European Radiology (2019) 29:6489–6498
https://doi.org/10.1007/s00330-019-06329-y

GASTROINTESTINAL

Doughnut-like hyperintense nodules on hepatobiliary phase without arterial-phase hyperenhancement in cirrhotic liver: imaging and clinicopathological features

Kazuto Kozaka[1] · Satoshi Kobayashi[2] · Norihide Yoneda[1] · Azusa Kitao[1] · Kotaro Yoshida[1] · Dai Inoue[1] · Takahiro Ogi[1] · Wataru Koda[1] · Yasunori Sato[3] · Toshifumi Gabata[1] · Osamu Matsui[1]

Received: 10 April 2019 / Revised: 4 June 2019 / Accepted: 13 June 2019 / Published online: 5 July 2019

Abstract

Objectives To determine the imaging and clinicopathological features of MRI doughnut-like nodules (HBP-doughnut nodules), hyperintense at the hepatobiliary phase (HBP) after injection of gadoxetic acid (EOB) and without arterial-phase hyperenhancement (APHE) in cirrhotic liver.

Methods The Institutional Review Board approved this retrospective study and informed consent was waived. We enrolled 309 consecutive patients with liver cirrhosis who were examined by EOB-MRI, dynamic CT, and angiography-assisted CT between 2008 and 2012 and searched for HBP-doughnut nodules. We evaluated imaging characteristics including haemodynamics and signal intensity of MRI, pathological findings, and frequency of malignant transformation.

Results One hundred and one HBP-doughnut nodules without APHE were identified in 18 patients (6%), including seven of 59 (12%) patients with hepatitis-B-virus-related, nine of 230 (3.9%) with hepatitis-C-virus-related, and two of 33 (6.1%) with alcoholic cirrhosis. All nodules showed enhancement peaks in the portal phase, the same or increased intranodular portal supply on CT during arterial portography, and the same or decreased intranodular arterial supply on CT during hepatic arteriography. On T2-weighted and diffusion-weighted images, 37 (36%) and 24 (24%) nodules, respectively, showed hyperintensity predominantly in the central area. Three nodules were diagnosed by fine needle biopsy as non-neoplastic hepatic nodules. Ninety-three of 101 (92%) nodules in 16 patients were followed up during an observation period of 1163 ± 902 days (range 57–2920 days), and none showed malignant transformation.

Conclusion HBP-doughnut nodules without APHE in cirrhotic liver were not infrequent. None became malignant. We propose calling them 'multiacinar cirrhotic nodules' based on the classification by an International Working Party.

Key Points

- *HBP-doughnut nodules without APHE were seen in 6% of patients with liver cirrhosis.*
- *The enhancement peak of HBP-doughnut nodules without APHE was in the portal phase, which reflected the fact that they were supplied predominantly by the portal vein, based on angiography-assisted CT findings.*
- *None of the HBP-doughnut nodules without APHE in cirrhotic liver became malignant, and in conjunction with limited pathological features, they may be corresponding to multiacinar cirrhotic nodules in the International Working Party classification.*

Keywords Diagnosis · Magnetic resonance imaging · Gadolinium · Multidetector computed tomography

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00330-019-06329-y) contains supplementary material, which is available to authorized users.

✉ Kazuto Kozaka
k-kozaka@staff.kanazawa-u.ac.jp

[1] Department of Radiology, Kanazawa University Graduate School of Medical Sciences, 13-1 Takara-machi, Kanazawa 920-8640, Japan

[2] Department of Radiological Technology, School of Health Sciences, College of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan

[3] Department of Human Pathology, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan

Abbreviations

APHE	Arterial-phase hyperenhancement
CTAP	CT during arterial portography
CTHA	CT during hepatic arteriography
DWI	Diffusion-weighted images
EOB	Gadoxetic acid
FNH	Focal nodular hyperplasia
HBP	Hepatobiliary phase
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
IPH	Idiopathic portal hypertension
LRN	Large regenerative nodule
NRH	Nodular regenerative hyperplasia
OATP	Organic anion transporter polypeptide
RN	Regenerative nodule
T1WI	T1-weighted images
T2WI	T2-weighted images

Introduction

Gadoxetic acid (EOB) is an extracellular and hepatocyte-specific MR contrast agent, which is effective in the detection and characterisation of hepatic mass lesions [1, 2]. Most hepatic cancers appear as hypointense nodules in the hepatobiliary phase (HBP) of EOB-MRI [3]. In contrast, hyperintense nodules in the HBP of EOB-MRI in patients with or without liver diseases are commonly encountered. These nodules include regenerative or hyperplastic nodules as well as neoplastic nodules [4]. Hepatocellular carcinoma (HCC) with β-catenin mutation, β-catenin-activated hepatocellular adenoma (HCA), and focal nodular hyperplasia (FNH) are frequently hyperintense on the HBP. This is related to the overexpression of organic anion transporter polypeptide (OATP) 1B3 (synonym with OATP8), in neoplastic or hyperplastic cells [5–9]. However, there are still some unclassified regenerative or hyperplastic nodules that are hyperintense in the HBP without arterial-phase hyperenhancement (APHE) with nodular regenerative hyperplasia (NRH) [10], idiopathic portal hypertension (IPH) [11], chronic hepatitis, and liver cirrhosis [12].

