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Ultrasound Doppler technique for the diagnosis of focal nodular hyperplasia – case series and systematic review

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Abstract

With the Superb Micro-Vascular Imaging (SMI), the established Doppler technology has been extended by another mode. With this technique, microvascular structures with slow blood flow can now also be displayed in real time. As with the introduction of Doppler ultrasound, this new technique opens further diagnostic fields for the examiner, which were previously reserved for magnetic resonance imaging (MRI), computed tomography (CT) or contrast ultrasound (CEUS). Focal nodular hyperplasia (FNH) of the liver is characterized by a typical spoke-wheel vascular malformation (spoke-wheel sign, SWS) and a good example using SMI for the diagnostic profit of our patients. The aim of this report is to describe the use of SMI as a new non-invasive, quick, and probably cost-effective diagnostic imaging tool.

Keywords: liver; ultrasound; focal nodular hyperplasia; contrast enhanced ultrasound; Color Doppler; superb microvascular imaging

Introduction

Doppler ultrasound (US) has been used routinely in various areas of medicine for more than fifty years [1,2]. From angiology to cardiology, gynaecology to gastroenterology and hepatology, Doppler technology found its way into the everyday medical routine and into current guidelines [3-5]. A disadvantage was always the insufficient visualisation of small vessels with slow blood flow. The subtle Doppler signals are superimposed by the body's own movement artefacts such as respiration and heartbeat (clutter) and therefore beyond a reliable visualisation [6-8]. With the introduction of contrast enhanced ultrasound (CEUS) and with the new generation of contrast media (SonoVue® 2001), also small vessels became visible [3-5,9-14]. Now this evolution is continued with the development of sensitive Doppler techniques, herewith superb micro-vascular imaging (SMI) by Canon (formerly Toshiba). The SMI mode now allows the visualisation of slow blood flow in small vessels with the use of a contrast agent.

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Introduction into Superb Microvascular Imaging (SMI)

The principle behind SMI

In conventional Doppler, there is an overlap in the visualisation of slow blood flow and simultaneous tissue movement (clutter). To reduce these motion artifacts, the conventional Doppler uses a one-dimensional wall filter. However, this results in a reduced visualisation of the slow flow signals (fig 1). In SMI, the tissue move-

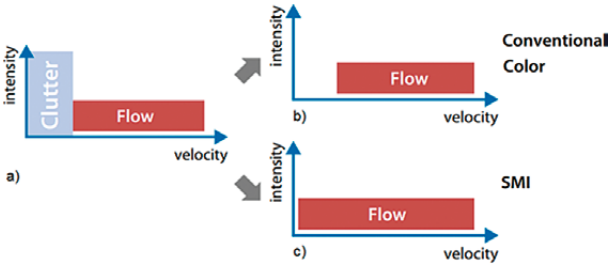

Fig 1. Schematic illustration of the SMI algorithm. In conventional Doppler, tissue movements (clutter) overlap with slow blood flow (a). With conventional Doppler, one-dimensional wall filter (line) is used, which also leads to a reduced visualization of slow blood flow (b). In SMI mode, multidimensional filter is applied, preserving the signals of slow blood flow (c). Adapted after Hata J (2014) "Seeing the unseen new techniques in vascular imaging" with permission of Toshiba Medical Systems Corporation© [16].

ments are analyzed with an adaptive algorithm and then the movement artifacts are removed with a multidimensional filter, which also allows to show the slow blood flow [15,16].

Color and monochrome SMI (cSMI und mSMI)

Two modes can be used within SMI. In colour mode (cSMI) grayscale and colour information are simultaneously displayed. In the monochrome mode (mSMI) the focus lies on the pure visualisation of the vessel structures. The sensitivity of the vessel image is increased by the exclusive visualisation of the grey scale with subtraction of the background information (fig 2). Furthermore, the time smoothing function (also known as frame averaging) on a scale of 1-7 can be set manually [8,17]. By increasing the scale, the flow signals are accumulated frame by frame. This allows to visualize the continuity of the vessels more accurately [15].

