Focal nodular hyperplasia: new findings at Doppler ultrasonography

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Abstract. – OBJECTIVE: The aim of our study was to explore the features of focal nodular hyperplasia (FNH) at Doppler ultrasonography, analyzing specifically the presence of intratumoral venous flow in patients with an established diagnosis of FNH. Previous studies showed that using a venous Doppler spectrum, intratumoral vessels are often depicted in hepatocellular adenoma (HCA) but less frequently in FNH.

PATIENTS AND METHODS: Forty-five FNHs from thirty-three consecutive patients (26 female, 7 male; mean±SD age: 40±13) underwent color Doppler ultrasonography and spectral analysis according to a standardized protocol. FNH diagnosis was established by the presence of typical behavior at contrast-enhanced ultrasound (CEUS) associated with another imaging technique (contrast-enhanced computed tomography [ceCT] or contrast-enhanced magnetic resonance [ceMR]). A biopsy was performed when imaging was inconclusive. All data concerning Doppler analysis were reviewed by two more operators, blinded to the final diagnosis, and the interobserver agreement for the presence of venous Doppler signal was determined by Cohen's Kappa.

RESULTS: Of the 33 patients, 24 had a single solitary focus, and 9 had multiple foci. Lesion diameter ranged between 1.2 and 8.9 cm (mean ± SD 3.2±1.6 cm). The central feeding artery with the typical arterial spectrum was detected in all 45 lesions, whereas the spoke-wheel sign was observed in 18 cases (40%). A venous Doppler signal was detected in 35 FNHs (77.8%), and in 60% of them, it was identified in the center of the lesion.

CONCLUSIONS: Venous Doppler signal located in the center of the lesion suspected to be a hypervascular benign lesion cannot be considered a typical HCA feature since it has been detected in a high percentage of FNH cases.

Key Words:
Ultrasound imaging, FNH, Color Doppler, Venous Doppler signal.

Abbreviations

FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma; US, ultrasound; CDUS/PDUS, color Doppler US/power Doppler US; ceCT, contrast-enhanced computed tomography; ceMR, contrast-enhanced magnetic resonance; CEUS, contrast-enhanced ultrasound; CT, computed tomography; DA, diagnostic accuracy; HCC, hepatocellular carcinoma; MI, mechanical-index; NPV, negative predictive value.

Introduction

Focal nodular hyperplasia (FNH) is the second most frequent benign liver tumor with an incidence of 3%-5% and it is increasingly diagnosed as a result of the widespread use of abdominal ultrasound (US)[1]. Although FNH pathogenesis is not yet known, it is considered a hyperplastic response of the hepatic parenchyma to a pre-existing arterial malformation[2].

Histopathologically, FNH is a well-circumscribed lesion with a characteristic architecture consisting of a stellate scar surrounded by multiple nodules of benign-appearing hepatocytes[2].

The angioarchitecture is characterized by large arterial vessels in the fibrous body that run through the scar tissue, branched to form a spider-like struc-

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ture. There are not portal vessels within FNH, but there are venous vessels connected to the central or hepatic veins surrounding the lesions[3].

The differentiation of FNH from other hypervascular liver lesions such as hepatocellular adenoma (HCA), hepatocellular carcinoma (HCC), and hypervascular metastases is important for clinical practice. However, while the distinction from malignant liver lesions is usually not difficult associating results from imaging techniques to the specific clinical setting, the differential diagnosis with adenoma might be considerably more difficult. Both HCA and FNH are characterized by hepatocyte alterations, predilection for young women and arterial phase hypervascularity on contrast-enhanced imaging.

On the other hand, differentiation of these two benign lesions is essential because of different therapeutic approaches: treatment for FNH is based on conservative clinical follow-up[4,5] whereas HCA is an indication for surgery, due to the risk of complications such as hemorrhage, rupture or malignant transformation[6,7].

Therefore, the challenge for non-invasive differentiation of these two focal liver masses has received attention in the past years[8-11].

Nowadays, the diagnosis is generally performed noninvasively by detection of pathological landmarks, including the feeding arteries and stellate scar that are responsible for imaging behavior[1,12-15]. All contrast imaging modalities, such as contrast-enhanced computed tomography (ceCT), contrast-enhanced magnetic resonance (ceMR), and contrast-enhanced US (CEUS) show a highly vascularized tumor characterized by large surrounding vessels that communicate with a central feeding artery, producing the typical spoke-wheel pattern[12,13,15-17]. In particular, FNH nodules show an early hyperenhancement in the arterial phase with the typical centrifugal filling and persistence of enhancement without a clear wash out during the portal and late phase[1,14,15,17].