Regenerative nodules (RNs) in cirrhotic liver are usually < 5 mm in diameter and appear iso- to hyperintense on T1-weighted images (T1WI) and iso- to hypointense on T2-weighted (T2WI) and diffusion-weighted images (DWI) [13]. Nodules > 5 mm in diameter showing no definite APHE and hyperintense on the HBP are not uncommonly found. These nodules often show a doughnut-like hyperintensity pattern in the HBP and have a benign clinical course. However, as HCC can sometimes be hyperintense on the HBP, some confusion may arise [7].

The purpose of this study was to explore imaging and clinicopathological features of doughnut-like nodules, which are hyperintense on the HBP without APHE in cirrhotic liver, with reference to the classification of hepatocellular nodules by an International Working Party [14].

Materials and methods

Patients

The Institutional Review Board of Kanazawa University Graduate School of Medical Sciences approved this retrospective study, and informed consent was waived. We assessed 322 consecutive patients with liver cirrhosis who had undergone by EOB-MRI, dynamic-enhanced CT, and angiography-assisted CT, including CT during arterial portography (CTAP) and CT during hepatic arteriography (CTHA), from April 2008 to June 2012. We excluded the patients with > 6 months between each examination. The final population of this study was 309 patients, and their clinical backgrounds are provided in Table 1.

Among these patients, the frequency of ‘doughnut-like hyperintense nodules on HBP of EOB-MRI (HBP-doughnut nodules) without APHE’ and their imaging features and prognosis were assessed.

MRI

All individuals underwent MRI of the liver using a 1.5- or 3-T MR system (Signa HDx; GE Healthcare). Each patient received an intravenous bolus injection of gadoxetic acid (Primovist; Bayer Schering Pharma) at a dose of 0.25 mmol/kg body weight and a flow rate of 1 mL/s, followed by a 20-mL saline flush. Dynamic (arterial, portal, and transitional phase) imaging was performed using a fat-suppressed 3D T1WI gradient echo sequence. Fat-suppressed T2WI and DWI were also obtained (Table 2). The HBP was obtained 20 min after injection of contrast material.

Dynamic CT imaging

Dynamic CT was performed with a CT system (Light Speed VCT64, GE Medical Systems, or Somatom Definition Flash, Siemens) with the following parameters: voltage, 120 kV; current, 300–350 mA; rotation period, 0.5 s; detector collimation, 0.6–0.625 mm; pitch, 0.516–1.0; and section thickness, 2.5–3.0 mm. After precontrast scanning, 100–150 mL contrast material with 600 mg/kg iodine (Iopamiron (Bayer Schering Pharma), Omnipaque (Daiichi–Sankyo), or Optiray (Mallinckrodt Japan)) was injected over 30 s. The arterial phase was determined using the bolus-tracking method, as the time at which the CT value of the abdominal aorta reached

Table 1 Patient cohort in this study

Sex	Age (years)	Hepatitis virus test and alcohol consumption		
Male/female	Mean ± SD	HCV-Ab positive	HBsAg positive	Alcohol consumption
208/101	68 ± 8.9	230	59	33

Consecutive 309 HCV-, HBV-, and/or alcohol-related cirrhosis patients who were examined by both EOB-MRI and CTAP during April 2008 to June 2012. Alcohol consumption was defined by daily ethanol intake > 40 g

CTAP computed tomography during arterial portography, *EOB-MRI* gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid-enhanced magnetic resonance imaging, *HBV* hepatitis B virus, *HCV* hepatitis C virus

200 HU plus 17 s. The portal phase was obtained 30 s after starting the arterial-phase scanning. The delayed phase was reached 150 s after starting the injection of contrast media.

Angiography-assisted CT imaging

All individuals underwent angiography-assisted CT using a 64-slice multidetector row CT scanner (Aquilion; Canon Medical Systems) including CTAP and CTHA. The angiography-assisted CT protocol in our institute was the same as described previously [15]. Angiography-assisted CT was carried out for the precise preoperative evaluation of tumour extension or precise evaluation of the lesions for their diagnosis.

Analysis of imaging findings

HBP-doughnut nodules are defined as hyperintense nodules relative to the surrounding liver parenchyma, with a central hypointense portion, similar to the findings often seen in FNH [16]. The shape of the central hypointense portion is commonly round, sometimes linear or scar-like (Fig. 1). The thickness of the peripheral enhancing portion is variable. No apparent APHE of each nodule was assessed by both dynamic CT and EOB-MRI.