Image optimization

As in conventional Doppler, the US picture can be improved in SMI with several parameters. The sensitivity of the flow signal can be improved by increasing the color gain [8,17,18]. The reduction of the region of interest (ROI) also improves sensitivity. An increase in ROI, on the other hand, results in a reduction of the frame rate. Park et al therefore recommend a reduction of the ROI to less than 2.5 cm for an optimal display [15]. However, if the color gain is increased too much while the ROI is reduced at the same time, so-called flash artifacts can occur [19,20]. For an optimal result, color gain and ROI are fine-tuned in a way that just no flash artifacts appear anymore. Another factor is the level of depth of the ROI. The deeper it lies, the longer the echoes need for the way there and back. Thus, small and superficial ROI produce better image results. To avoid motion artifacts, the patient should be asked to hold his breath. Furthermore, applying not too much pressure on the tissue prevents the vessels from collapsing, especially in the case of superficial ROI [15,21]. In our experience, microcalcifications can also cause signal artefacts, sometimes difficult to distinguish from vessels in small structures such as gallbladder polyps [22-25]. In this case, the observation of pulse-synchronous flow patterns can help to identify true vessels.

Overview of existing publications

The publications on the subject of SMI are limited so far, which is no surprise for a new imaging tool. A literature search in PubMed (June 2023) shows 87 articles published so far. However, analysis of the last years suggests that this number will rise in the next few years. A more detailed analysis until 2020 shows the following indications. Female breast (n=11) [15,26-35] followed by thyroid diagnostics (n=8) [36-43] and larger vessels (n=8) [44-52], arthritis (n=5) [53-57] and focal liver lesions (n=5) [52,58-62]. Most (n=40) publications compared SMI to another examination method such as Doppler or CEUS. Furthermore, there are 3 (5%) case-control studies, one cohort study, 8 (13%) case series and 7 (11%) case reports. Finally, there is one review article each on breast and thyroid [15,36]. Randomized controlled trials (RCT) are still lacking.

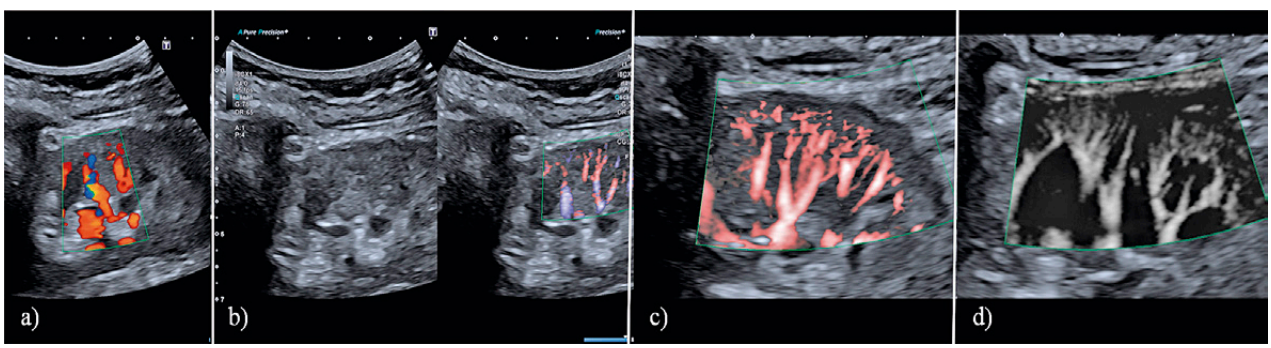

Fig 2. Kidney cortex using different display modes. Color Doppler (a). Advanced Dynamic Flow mode (b). Color SMI (cSMI) (c). Monochrome SMI (mSMI) (d).