Sustained portal phase enhancement is more common in FNH than in HCA[9] and this is probably due to the venous vascular architecture.

Conventional US is the first-line imaging modality for the detection of liver lesions. Specifically, FNHs are generally discovered incidentally, often in young women and are characterized by an aspecific echo pattern in B mode study[18]. Color, power, and pulsed Doppler US may show a characteristic spoke-wheel arterial pattern, thus providing further clues to the diagnosis[1]. The Doppler features of FNH were the object of many studies published before 2000[19]. According to these papers, the characteristic vascular pattern of FNH showed the presence of multiple well-defined vessels radiating from the center to the periphery with a pulsatile Doppler spectrum[20]. In addition, the importance of detecting vascular Doppler signal with a stellate appearance due to the presence of arteries with low resistivity index (RI) was highlighted[20]. Vessels with the continuous flow were also described in the peripheral part of a few FNH lesions (9%), whereas the continuous central flow was not depicted in any of the FNHs[21].

In the past years, improvement in diagnostic technology has drawn much attention to the special vascular features of FNH, and recent technical advances have improved the sensitivity of color/power Doppler US (CDUS/PDUS), opening up new diagnostic possibilities.

The aim of the present study was to investigate the Doppler pattern of FNH, analyzing the presence of intratumoral venous flow in patients with an established FNH diagnosis.

Patients and methods

Patients

Consecutive patients diagnosed with FNH referred to the ultrasound unit of "Sant'Orsola" Hospital (Bologna, Italy) between April 2006 and February 2008 were offered to participate in this prospective study.

All lesions were previously detected by US and characterized as FNH based on at least two imaging techniques: CEUS and either ceCT or ceMR. In cases of inconclusive imaging, a biopsy with histological analysis was performed.

Subjects without an established radiological diagnosis of FNH or with an inadequate US visualization of the lesion were excluded.

Other exclusion criteria were previous history of malignancy, liver cirrhosis, hepatitis B and hepatitis C infection, high serum level of alpha-fetoprotein.

The clinical protocol was reviewed and approved by the Hospital Institutional Board for research involving human subjects, and written informed consent was obtained before the enrollment in the study.

Study Protocol

Real-time B mode US, color/power Doppler US (CDUS/PDUS), and CEUS were performed using Technos MPX or Mylab 70 XVG ultrasound scanners (Esaote, Genova, Italy) equipped with a 3.5-5 MHz convex probe. All examinations were carried out by one operator, specially trained in liver and Doppler US. The B-mode US was carried out first to assess the location, size, and echogenicity of the lesions. The pattern of tumors was described as hypoechoic, isoechoic, or hyperechoic compared to the surrounding liver tissue. Subsequently, CDUS/PDUS were performed to detect the presence of tumor vascularity and spectral Doppler analysis to characterize the type of vascular signal inside the lesion[5]. Briefly, a low value of pulse repetition frequency (500 Hz) was chosen for the detection of weak signals. The wall filter was set at its minimum value (50 Hz). The color-or-power-encoded area was restricted as much as possible to maximize color sensitivity and frame rate. The color areas were carefully searched, and the distribution of blood flow was assessed for each lesion. For spectral analysis, the color signals were used as a guide for obtaining the Doppler spectrum. Real-time B-mode, color or power Doppler images and spectra were simultaneously displayed on the screen to check the correct position of the sample volume when obtaining the Doppler waveform. The sample volume used for spectral analysis varied in size from 2 to 4 mm. The presence of the typical arterial pattern and the venous flow were evaluated for each lesion. The video clips and images containing CDUS/PDUS examinations were reviewed retrospectively and independently in a random sequence by two other examiners, who were blinded to the final diagnosis. The observers were asked to assess the presence and distribution (peripheral or central) of color and power Doppler signals and to define the characteristics of flow (pulsatile or continuous waveform) for each lesion. The results were then compared to reports from the observer who performed the examinations. Finally, all the lesions were studied with CEUS as part of the clinical workup of the patients.

For the final FNH diagnosis, our department's standard practice included two different imaging procedures (CEUS, ceCT, ceMRI) with concordant findings, or in case of discordance or inconclusive diagnosis, histological analysis. In case of multiple lesions, the one-to-one correlation of ceCT or ceMR with CEUS was guaranteed by a careful review of each nodule with different imaging modalities.