Hepatic nodules that met the above definition of HBP-doughnut nodules without APHE were identified from the radiological records of Kanazawa University Hospital, and they were selected based on previous reports, without re-reading. To reduce the influence of partial volume effect, HBP-doughnut nodules without APHE less than 8 mm in the maximum diameter were excluded. The 'positive' cases were submitted to the readers. Then, their density or signal intensity was assessed by two board-certified radiologists with 11 years' and 10 years' experience (A.K. and N.Y.), separately, and when the decisions differed, the final evaluation was made by consensus. Readers were aware of the existence of HBP-doughnut nodules without APHE. On dynamic CT, the nodules were classified as high, iso-, and low density compared with the surrounding liver parenchyma and we calculated the changes in relative density of these nodules. On EOB-MRI, HBP-doughnut nodules without APHE were classified as hyper-, iso-, or hypointense at each dynamic phase, and the HBP compared with that of surrounding liver parenchyma, and we calculated the changes in relative intensity of these nodules. T2WI and DWI were classified as hyper-, iso-, or hypointense compared with that of surrounding liver parenchyma. On angiography-assisted CT, the intranodular blood supply in each nodule was classified by CTAP and CTHA into increased (high density), almost the same (iso-density), or decreased (low density) relative to the surrounding liver parenchyma.

Table 2 Protocol for magnetic resonance imaging

	T1-weighted imaging	T2-weighted imaging	Diffusion-weighted imaging
Sequence	3-dimensional gradient echo	Fast spin echo	Spin-echo echo planar
Fat saturation	Positive	Positive	Positive
Repetition time (ms)	3.4–3.6	2000–15,000	7500–12,000
Echo time (ms)	1.6	80–90	64–73
Flip angle (°)	12–15	90	90
Field of view (cm)	42 × 42	40 × 40	40 × 40
Matrix	320 × 192–384 × 256	320 × 224	128 × 160
Section thickness (mm)	4.2	4	6

T1-weighted imaging was acquired during precontrast and each phase of dynamic study including the hepatobiliary phase. T2-weighted and diffusion-weighted imaging were performed after contrast material enhancement. The *b* value for diffusion-weighted imaging was 800 s/mm^2

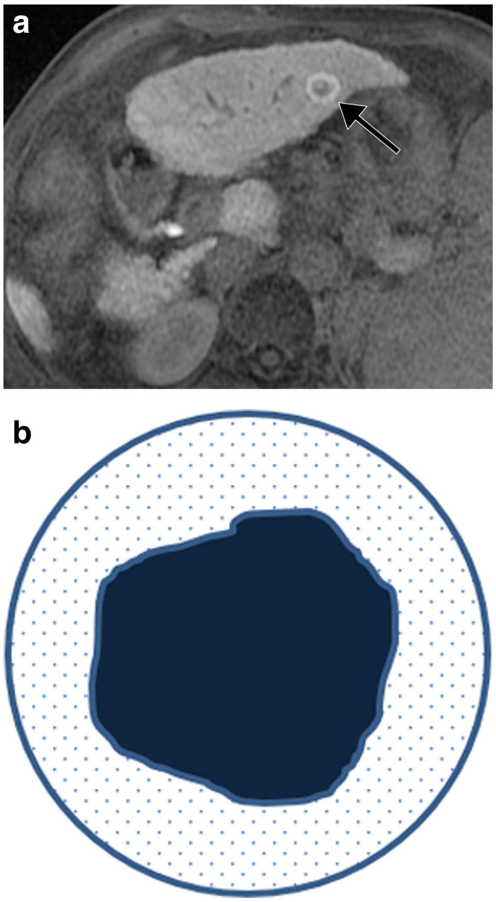

Fig. 1 The hepatobiliary phase of gadoxetic acid-enhanced magnetic resonance imaging findings of doughnut-like hyperintense nodules. A doughnut-like hyperintense nodule can be seen in the lateral segment of the liver (**a**, arrow). The bottom image (**b**) indicates the doughnut-like hyperintense nodule

Pathological examination

The pathological diagnosis was retrieved if available. Histological diagnosis was performed by a board-certified pathologist (Y.S.) in accordance with the criteria outlined by an International Working Party [17].

Follow-up for HBP-doughnut nodules without APHE

To clarify the prognosis of HBP-doughnut nodules without APHE, their malignant transformation to typical hypervascular HCC and change in size were assessed by follow-up dynamic CT and/or MR imaging. When some treatments for coexisted HCC were performed, the nodules were excluded from the assessment.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Statistical analysis was performed using R statistical software version 3.6.0. The Fisher exact test and χ^2 test were conducted to evaluate differences in the frequencies of HBP-doughnut nodules without APHE in liver cirrhosis of varying aetiologies. A p value of < 0.05 was considered to be significant.

Results

Frequency of HBP-doughnut nodules without APHE in cirrhotic liver

Among our cohort of 309 patients, 101 HBP-doughnut nodules without APHE were identified in 18 patients (6%), including 7 in 59 (12%) patients with hepatitis B virus (HBV)-related cirrhosis, 9 in 230 (3.9%) with hepatitis C virus (HCV)-related cirrhosis, and 2 in 33 (6.1%) with alcoholic cirrhosis. There were significant differences in the frequency of HBP-doughnut nodules without APHE among patients with liver cirrhosis of different aetiologies ($p = 0.04$). There were 6.2 ± 5.3 (range 1–20) nodules per patient, and the size of the nodules was 13 ± 4.7 mm (range 8–36 mm) (Table 3).

