The frequency and clinical significance of the halo sign in focal nodular hyperplasia of the liver

Size Wu¹, Rong Tu², Guangqing Liu¹, Yusen Shi²

¹Department of Medical Imaging, ²Department of Radiology, Affiliated Hospital of Hainan Medical College, Haikou, China

Abstract

Objective: The purpose of this study was to investigate the frequency of the halo sign in focal nodular hyperplasia (FNH) of the liver and its clinical significance. Methods: Archives of 19 patients (6 men, mean age 35 years ± 11, range 22–53 years and 13 women, mean age 39 years ± 15, range 17–66 years) diagnosed from April 2005 through March 2012 with FNH were reviewed. All images were analyzed by three readers in a panel in order to depict the characteristics of the liver lesions and established in consensus a diagnosis. The halo appearance of lesions was focused upon. Result: The halo sign was found in 6 FNHs (31.6%, 6/19). The mean size of the FNHs was 34.2 mm ± 7.2 (range, 23–47 mm). Characteristics of FNH appearance were various in gray-scale ultrasound and color Doppler flow imaging, CT and MRI, and combined use of different modalities may enable diagnosis definitely. All patients with FNH reviewed were consistent with previous diagnoses. Conclusions: The halo sign was found in a high number of patients in this study, which implies that the halo sign may be not rare in FNH on sonography, and absence and presence of the halo sign may not help identifying FNH.

Keywords: liver, focal nodular hyperplasia, halo sign, ultrasonography

Introduction

Ultrasonography (US) is a noninvasive technique used for the examination of the liver and numerous hepatic focal lesions are found in daily routine workups. Some of these focal lesions have typical US characteristics such as hemangioma or simple cyst and generally further investigation are not required. Others focal lesions have atypical US characteristics and a conclusion can difficult to be drawn, especially when the differentiation between benignancy and malignancy is necessary. Focal nodular hyperplasia (FNH) is a benign lesion occasionally encountered at practice. Previous studies [1-3] concluded that FNH should be considered as a tumor-like lesion without malignant potential and may be the result of a focal hyperplastic response of hepatocytes to a congenital vascular anomaly. Histologically, FNH is characterized by the presence of normal hepatocytes with a malformed biliary system that leads to a slowing of biliary excretion [1-3].

US features of FNH are characterized by hypo- or isoechoic, homogeneous, circumscribed lesion, with hypo- or hyperechoic central scar [3-6]; color Doppler flow imaging may show a central stellate vascular appearance which corresponds to the angiographic appearance of a central feeding artery with a spoke-wheel sign [3-6]. Some studies [3-7] conclude that characteristics of FNH overlap characteristics of other lesions and only the presence of the central scar is the helpful characteristic for the identification of FNH. However, a central scar is not often conspicuous on US [3], in addition, the halo sign, which is suggestive of liver malignancy, can be found in FNH, which brings more challenge to recognition. The halo sign is a hypoechoic area at the periphery of
a lesion relative to the surrounding hepatic parenchyma and lesion. Previous literature [6-17] documented that a halo appearance presents frequently on the US of primary hepatocellular carcinomas (HCC), metastases, and with lesser frequency around hemangiomas, inflammatory granulomas, pseudotumors, early abscess, and so on. To the best of our knowledge, though the halo sign has been addressed in some studies [1,3,4,6], its incidence and role in the diagnosis has not been determined. The purpose of this study is to investigate the frequency of the halo sign in the FNH of the liver.

**Patients and methods**

Archives of 19 patients with FNH referred to our institute from April 2005 through March 2012 were reviewed, including sex, age, imaging study (US, CT and MRI), laboratory test (serum alpha-fetoprotein, AFP) and clinical manifestation. The study group consisted of 6 men, with a mean age of 35 years ± 11 and age range of 22–53 years, and 13 women, with a mean age of 39 years ± 15 and age range of 17–66 years. The patients had no particular symptoms and sign relative to the FNH except a 22 year old patient who had a painless gross hematuria. The diagnosis of FNH was based on US, CT, MRI and a histopathological study. Approval of the institutional review board had been obtained and the requirement of informed consent was waived.