Statistical Analysis

An exploratory analysis was performed to evaluate the interobserver agreement for the detection of venous Doppler signal inside the target lesion between two examiners, using Kappa statistics proposed by Cohen[21-23]. Two univariate logistic regression model analyses were performed: the first to evaluate the association between the venous Doppler signal and the echostructure of the lesion and the second to evaluate the association between the venous Doppler signal and the size of the lesion. The lesions were divided into two groups according to the largest diameter: < 30 mm and ≥ 30 mm. To assess the test performance of the venous Doppler signal in FNH nodules according lesion size, sensitivity, specificity, positive and negative predictive values (PPV and NPV) with 95% confidence intervals (CIs) were calculated. The same analysis was performed by selecting lesions with venous flow located at the center of the lesion. A *p*-value below 0.05 was considered statistically significant. Statistical analysis was performed using Stata 16.0 (StataCorp LP, College Station, TX, USA).

Results

Thirty-three patients (7 men, 26 women; median age 36 years) with a total of 45 target lesions were enrolled in this prospective study.

All the lesions were evaluated with CEUS, 34 lesions were studied with ceCT, 10 with ceMR, and 1 with both ceCT and ceMR. In one case, the diagnosis was established by histological examination.

Twenty-four patients had one lesion, whereas the remaining 9 had multiple lesions (7 patients had two lesions, one patient had three lesions, and one had four lesions). Lesion size ranged from 19 to 89 mm (mean ± SD, 32.1±16.2). Twenty-four lesions were located in the right lobe and 21 lesions in the left lobe. All liver segments were involved. The echogenicity of FNH on gray-scale sonography was hypoechoic in 20 out of 45 lesions, isoechoic in 16 and hyperechoic in 9. Patients and lesions characteristics are summarized in Table I.

At Doppler analysis, intratumoral flow with the typical arterial spectrum characterized by high frequency and low resistance index was detected in all 45 lesions. Morphologically, the spoke-wheel sign based on the presence of multiple well-defined vessels radiating from the center to the periphery of the lesion was depicted in 18 out of 45 lesions (40%) (Table II, Figure 1B and 2B). Vessels with a venous Doppler spectrum were detected in 35 lesions (77.8%) (Table II, Figures 1C and 2C). In particular, the detection of continuous flow in the center of the lesion was depicted in 27 cases (60%) (Table II, Figure 1D).

The interobserver agreement for the detection of venous Doppler signal was perfect (Kappa value = 1).

A significant association between the presence of venous Doppler signal and the size of the lesion was identified at logistic regression analysis (LR=5.24, p=0.022).

When the size of the lesion is ≥30 mm, the possibility to detect a venous Doppler signal is significantly greater than for lesions <30 mm (OR [95% CI]: 6 [1.10-32.54]; p = 0.038). The sensitivity, specificity, accuracy, PPV and NPV of venous Doppler signal were 60%, 80% 64.4%, 91.3% and 36.36%, respectively (Table III). When we restricted the analysis only to the venous signals located in the center of the lesion, the accuracy of this Doppler findings was lower (sensitivity, specificity, PPV and NPV of 56%, 55% 60.9%, 50%, respectively, Table III).

Taken together, no association has been found between the detection of venous Doppler signal and lesion echostructure (OR [95% CI]: 1.4 [0.54-3.77]).

Discussion

FNH is a benign hypervascular tumor in which the venous angioarchitecture has not been completely investigated so far. All papers published on this topic focused on the detection of the spoke wheel sign and, in particular, on the depiction of the feeding arteries with low resistive index that are considered pathognomonic signs. The pres-