Changes in relative density of HBP-doughnut nodules without APHE on dynamic CT

One hundred and one HBP-doughnut nodules without APHE were retrospectively analysed by measuring changes in relative density on dynamic CT (Fig. 2a). Sixty-eight (67%) of these nodules could not be identified on dynamic CT (isodensity from precontrast through all enhanced phases) (Fig. 2a and 3a, supplement 1).

Changes in relative intensity on dynamic T1W, T2W, and DWI

The results of EOB-MRI are shown in Fig. 2b. Concerning T1W, on precontrast, hepatic arterial, portal, transitional, and

Table 3 Frequencies and background liver of HBP-doughnut nodules without APHE

Sex Male/female	Age (years) Mean ± SD	Aetiology of liver cirrhosis HCV/HBV/alcohol	Number of nodules Mean ± SD (range)	Size of nodule (mm) Mean ± SD (range)
11 / 7	67 ± 7.9	9 / 7 / 2	6.2 ± 5.3 (1–20)	13 ± 4.7 (8–36)

101 doughnut nodules without APHE were identified in 18/309 (6%) cirrhotic patients

HBP hepatobiliary phase, *APHE* arterial-phase hyperenhancement, *HBV* hepatitis B virus, *HCV* hepatitis C virus

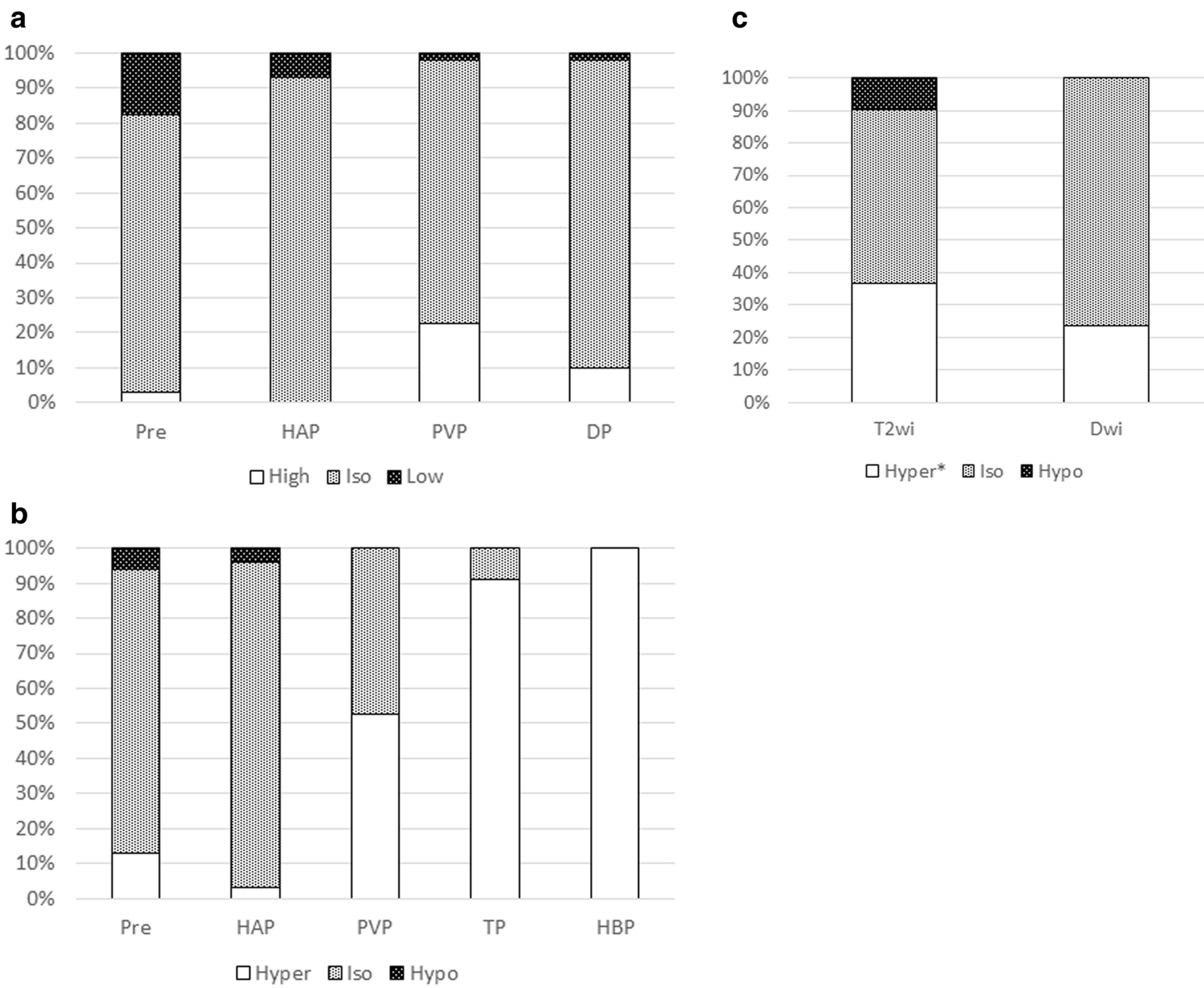

Fig. 2 **a** Changes in relative density of HBP-doughnut nodules without arterial-phase hyperenhancement on dynamic computed tomography. **b** Changes in relative density of HBP-doughnut nodules without arterial-phase hyperenhancement on Gd-EOB-DTPA dynamic MRI. **c** The signal intensities of HBP-doughnut nodules without arterial-phase hyperenhancement on T2-weighted and diffusion-weighted images. * Among HBP-doughnut nodules without APHE that showed hyperintensity on both T2-weighted and diffusion-weighted images, the hyperintensity area was seen in the central part of