**Imaging Study**

All patients underwent an abdominal US examination, performed by 3 sonologists with 10-17 years of experience, using Logiq 9 (GE Healthcare, Waukesha, WI), Voluson expert 730 (GE Healthcare, Piscataway, NJ), HD11XE (Philips Medical systems, Shanghai, China), and Sonos 5500 (Philips Medical systems, Netherlands, USA), with 5-2 MHz convex transducer. The patients were instructed to fast overnight (about 12 hours) before the ultrasonic scan. The liver was observed carefully with gray-scale ultrasound and color Doppler flow imaging and representative images were saved digitally in the computer of the workstation. Sixteen patients underwent contrast enhanced CT (using a 64-MDCT scanner; LightSpeed VCT, GE Healthcare, Milwaukee, WI, USA) evaluation and 8 patients underwent contrast enhanced MRI (using Signa Excite Xi Twin Speed 1.5T system, GE Healthcare, Milwaukee, WI, USA) evaluation. The size, echo patterns, characteristics of enhancement, and associated findings of the hepatic lesions were documented. All images were evaluated in the panel by three readers (with 10-22 years of experience) in order to depict the characteristics of the liver lesions and to establish a diagnosis. The readers were blinded to the previous diagnosis of the lesion, and the halo appearance on the sonography was the centre of focus. Findings of US, CT and MRI study were documented. We used the following US diagnostic criteria for typical FNH: in gray-scale US a round, ovoid or lobulated mass in sectional shape, hypoechoic, isoechoic, or complex echoic, with homogeneous circumscribed margin and distinct border, with or without posterior acoustic enhancement, with hypo or hyperechoic scar in the centre; in color Doppler US hypervascularity with a central stellate vascular appearance [3-6]. Contrast enhanced CT and MRI criteria for the diagnosis of FNH should meet the rapidly entire enhancement of lesion at the arterial phase, persistent enhancement at portal venous and late phase, presence of central scar, septa, and pseudocapsule [1,3,5].

**Statistical Analysis**

The continuous data were expressed as mean± standard deviation and incidences of the halo sign and other findings were described as percentage.

<table>
<thead>
<tr>
<th></th>
<th>Color Doppler US (n=19)</th>
<th>Enhanced CT (n = 16)</th>
<th>Enhanced MRI (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halo sign</td>
<td>6(31.6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Central scar</td>
<td>6(31.6%)</td>
<td>8(50.0%)</td>
<td>4(50.0%)</td>
</tr>
<tr>
<td>Septum</td>
<td>0</td>
<td>11(68.7%)</td>
<td>5(62.5%)</td>
</tr>
<tr>
<td>Pseudocapsule</td>
<td>0</td>
<td>12(75.0%)</td>
<td>6(75.0%)</td>
</tr>
<tr>
<td>Central stellate vascularity</td>
<td>9(47.4%)</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Central vascular nidus</td>
<td>13(68.4%)</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Peripheral vascularity</td>
<td>14(73.7%)</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Entire enhancement at arterial phase</td>
<td>/</td>
<td>15(93.7%)</td>
<td>7(87.5%)</td>
</tr>
<tr>
<td>Enhancement at portal phase (Slight washout)</td>
<td>/</td>
<td>15(93.7%)</td>
<td>7(87.5%)</td>
</tr>
</tbody>
</table>

Note: The number in the parenthesis is the percentage of finding receiving US, CT and MRI workup; / refers to the inability to evaluate.
Results

The halo sign was found in 6 cases (31.6%, 6/19). Characteristics of FNHs demonstrated on ultrasound, CT and MRI study of 19 FNHs were summarized in table I. The mean size of the FNHs was 34.2 mm ± 7.2 (range, 23–47 mm). The diagnoses were fully consistent with previous diagnoses. Representative findings are illustrated in figures 1 and 2.

Discussion

The halo sign is often suggestive for malignancy in clinical practice [7,8,16,17], but in some studies [1,3,4,6] this sign is mentioned in FNHs. HCC and hepatic metastatic tumors are frequently encountered compared with FNH which is a relative rare benign lesion. Bruneton et al [7] reported that a halo sign was found to be highly predictive of malignancy (97%-100%), while other studies [8-13] reported that the halo appearance existed also in other liver focal entities. These contradictions challenge the exact role of the halo sign in the identification of liver malignancies. The halo sign was found in FNH, but it has never been regarded as a characteristic of FNH. Typically, at US the FNH is evidenced as a circumscribed round isoechoic or hypoechoic focal lesion, with a profound hypoechogenicity in the center, and a central stellate vascular appearance and peripheral flow on color Doppler flow imaging [3-6]. In this study, all lesions showed the majority of these characteristics, but not all characteristics could be demonstrated in a single imaging method. FNH sometimes mimics HCC and hepatic metastases, especially in cases with a halo sign, which can cause a US diagnostic dilemma. Six lesions in our