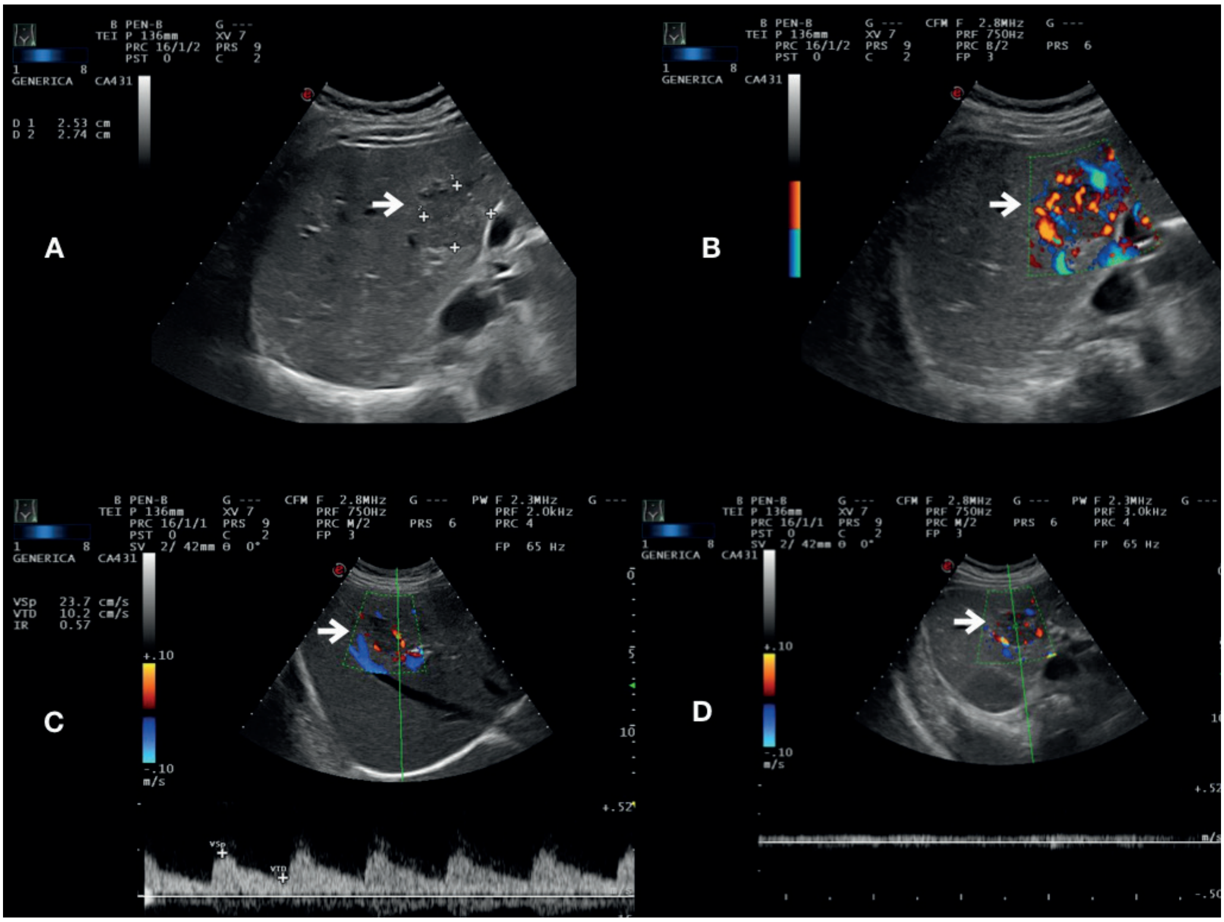

Figure 1. A 32 years old woman with a 2.5 cm FNH nodule of the segments VIII studied by conventional ultrasound (panel A), color (panel B) and pulsed wave Doppler analysis (panels C and D). **Panel A,** Hypoechoic lesion at B mode US. **Panel B,** color Doppler evaluation shows an intratumoral flow with the typical arterial spectrum characterized by the spoke-wheel sign. **Panel C,** pulsed wave Doppler analysis shows an arterial flow with low resistivity index. **Panel D,** pulsed wave Doppler analysis shows the presence of a central venous flow inside of the lesion.

Table I. Patient's characteristics.

Characteristic	All patients n=33
Age, yrs	
mean ± SD	40 ± 13
Gender	
Female (%)	26 (78.8)
Male (%)	7 (21.2)
Total lesions	45
Right hepatic lobe (%)	24 (50.3)
Left hepatic lobe (%)	21 (46.7)
Number of lesions	
Solitary	24
Two	7
Three	1
Four	1
Dimension of the lesions (mm)	
Median (interquartile range)	30 (20-36.5)
Echostructure	
Isoechoic	16
Ipoechoic	20
Hyperechoic	9

Table II. Findings at color and power Doppler.