the nodules. HBP, hepatobiliary phase; APHE, arterial-phase hyperenhancement; CT, computed tomography; EOB-MRI, gadoxetic-acid-enhanced MRI; pre, precontrast; HAP, hepatic arterial phase; PVP, portal venous phase; TP, transitional phase; T2WI, T2-weighted image; DWI, diffusion-weighted image

HBP, 75 of 101 (74%) HBP-doughnut nodules without APHE showed a pattern of either iso-, iso-, hyper-, hyper-, and hyperintensity ($n = 44$) (Figs. 2b and 3b) or iso-, iso-, iso-, hyper-, and hyperintensity ($n = 31$), respectively (Fig. 2b). The remaining 26 nodules demonstrated various patterns, but all these nodules showed a gradual increase of signal intensity ($n = 24$) or hyperintensity throughout all phases ($n = 2$) (supplement 2). The central part of the nodules always appeared hypointense when the periphery part of the nodules showed hyperintensity on portal, transitional, and HBP. On T2WI, these nodules displayed hyperintensity ($n = 37$, 36%), isointensity ($n = 54$, 53%), and hypointensity ($n = 10$, 10%). On DWI, the nodules were hyperintense ($n = 24$, 24%) or isointense ($n = 77$, 76%) (Fig. 2c, supplement 2). Among these nodules that showed hyperintensity on both T2WI and DWI, the hyperintensity was seen in the central part of the nodules (Fig. 3c).

Intranodular blood supply evaluated by angiography-assisted CT

On CTAP, almost the same or increased intranodular portal supply relative to the surrounding liver was seen in 101 HBP-doughnut nodules without APHE. In 93 of 101 (92%) nodules, tiny or slightly dilated distal portal venules at the central portion and distributing toward the periphery of the nodule were identified on CTAP (Fig. 4b). On CTHA, all of the