Hypervascular focal liver lesion (FLL) using SMI, Focal Nodular Hyperplasia (FNH)

Epidemiology

Focal nodular hyperplasia (FNH) is the second most common benign liver tumor after hemangioma [7,14,63,64]. The prevalence varies depending on the source from 0.4% to 3% and accounts for about 8% of all primary liver tumors [65-68]. Although FNH is found in men and women, it most commonly affects women between 30 and 50 years with a woman-to-man ratio from 8:1 to 12:1 [68-70]. Occasionally FNH are found in children as well and CEUS and elastography are applied [14,71-78]. Bouyn et al described in children a prevalence of 0.02% based on 11000 liver sonographies [79]. In most cases FNH occur solitary, but in up to 20-30% of cases occurence is multiple and often combined with other FLL [65,68,70,80]. Multiple FNH are sometimes observed in a specific clinical context. This includes Budd-Chiari syndrome [81-83], obliterative portal venopathy [84,85] and congenital disorders such as hereditary haemorrhagic telangiectasia and portal vein agenesis [14,86]. FNH also appear in 20% together with liver hemangiomas [70,87,88]. On the other hand, neither pregnancy nor oral contraceptives are associated with the occurrence of FNH [89-95].

Clinical symptoms and natural course

In case series, it has been shown that the size of FNH usually remains stable over many years, causes no symptoms and almost no complications [89,96]. In up to 30% of patients elevated liver enzymes are observed [97]. The α-fetoprotein is typically not elevated. Other symptoms are uncommon: palpable abdominal mass in 2-4% of cases, hepatomegaly and fever in <1% of the cases [70,98,99]. Since the FNH represents a benign condition, a conservative approach can be chosen in most cases. Even in symptomatic patients, the indication for resection should be considered cautiously, as there is only a poor correlation between FNH and symptoms [100]. Resection of the FNH is only recommended in exceptional circumstances such as pediculate lesions, exophytic growth or increase in size. On the other hand, non-surgical treatment methods should only be chosen when the patient is not operable. In case of confirmed diagnosis and asymptomatic patients no follow-up is recommended. In addition, oral contraceptives do not have to be stopped and follow-up during pregnancy is not necessary [65,101,102].

Histology and pathogenesis

The generally accepted hypothesis for the development of FNH postulates a local hyperperfusion or hypoxia at the site of an arterial malformation. This hemodynamic instability leads to local polyclonal hyperplasia of the hepatocytes [14,68,98]. This hypothesis is supported by the fact that patients with FNH also have a higher incidence of hemangioma [80,83,88]. A second indication is that in families with hereditary haemorrhagic telangiectasia, an autosomal-dominant genetic disorder characterized by vascular malformations, FNH also occurs more frequently [14,103].

FNH is typically described as an unencapsulated nodule with a central fibrotic scar in up to 70 % with dystrophic arteries [3-5,92,104]. From the center several septa usually grow radially. In various degrees, ductular proliferations and inflammatory cells can also be seen in these septa. The characteristic feature is a central feeding artery that branches to the periphery and centrifugally perfuses the nodule (fig 3, fig 4).

Furthermore, the FNH shows atypical portal veins [92,93,97]. Molecular studies showed an upregulation of extracellular matrix genes. They are associated with an activation of the transforming growth factor beta (TGF-β) and an overexpression of Wnt/β catenin target genes coding for glutamine synthesis [107]. This β-catenin activation without β-catenin-activating mutations leads to a map-like pattern of glutamine synthase overexpression in

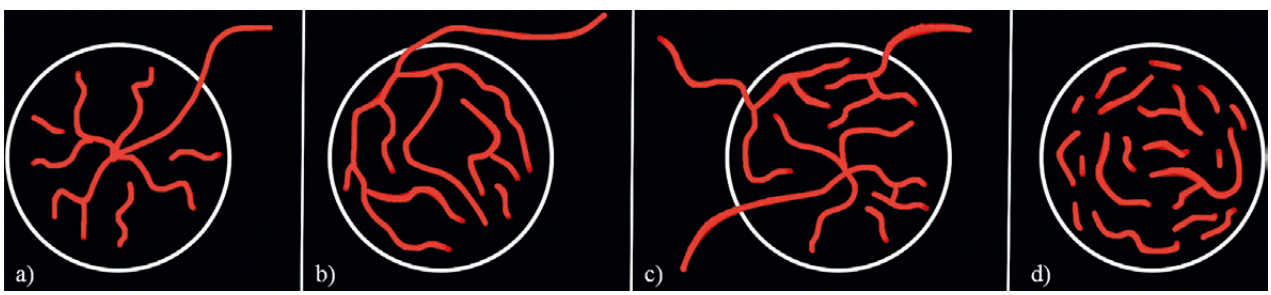

Fig 3. Classification of FNH by CEUS [14,97,105]. Type I (85%): classical type with spoke-wheel sign (SWS). Vessels run to the center using colour coded doppler ultrasound with or without a central scar (a). In the eccentric type II the central point of the vessel star is shifted to the edge. Type III (15%): Teleangiectatic "atypical" FNH, peliotic sinusoid (b) [106]. Type IV shows homogenous enhancement.

