor that was almost equal to that of the abdominal aorta in the arterial phase and lower enhancement of the central scar in both arterial and portal venous phases. Delayed enhancement of scar was diagnostic but uncommon (three of eight lesions). Central scar and abnormal blood vessels are often found during the pathological examination of FNH lesions. In our study, pathology showed central scars and abnormal blood vessels in 17 and 21 of 25 lesions, respectively, while MSCT with multiphase enhancement showed central scars in eight of the 17 lesions (47.1%) and abnormal arteries or draining veins in 13 of the 21 lesions (61.9%). Furthermore, abnormal draining veins in five lesions

Table 1 Enhancement pattern of 25 FNHs with pathology correlation

Case	Sex	Age (years)	Shape	Arterial phase			Portal vein phase			Delayed phase			Preoperative diagnosis		Pathology	
				CT value (HU)	Scar density	Abnormal artery	Enhancement type	Scar density	Draining vein	Enhancement type	Scar density				Scar	Abnormal artery/vein
1	F	15	Irregular	115	Low	-	Slightly high	Low	+	Iso	Low		FNH		+	+
2	F	37	Oval	89	-	-	Iso	-	-	Iso	-		FNH		+	+
3	M	35	Round	123	-	-	Slightly high	-	-	Slightly high	-		Hepatic cell adenoma		-	+
4	F	40	Round	112	Low	-	Slightly high	Low	-	Iso	Low		FNH		-	+
5	M	26	Oval	98	-	+	Iso	-	-	Iso	-		FNH		+	+
6	M	32	Round	95	-	-	Iso	-	+	Iso	-		FNH		+	+
7	F	37	1. Oval 2. Round	90	-	+	Iso	-	-	Iso	-		FNH		+	+
8	F	62	Round	120	-	-	Slightly high	-	-	Slightly high	-		Hemangioma		-	-
9	F	43	Irregular	115	Low	+	Iso	Low	-	Iso	High		FNH		+	+
10	M	25	Irregular	112	-	+	Slightly high	-	-	Iso	-		FNH		+	+
11	F	19	1. Round 2. Round	96	Low	+	Slightly high	Low	-	Iso	Low		FNH		+	+
12	M	27	Oval	115	-	-	Slightly high	-	+	Slightly high	-		Hemangioma		-	+
13	M	33	Irregular	85	Low	-	Iso	Low	+	Iso	Low		FNH		+	+
14	M	54	Round	110	Low	-	Iso	Low	-	Iso	High		FNH		+	-
15	F	26	Round	95	-	-	Low	-	-	Low	-		HCC		-	-
16	F	57	Oval	95	-	-	Slightly high	-	-	Iso	-		FNH		+	+
17	F	38	Oval	105	-	-	Iso	-	+	Iso	-		FNH		+	+
18	F	36	Round	103	-	-	Iso	-	-	Iso	-		FNH		-	+
19	F	25	1. Irregular 2. Irregular	95	Low	+	Slightly high	Low	-	Slightly high	Low		FNH		+	+
20	M	40	Oval	120	-	-	Slightly high	Low	-	Iso	-		FNH		-	-
21	F	32	Round	85	Low	+	Iso	Low	-	Iso	High		FNH		+	+
22	M	34	Round	95	-	+	Slightly high	-	-	Iso	-		FNH		+	+
23	F	37	Oval	89	-	-	Slightly high	-	-	Slightly high	-		FNH		-	+
24	F	45	Round	115	-	-	Iso	-	-	Iso	-		FNH		+	+
25	F	50	Round	108	-	-	Iso	-	-	Iso	-		FNH		+	+

**Abbreviations:** CT, computed tomography; FNH, focal nodular hyperplasia; F, female; HCC, hepatocellular carcinoma; M, male; -, negative; +, positive.

were found to be diagnostic, which is another important finding. With the help of these CT findings, the diagnostic accuracy of 16-slice MSCT with multi-phase enhancement for FNH reached 84%.

The term FNH was coined by the World Health Organization in 1975 and adopted by the International Association for the Study of the Liver since 1976. Before helical multiphasic hepatic CT became prevalent, FNH was rarely diagnosed with confidence.<sup>9</sup> Several decades before MSCT was founded, preoperative CT was used with a low frequency for FNH diagnosis because of limitations in the acquisition time and poor understanding of the disease. With the development of CT technology, dual- or triple-phase enhancement scans can depict the blood support for the liver and the enhancement pattern of the lesions, thus increasing the understanding of the blood supply in FNH lesions.

FNH is characterized by regenerative hepatic nodules with a central scar and radiating fibrous cords that contain dystrophic vessels and reactive ductules.<sup>10</sup> The majority of FNH lesions are solitary, <5 cm in diameter, and develop near the surface of the liver.<sup>11</sup> Under most circumstances, FNH develops at the edge of the liver and is basically filled with normal liver tissue, with no density discrimination on plain CT. In our patients, however, 21 lesions showed slightly lower density (75%). Calcifications may be observed in rare cases.<sup>12</sup> Caseiro-Alves et al<sup>13</sup> reported five FNH lesions with calcification in a series of 295 patients. None of the lesions in our study showed calcification on CT images or pathological examination.