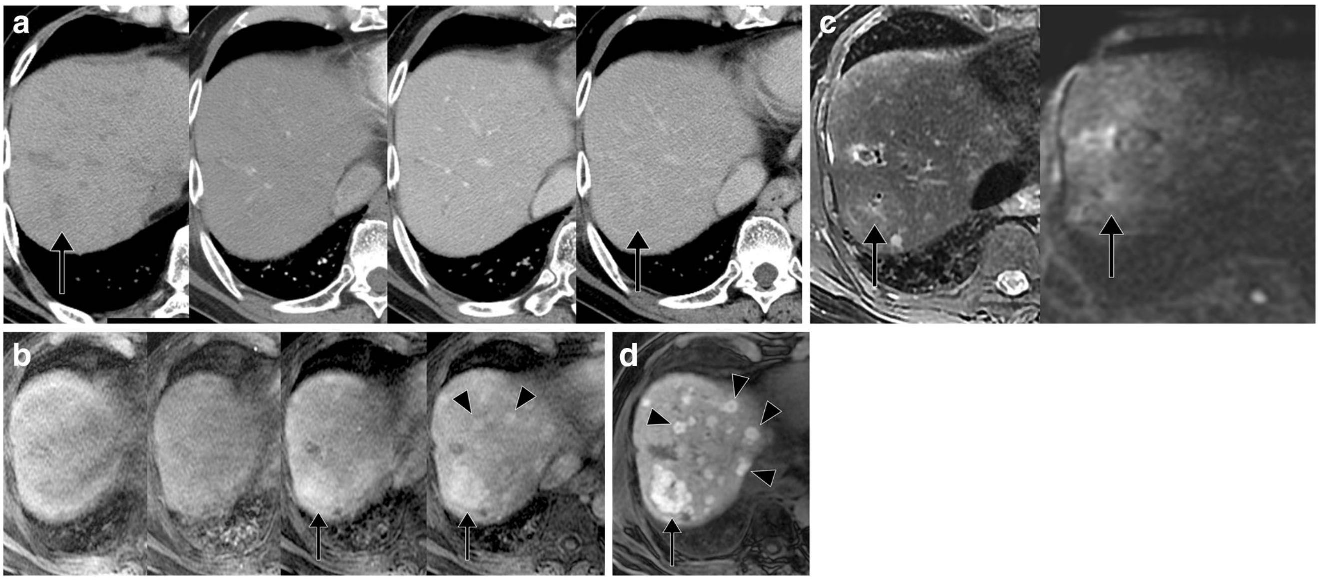

Fig. 3 A representative case of HBP-doughnut nodule without APHE. A 65-year-old male patient with hepatitis-B-virus-related liver cirrhosis. **a** Contrast-enhanced dynamic CT (precontrast, HAP, PVP, and DP: left to right) did not show hepatic nodules. **b** Gd-EOB-DTPA dynamic MRI (precontrast, HAP, PVP, and TP: left to right) demonstrated many nodules without APHE (arrow and arrowheads). These nodules could be visualised in PVP and they were more conspicuous in TP. **c** Fat-suppressed T2-weighted images (left) showed slight hyperintensity in the central area of the largest nodules (arrow). Diffusion-weighted imaging (right) could not demonstrate the nodules. **d** Hepatobiliary phase of EOB-MRI demonstrated doughnut nodules without APHE most clearly (arrow and arrowheads). There were tiny nodules < 8 mm in diameter that were not included in this study. APHE, arterial-phase hyperenhancement; EOB-MRI, gadoxetic-acid-enhanced MRI; HAP, hepatic arterial phase; PVP, portal venous phase; TP, transitional phase

nodules showed the same or decreased intranodular arterial supply compared with the surrounding liver parenchyma.

Pathological features of HBP-doughnut nodules without APHE

Biopsy had been performed on only three lesions, because most nodules were not well depicted by ultrasound. Three nodules were diagnosed by fine needle biopsy as hyperplastic lesions without cellular atypia (Fig. 5). In one patient who underwent surgical resection for coexisting HCC, the nodular lesion could not be identified macroscopically or microscopically.

Follow-up observation of HBP-doughnut nodules without APHE

Seventy-three of 101 (72%) HBP-doughnut nodules without APHE in 14 patients were followed up without any therapy for 1163 ± 902 (range 57–2920) days. Follow-up imaging modalities were dynamic CT in six patients (32 nodules) and EOB-MRI in eight patients (41 nodules). There was no evidence of arterial hypervascularity to suggest malignant transformation (Fig. 6). Four of 93 (4%) nodules showed a slight increase in size (12.3 ± 1.1 to 16.2 ± 0.6). The remaining 69 of the 73 (95%) followed-up nodules either showed no apparent change in size or became undetectable.

Discussion

According to the classification by an International Working Party [14], nodular hepatocellular lesions are divided into regenerative and dysplastic or neoplastic lesions. Regenerative lesions include monoacinar RN, multiacinar RN, and FNH. Diffuse monoacinar RNs without fibrous septa are also called NRH. A monoacinar RN is a regenerative nodule containing no more than one portal tract (1–3 mm in diameter), and a multiacinar RN (also called a large regenerative nodule [LRN]) is a regenerative nodule containing more than one portal tract [14, 18]. When monoacinar or multiacinar RNs are seen in cirrhotic liver, they are called monoacinar or multiacinar cirrhotic nodules, respectively. HBP-doughnut nodules without APHE had some characteristic findings on dynamic CT imaging, namely the enhancement peak is in the portal rather than hepatic arterial phase on dynamic CT with low density on CTHA and iso- to high density on CTAP with visualisation of tiny portal venules at the centre of the nodules indicating portal blood flow as their feeding source. HBP-doughnut nodules without APHE in this study were considered to be regenerative lesions in cirrhotic liver, although multiacinar cirrhotic nodules is a more suitable term regarding their size, based on the fact that RNs are mainly fed by portal veins with minimal contribution from hepatic arteries, and they usually do not show arterial enhancement [19, 20]. In addition to this, in our study, histopathologically confirmed HBP-doughnut nodules without APHE showed histological findings