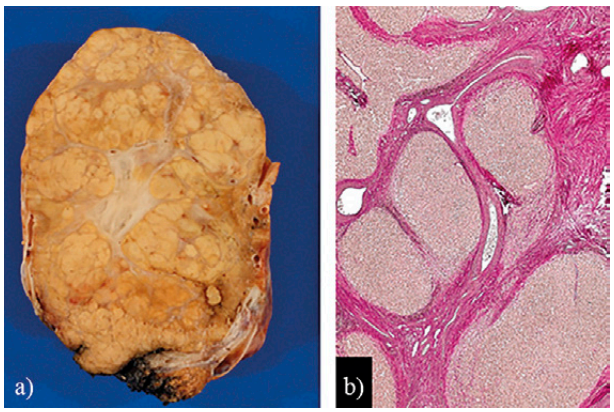

Fig 4. Resected FNH showing a central fibrotic artery (red arrow) (a). Histopathological analysis demonstrated fibrous and thickened walls of the blood vessels (Elastica-van-Gieson-stain) (b).

the perivenous areas of the nodules, which is characteristic for FNH [108,109]. This characteristic feature can be used for histopathological diagnosis in difficult cases [65,110,111].

Imaging

The image properties of FNH are very similar to the underlying histopathological abnormalities in all diagnostic modalities [65]. US including CEUS, contrast enhanced CT or contrast enhanced MRI are used for diagnostic purposes. In the current EASL Guidelines, the typical features regardless of the imaging modality are summarized as follows: 1) lesion homogeneity except the central scar, 2) slightly different from the adjacent liver on pre-contrast US, CT or MRI, 3) strong and homogeneous enhancement on arterial phase CEUS, CT or MR with a central vascular supply, which becomes similar to adjacent liver on portal and delayed phases, 4) central scar best seen on MRI (hypointense on pre-contrast T1-weighted images, strongly hyperintense on T2-weighted images, and becoming hyperintense on delayed phase using extracellular MR contrast agents because of the accumulation of contrast material in the fibrous tissue), and 5) lack of capsule with often lobulated contours [65].

Generally, the diagnosis of FNH is based on the combination of several imaging modalities, whereby the MRI and CEUS has the highest sensitivity, especially for lesions >3 cm [3,4,112-115]. Compared to US and CT, the MRI has the highest sensitivity, although according to Soussan et al it is strongly dependent on the examiner (63-88%). On the other hand, the specificity of the MRI for FNH diagnostics is with almost 100% very high. However, especially for small FNH without central scar, MRI diagnosis is difficult. For FNH <3 cm CEUS is recommended [65,112,116].

Ultrasound

The FNH is usually an incidental finding [64,117-120]. It often presents isoechogenic or discreetly hypoechogenic to the surrounding liver tissue and is therefore often not clearly visible in the B-mode. In the fatty liver, the FNH can also appear considerably hypoechogenic [7,121,122]. Occasionally, the typical spoke-wheel sign (SWS), which is caused by the central feeding artery with radially spreading septa, can sometimes already be seen in the B-mode. Typically, the FNH shows no signs of infiltration, but it can compress nearby vessels [52,60]. In native colour or power mode US, the central artery can often be seen with increased blood flow compared to the surrounding liver tissue [52,123]. Therefore, Doppler US can be used to detect the flow signal in the feeding artery and determine the resistive index [6,124,125] (fig 5).