Doppler features	Number of lesions (total lesions 45)
Spoke-wheel sign	18
venous Doppler spectrum:	35
- Peripheral (%)	8 (22.9)
- Central (%)	25 (71.4)
- Central and peripheral (%)	2 (5.7)

ence of a venous signal in FNHs nodules was reported for the first time by Wang et al[24] without a discrimination of the position inside the lesion. Subsequently, Bartolozzi et al[21] described the presence of a continuous flow located in the periphery of the lesion in a small number of FNH (13%). In our series, the presence of venous Doppler signal has been detected in a higher number of cases (77.7%), both in the center and on the border of the nodule. In particular, 60% of the cases showed a continuous and flat flow in the central part, 17% in the peripheral part and 4% showed both distributions (either in the center and on the border). Interestingly, the absence of venous signal in 22% of nodules has been related the smaller size of the lesion, whereas the PPV was nearly 91% for nodules bigger than 3 cm.

The discrepancies between our study and previous reports could be due to an updated Doppler technology with an improvement of software dedicated to slow flow detection. The use of modern US equipment enables a more precise delineation of the typical vascular architecture of the lesion, allowing the detection of signals rarely reported in this kind of lesions. Indeed, we described not only the possibility of detecting venous vessels in most FNH nodules but also their presence in the central part of the lesion, connected to central or hepatic veins.

Table III. Sensitivity, specificity, positive predictive value and negative predictive value for the presence of venous Doppler signals according to the size of the lesion both for all venous signals and central venous signal.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
All venous signals				
Size ≥ 30 mm	60% (42.1-76.1)	80% (44.4-97.5)	91.3% (72-98.9)	36.4% (17.2-59.3)
Size < 30 mm	40% (23.9-57.9)	20% (2.5-55.6)	63.6% (40.7-82.8)	8.7% (1.1-28)
Central venous signal				
Size ≥ 30 mm	56% (34.9-75.6)	55% (31.5-76.9)	60.9% (38.5-80.3)	50% (28.2-71.
Size < 30 mm	44% (24.4-65.1)	45% (23.1-68.5)	50% (28.2-71.8)	39.1% (19.7-61.5

PPV, positive predictive value; NPV, negative predictive value.