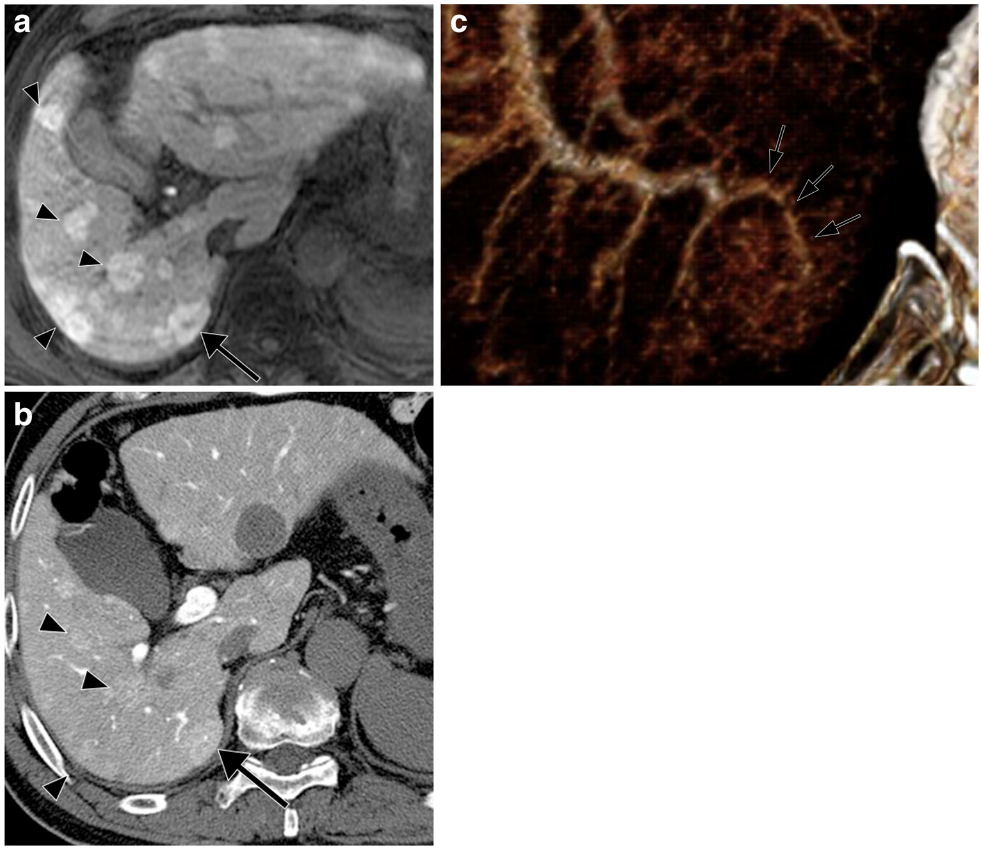

Fig. 4 A 65-year-old male patient with hepatitis-B-virus-related liver cirrhosis. **a** Hepatobiliary phase of gadoxetic-acid-enhanced MRI demonstrated multiple doughnut-like hyperintense nodules in the right and left lobes (arrowheads). **b** On CTAP, there were no portal perfusion defects and some nodules could be identified with relative high density compared with surrounding liver parenchyma (arrowheads). The arrow indicates that the portal branch ran into the centre of the nodule. **c** 3D image generated by CTAP images clearly demonstrated that the peripheral portal branch ran into the centre of the nodule. CTAP, computed tomography during arterial portography. CTAP, CT during arterial portography

compatible with RNs, and they demonstrated no malignant transformation. The reason why they showed hyperintensity on HBP of EOB-MRI compared to the surrounding RNs may be probably due to more hyperplastic change than surrounding monoacinar cirrhotic nodules (RNs) [21].

In this study, HBP-doughnut nodules without APHE were seen in 6% of the patients with cirrhosis. The frequency of the nodules differed significantly among patients with different aetiologies of cirrhosis. Patients with HBV-related cirrhosis had a higher rate of nodules than those with HCV- or alcohol-related cirrhosis. It is known that patients with HBV-related cirrhosis develop larger RNs than those with HCV-related cirrhosis [18, 22], probably due to less persistent inflammatory changes in the former. Some of such larger RNs may progress to larger HBP-doughnut nodules; however, the real mechanism of HBP-doughnut nodules remained unclear because of the limited pathologic specimens in this study. Furthermore, the small sample size in HBV- or alcohol-related cirrhosis may lead to statistical error so that further study is needed to validate this issue.

There are a few reports describing hepatocellular nodules similar to our present HBP-doughnut nodules without APHE under the term ‘RNs’ [12, 23], ‘large RNs (LRNs)’ [10], ‘hepatic hyperplastic nodules’ [24] and ‘NRH’ [25]. The reason why there are only rare reports of this kind of hypovascular hepatocellular nodule may be that they are often undetectable by conventional imaging modalities, except for EOB-MRI, and their histological diagnosis is uncertain, especially by biopsy. Yamamoto et al reported a case of hepatic hyperplastic nodules visualised as enhanced nodules on CTAP in IPH patients [24]. The vasculature of the nodules was similar to that of the nodules in our study, with wheel-spoke-like spread of portal branches from the centre of the nodules. It was also similar to the X-ray appearance of liver with NRH after portal vein injection of radiopaque latex and nodular areas reported by Wanless et al [26]. As mentioned above, NRH is defined as diffuse monoacinar RNs without fibrous septa and its blood supply is similar to that of multiacinar cirrhotic nodules. It is hypothesised that the pathological mechanisms for the formation of hyperplastic nodules may be related to inhomogeneously impaired intrahepatic portal blood flow [26].

Gentilucci et al reported a case of LRNs (multiacinar RN in non-cirrhotic liver) in non-cirrhotic portal hypertension in which multiple hypovascular nodules with doughnut-like hyperintensity in the HBP of EOB-MRI were seen [10]. Sugimori et al reported the imaging features of RNs in various chronic hepatic diseases using EOB-MRI and contrast-enhanced ultrasonography [12]. They revealed that the central vascular structure (both hepatic artery and portal vein) and doughnut-like hyperintensity in the HBP were characteristic findings of RNs. In their study, the mean maximum diameter of the RNs was 14.8 mm, which was large for common RNs seen in