CEUS

In CEUS, FNH typically shows early arterial phase hyperenhancement (APHE) compared to surrounding liver tissue [126-130]. Between 10-20 seconds after injection of the contrast agent, the specific radial vascular pattern (SWS) appears [110,131]. This is followed by a centrifugal uptake of the contrast agent so that the whole lesion appears hyperechogenic within seconds. This fast dynamic process can be missed by CT or MRI. In the

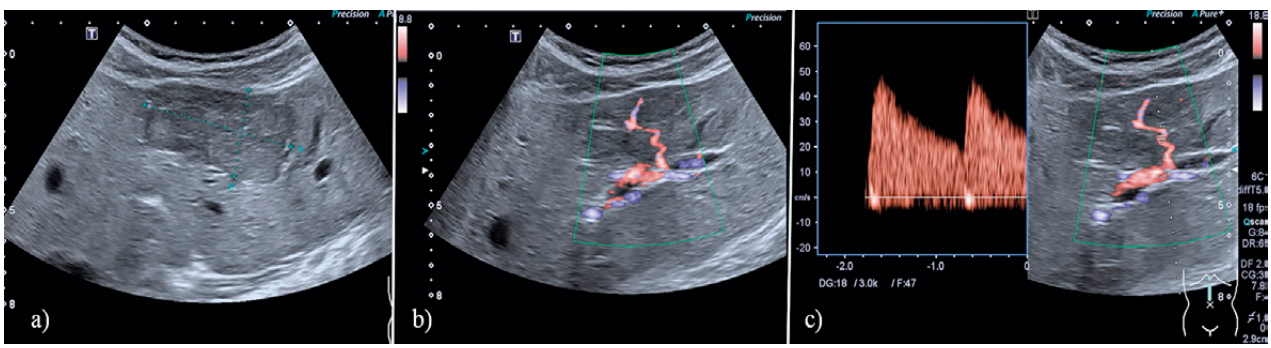

Fig 5. Flow signal of a feeding artery. B-mode ultrasound (a), color Doppler ultrasound (b) and spectral Doppler ultrasound showing a central feeding artery in FNH with low resistance profile (c) [6,124,125].

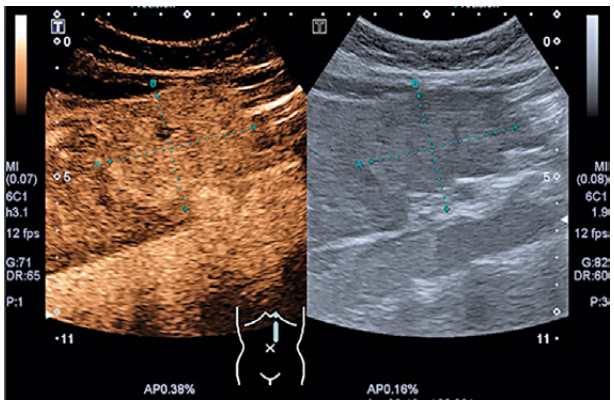

Fig 6. Central scar without contrast enhancement. CEUS with late venous phase with typical "scar star" due to dystrophic central artery.

portal venous phase, the contrast in FNH appears hyperenhancing (95 %) or at least isoenhancing compared to the surrounding liver [104,132]. In the late venous phase in typical FNH the central scar can be demonstrated with loss of contrast agent in up to 70% of patients (fig 6). CEUS represents the ideal diagnostic tool for FNH < 3 cm [65,97,112,116].

Superb Micro-Vascular Imaging

SMI appears to be an interesting diagnostic tool for the visualisation of microvascular structures of FNH since FNH is characterized by typical macro- and microvascular patterns. Since the SMI is still a new tool, there is still a small number of publications about this topic.

For the first time SMI was described as an option for the diagnosis of FNH 2016 by Lee et al in a case series of 29 liver lesions including 7 FNH, with a diameter of 8 mm to 28 mm. The typical SWS could be demonstrated in 3/7 cases with SMI, in 2/7 cases a radiating pattern could be seen and in 2 cases the signal was not specific. The size of the lesions for which the SMI signal was unspecific was unfortunately not mentioned [133]. Also, in 2016 Bonacchi et al described the diagnosis of FNH using SMI in two cases (diameter 30 mm and 15 mm) [62]. A prospective study by He et al followed in 2017, in which a total of 31 different liver lesions (FNH n=2) were analyzed. The typical SWS could be demonstrated in both FNH (4 cm) [58]. In 2017 Naganuma et al described another two cases of 70 mm and 50 mm FNH diagnosed with SMI [61]. In the first European experience on SMI and FNH, a case series (n=5) has shown