FNH exhibits a rich blood supply and is routinely enhanced from the center to the periphery. The entire lesion except the central scar is enhanced, with a density intermediate to that of the normal liver tissue and the aorta abdominalis. In our study, all 25 lesions exhibited arterial phase enhancement with CT values that were almost equal to those for the aorta abdominalis. FNH is considered a combination of arteriovenous malformation and liver tissue hyperplasia.<sup>14,15</sup> Therefore, the presence of thick and round vessels can be a unique sign. Eight of the 25 lesions in our study also showed such vessels, although the positivity rate was low compared to that obtained with pathology. Therefore, further technological developments are required to increase the detection of such arteries. The appearance of FNH in the portal venous phase can be vivid. In our study, the majority of lesions exhibited isodensity or slight hyperdensity. One lesion that exhibited slight hypodensity in this phase was misdiagnosed as HCC (Figure 1C). In addition, abnormal draining veins that appeared as linear or pseudocapsular hyperdense shadows

could be observed in this phase, and this was considered diagnostic. In the delayed phase, the enhancement pattern of FNH was almost similar to that observed in the portal venous phase. Three scars showed delayed enhancement, which increased our diagnostic accuracy.

Dynamic contrast-enhanced triple-phase CT plays a crucial role in FNH diagnosis, although contrast-enhanced ultrasound (CEUS) examination is considered as a fair imagistic method for FNH's characterization. The particular manifestations of CEUS are spoke-wheel aspect and centrifugal filling.<sup>16</sup> Recently, a research involving 85 histologically proven FNH cases done by Wang et al<sup>17</sup> showed that the area under the receiver operating characteristic curve, sensitivity, and specificity of CEUS and CECT did not show a significant difference. However, in clinical practice, CEUS has a lot of limitations. The biggest concern is that CEUS is a relatively subjective method. In another word, the sonographer's skill is crucial to the whole diagnosis. Besides, gas in the abdomen region and the background of the liver hinder the correct diagnosis. As for CT, in particular, delayed enhancement of the central scar is considered a strong indicator. However, the domestic data collected by Zhongshan Hospital Affiliated to Fudan University revealed that only 30% of FNH patients exhibited this sign. This proportion is ~50% overseas.<sup>9</sup> In the present study, eight of the 25 (32%) lesions showed ill-defined hypodense areas representing the central scar and three of these eight lesions (37.5%) exhibited delayed enhancement. The central scar is composed of fibrous tissue and thick-walled malformed vessels. These narrow and malformed vessels can obstruct the path of the contrast agent, resulting in delayed enhancement. Unfortunately, the central scar is not peculiar to FNH lesions; fibrous lamina, cavernous hemangioma, and hepatic carcinoma may also exhibit this feature. However, the scars observed in the other conditions tend to appear as radial stars without enhancement.

The atypical features of FNH may still hinder diagnosis.<sup>18</sup> Atypical lesions exhibited heterogeneous enhancement in the arterial phase and slight hypodensity in the portal venous phase. Such lesions account for ~20% of all lesions, and their imaging features are not characteristic. The extent of dynamic enhancement can be varied, with the enhancement observed in the arterial phase showing a tendency to disappear. The contrast agent may be evacuated early in the artery-portal vein and artery-vein shunt. In contrast, the density in the portal venous and delayed phases is generally low. During the delayed phase, capsule-like enhancement can be observed because of fatty degeneration, necrosis, and other atypical signs.<sup>19</sup> There were four atypical lesions in our study, which

were misdiagnosed as HCC, hemangioma (n=2), and hepatic cell adenoma, respectively.

The differential diagnoses for FNH must include the following conditions. First is HCC, which usually develops in patients with a history of viral hepatitis or liver cirrhosis. Supplied by the hepatic artery, the lesions appear to “wash in” and “wash out” during enhancement. Atypical FNH lesions should be distinguished from HCC using alpha fetoprotein and further magnetic resonance imaging examinations. The second is hemangioma. Typical hemangiomas are enhanced from the periphery to the center, with the delayed phase showing iso- or hyperdensity. On the other hand, FNH lesions are enhanced from the center to the periphery. The diagnosis can be confusing in patients with certain types of vascular tumors that exhibit iso- or hyperdensity in the portal venous and delayed phases. Even in our study, two patients were misdiagnosed with hemangioma. The third is hepatic cell adenoma. With lower enhancement, these lesions appear less bright and exhibit homogeneous enhancement compared with FNH.<sup>20</sup> Furthermore, hepatic cell adenomas show a tendency to bleed. Therefore, the presence of a hematoma can rule out FNH.

## Conclusion

The results of our study suggest that MSCT can serve as a useful tool for the diagnosis and differentiation of FNH. Multiphase scanning can provide panoramic views of FNH lesions and reveal their enhancement patterns and pathological characteristics. Abnormal blood vessels within or around the lesion are demonstrated more often than central scar, and both should be carefully observed for FNH diagnosis. Further studies are required to improve the detection of abnormal blood vessels within or around FNH lesions.

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## Disclosure

The authors declare no conflicts of interest in this work.

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