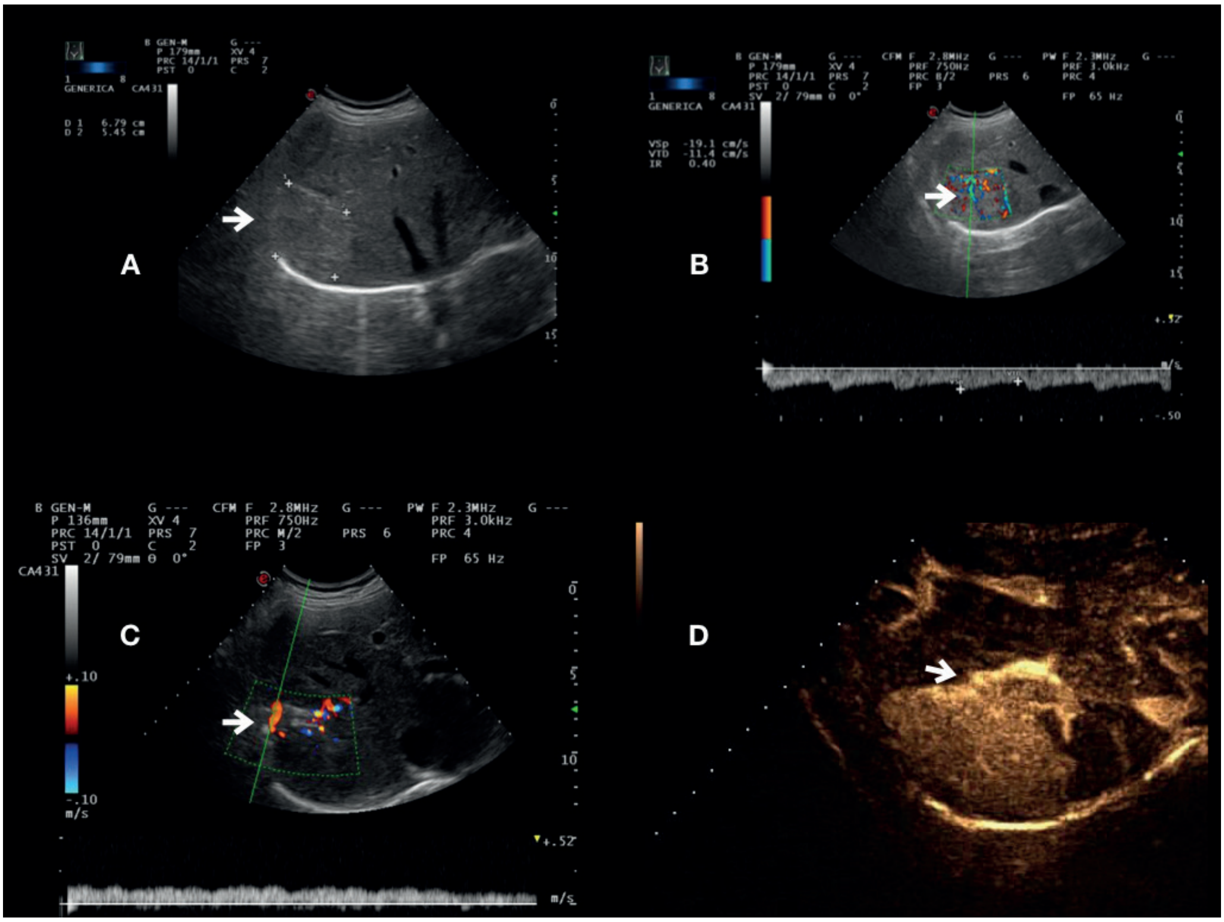

Figure 2. A 45 years old woman with a 6.8 cm FNH of the segment VII, studied by conventional ultrasound (panel A), color and pulsed wave Doppler (panels B and C) and CEUS (panel D). **Panel A,** Hyperechoic lesion at B mode US. **Panel B,** color and pulsed wave Doppler evaluation demonstrate the presence of intratumoral flow with the typical arterial spectrum characterized by the spoke-wheel sign and low resistivity index (*white arrow*). **Panel C,** evidence of peripheral venous flow coming out from the lesion, detected by both color and pulsed wave Doppler analysis (*white arrow*). **Panel D,** CEUS shows the persistence of enhancement during the venous phase. The *white arrow* indicates a venous vessel coming out from the lesion.

For several years this feature has been considered a trait of HCA[21]. Specifically, the Doppler criteria for the diagnosis of HCA and FNH were: the detection of intratumoral vessels with a central venous Doppler spectrum (possibly associated with either pulsatile or continuous peripheral flow) for HCA and the detection of color signals with an arterial Doppler spectrum, radiating from the center to the periphery of the lesion, (possibly associated with either pulsatile or continuous peripheral flow, but not with intratumoral venous flow) for FNH[5,25].

The detection of draining vessels coming out from FNH is the proof of the presence of a venous microcirculation inside the lesion. In a previous study, it has been shown that opacification of the hepatic vein on angiography is a typical finding in FNH[3] and this feature has been emphasized by preliminary experience based on ceCT and CEUS[26-32]. We demonstrated that venous signals can be depicted in most FNH lesions by performing color Doppler flow imaging with modern US equipment.

In particular, unequivocal hepatic veins functioning as draining veins were seen in 60% of the lesions. Our findings are very important in the diagnostic workup of suspected benign hepatocellular tumors.

The advantage of this new approach may be seen mainly in young patients where an incidental finding of focal liver lesion with an intralesional venous flow and with the typical features of FNH at Doppler and CEUS examination avoid unnecessary biopsy or surgical resection.

The present study has some limitations. First, the reliability of CDUS in the evaluations of FNH vascular architecture should be integrated with results obtained with the same technology in patients with HCA. Second, the small number of patients enrolled does not allow to draw conclusions on differently located venous signal (central or peripheral). Further studies with a large sample size are warranted to determine the diagnostic performance of this Doppler feature. Finally, the Doppler data are collected only by one operator and, since CDUS is a subjective evaluation, this aspect might affect data reproducibility. However, this weakness is in part counterbalanced by the perfect agreement with sonographers blinded to the final diagnosis who evaluated stored images and video clips.

In spite of these limitations, we think that a careful Doppler evaluation of FNH vascular features might offer new insights in the evaluation of these lesions, especially in first-level outpatient centers were is not possible to perform CEUS immediately.

Conclusions

We showed that the presence of venous Doppler signals located in the center of a nodule suspected to be a hypervascular benign lesion cannot be considered a typical feature of HCA since it has been detected in a high percentage of FNH cases.

Further studies, including also a direct comparison with HCA, should be performed to confirm our results in a larger number of series.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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