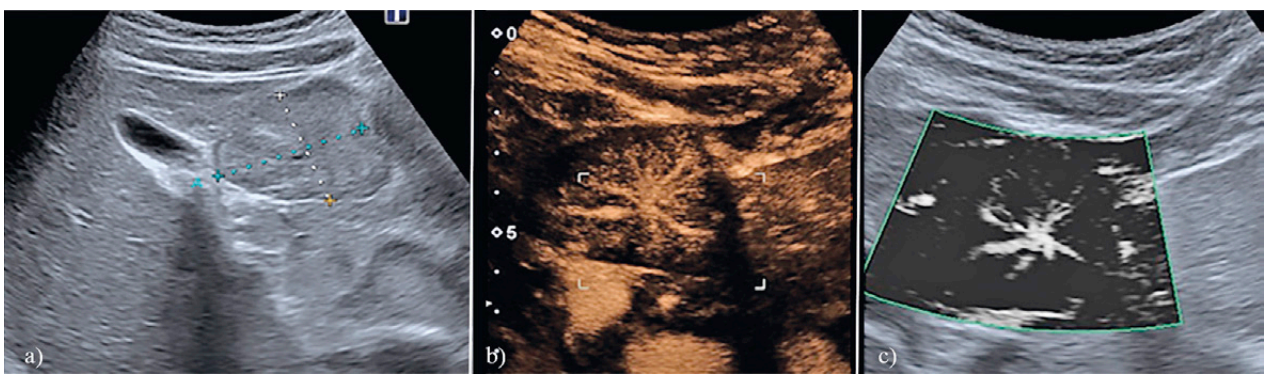

Fig 7. A 55-year-old asymptomatic woman with incidental focal liver lesion of 4 cm FNH on conventional ultrasound (a). CEUS with arterial spoke-wheel sign (b). SMI with typical spoke-wheel pattern (c).

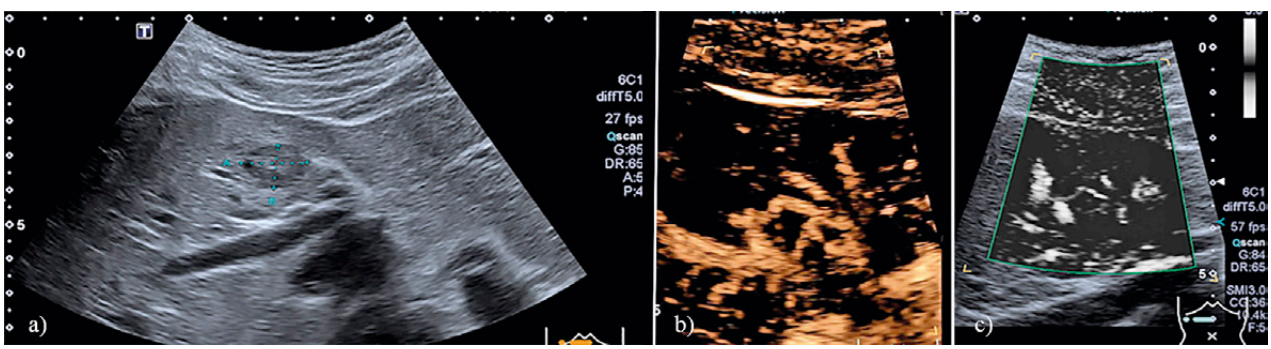

Fig 8. A 25-year-old woman who presented with suspected autoimmune pancreatitis. Pancreas-MRI incidentally showed an FLL of 1.8 cm of unclear dignity. SOR was CEUS with a of 18-month follow-up. B-mode Ultrasound showing 1.8 cm FNH (a), CEUS with arterial spoke-wheel enhancement(b) and SMI with spoke-wheel pattern (c).