![Fig 1: A 27-year-old woman with FNH. Sagittal ultrasound (a) shows profound hypoechogenicity encircling a slightly hypoechoic lesion relative to the peripheral liver parenchyma, and a punctate hypoechogenicity in the center suggests scar (arrowhead); color Doppler flow imaging (b) shows the hypervascular nidus in the center; contrast enhanced CT image obtained during the arterial phase (c) shows intensive homogeneous enhancement of the lesion (arrow) except a punctate unenhanced hypoattenuating central scar (arrowhead); during the portal venous phase (d) shows that the lesion (arrow) is still hyperattenuating relative to the liver parenchyma, and the central scar (arrowhead) has not yet enhanced.](image1)

![Fig 2: A 22-year-old man with FNH. Sagittal ultrasound (a) shows profound hypoechogenicity encircling a slightly hypoechoic lesion relative to the peripheral liver parenchyma; color Doppler flow imaging (b) shows that lesion is hypervascular, with significant peripheral flow and a central stellate vascular appearance; (arrow); contrast-enhanced CT image obtained during the arterial phase (c) shows intensive homogeneous enhancement of the entire lesion (arrow) and no central scar; sagittal gadolinium-enhanced T1-weighted GRE image obtained during the late phase (d) shows a slight washout of the lesion (arrow) that is isointense relative to the surrounding liver parenchyma with a hyperintense spoke wheel due to the presence of radiating septa and a hyperintense pseudocapsule.](image2)
study had a halo appearance, which made the differential diagnosis more difficult, especially in the 22 year old patient with painless gross hematuria. In US examination solid lesions were found in the liver and in the left kidney. The one in the kidney was assumed malignant and the lesion in the liver was firstly presumed to be a metastasis of the renal malignancy, but after enhanced CT and MRI studies, diagnosis of FNH was established. The lesion in the liver was removed together with the tumor of the left kidney; postoperative histopathology confirmed that the liver lesion was FNH and the kidney lesion a papillary renal cell carcinoma. The subsequent study of the 6 FNHs with enhanced CT and MRI did not find corresponding findings of the halo appearance, which suggests the halo appearance present only on US. Previous studies [1,3,18-20] show that reliable noninvasive diagnosis of FNH depends mainly on contrast enhanced imaging, including contrast enhanced ultrasound, CT and MRI. Results of this study show that the halo appearance causes a diagnostic dilemma, but through different imaging modalities, more information is acquired and suspicion is excluded. Compared with unenhanced imaging, contrast enhanced imaging can well delineate the characteristics of FNH and help render diagnosis, including swift enhancement at arterial phase due to hypervascularity, persistent enhancement at portal venous and late phase (except a scar in the center of some cases), spoke-wheel appearance, and pseudocapsule. This study agrees with previous studies [1,3,18-20]. In addition, enhanced sonography may demonstrate dynamic changes that initial central enhancement of the mass followed by centrifugal spread of enhancement to the periphery [10,18,21,22]. FNH with a halo sign accounts for 31.6% in this study, and this means that a halo sign is not rare at all in FNHs. The incidence of a halo sign is the same as that of a central scar which is a characteristic of the FNH in this study, but a halo sign may present widely in other liver lesions as mentioned before. It is not specific, therefore, a halo sign is not a characteristic of FNH but a common manifestation that may cause diagnostic challenging. The authors believe that presence of a halo sign can neither establish nor exclude the diagnosis of FNH.

The limitations of this study are that the study is retrospective, the halo sign is not studied in targeting in a real-time US study, the sample is smaller, and no study on the correlation between the halo sign and the histopathological change was performed.

In conclusion, the halo sign was found in a high number of patients in this study, which implies that the halo sign may be not rare in FNH on US, and the absence or the presence of a halo sign may not help determining FNH. With an ambiguous case in clinical practice, contrast enhanced US, CT, MRI and/or biopsy may secure a confident identification.

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**References**

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