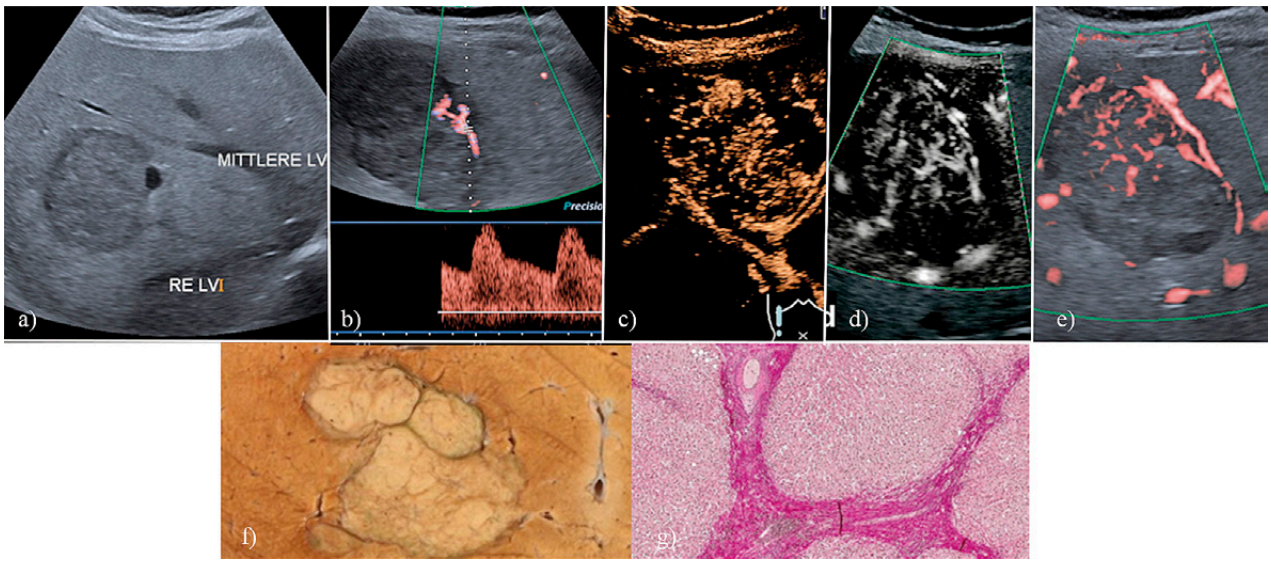

Fig 9. A 24 year-old women with pain in the upper right abdomen with an FLL, doubling in size from 3 cm to 6 cm within 2 years in liver segment VIII (a). Flow signal of a feeding artery with Doppler ultrasound showing a eccentric feeding artery in FNH with low resistance profile (b), CEUS with teleangiectatic "atypical" FNH (Type III) (c), monochrome SMI (d), color SMI (e). Resected FNH (f). Histopathological analysis demonstrated fibrous and thickened walls of the blood vessels (Elastica-van-Gieson-stain) (g).

a reliable representation of the SWS in SMI mode [134]. The lesions ranged from 18 mm to 60 mm diameter.

Principally, the device settings on the US machine are based on the general recommendations shown above. A more detailed description of the settings can be found in the reports by Lee et al and He et al. Both groups used the following settings: convex probe (1-6 MHz), color velocity scale ≤2.0 cm/s, frame rate >30 fps, color frequency 5-7 MHz, and the gain setting adjusted to show optimal imaging [58,60].

In our experience, the ROI should be as small as possible but finally adapted to the size of the FNH. Principally we first use the conventional Doppler and then the more specific modes (first cSMI and then the mSMI mode) to get an overview of the lesion and to adjust the ROI. Finally, a fine adjustment is made with the time smoothing function (frame averaging) starting using the scale "1" and scaling upwards until the optimal vascular visualization is reached. For documentation purposes, the patient is asked for breath holding, what further improves the image despite the propagated automatic correction of motion artifacts (fig 7-9).

Conclusion

With the introduction of SMI, the spectrum of ultrasound has been extended by another promising non-invasive diagnostic imaging tool to visualize small vessels with slow blood flows in real time and without intravenous contrast agents. The analysis of contrast enhancement using time intensity curve analysis cannot be replaced [5,135,136], which are important to differentiate malignant and benign FLL [3,4]. In conclusion, SMI rather represents an additive tool than a substitute for CEUS or MRI.

Conflict of interest: none

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