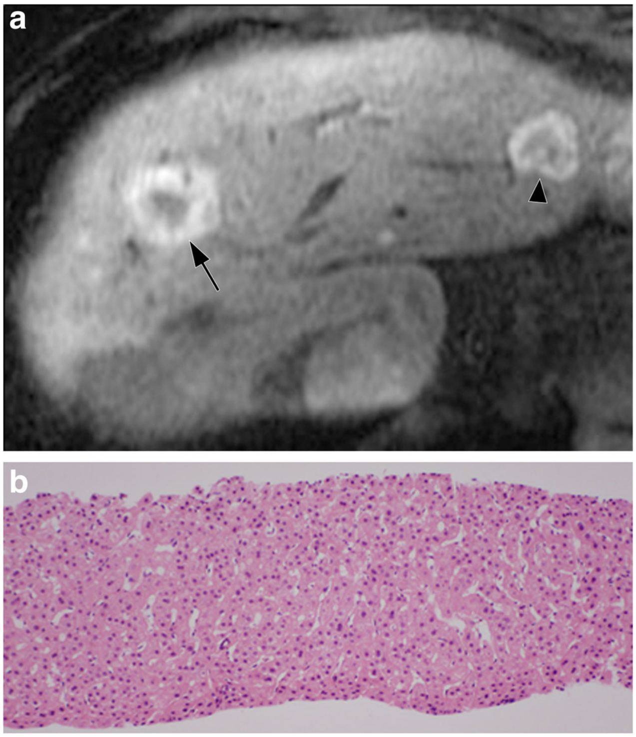

Fig. 5 A 60-year-old male patient with alcohol-related liver cirrhosis without hepatocellular carcinoma. **a** Hepatobiliary phase of gadoxetic-acid-enhanced MRI demonstrated doughnut-like hyperintense nodules in segment 4 (arrow) and segment 2 (arrowhead). **b** The pathological specimen obtained by fine needle biopsy from the nodule in segment 4 showed hyperplastic change without cellular atypia and slightly dilated hepatic sinusoids (haematoxylin and eosin stain). Neither nodule showed malignant transformation after 416 days' follow-up

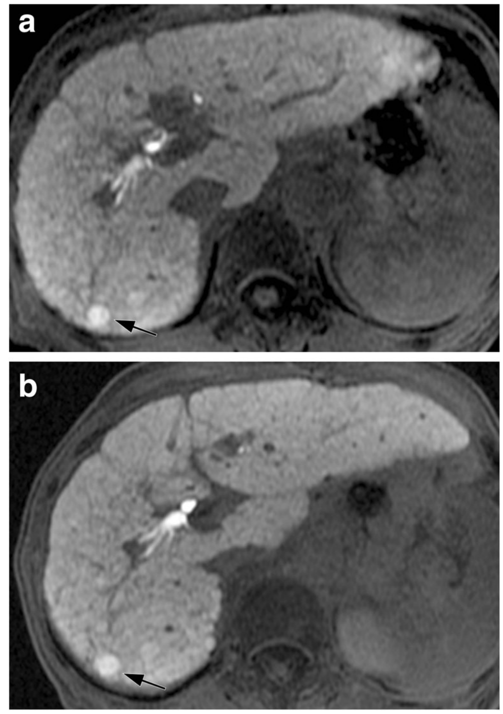

Fig. 6 A 60-year-old female patient with hepatitis-C-virus-related liver cirrhosis. The hepatobiliary phase of EOB-MRI demonstrated a peripherally hyperintense nodule (arrow) with a scar-like area in segment 7. **b** After 2466 days, EOB-MRI demonstrated no arterial hypervascularisation and no growth in size (arrow). EOB-MRI, gadoxetic-acid-enhanced MRI

chronic liver diseases. These imaging features are the same as those of the nodules in our study; thus, they can be considered to be the same entity. As mentioned above, multiacinar cirrhotic nodules may be the most suitable term for these nodules in cirrhotic liver based on the classification of an International Working Party [14].

It is important to ascertain what is the central hypointense area in the HBP of EOB-MRI. Fujiwara et al reported a case of FNH showing ring-like enhancement in the HBP of EOB-MRI and correlated EOB-MRI and pathological findings using immunohistochemistry for OATP1B3 [5]. Although the peripheral hyperintense area in the HBP was well correlated with the area showing OATP1B3 expression, the central area of FNH, including scar and surrounding hyperplastic hepatocytes, did not always show OATP1B3 expression [27]. Thus, we consider that the central hypointense area in the nodules in our study may have arisen from a similar mechanism to that of FNH which is fed by the hepatic artery. Unfortunately, we could not conclude this issue because we could not correlate the EOB-MRI findings with the histopathological findings.

There are some hepatocellular nodules showing hyperintensity on the HBP, including some RNs in the cirrhotic liver [21], FNH [5], low-grade dysplastic nodules (up to 20% of nodules may show hyperintensity) [6], some HCCs [7], and some hepatocellular adenomas (β-catenin mutated subtype) [8, 9]. Ten to 15% of HCCs can be demonstrated as hyperintense in the HBP [28, 29], because of intense uptake of Gd-EOB-DTPA secondary to overexpression of OATP1B3 [30]. According to previous reports, the majority of HCCs showing hyperintensity on HBP demonstrate a different arterial enhancement from the nodules in this study. In addition, doughnut-like hyperintensity in the HBP of EOB-MRI is extremely atypical in HCCs [31]. Differentiation from FNH is also possible by definite enhancement of FNH on the arterial phase of dynamic CT/MRI in spite of similar doughnut-like hyperintensity on HBP [32]. FNH-like nodules arising in Budd–Chiari syndrome are also reported to show doughnut-like hyperintensity on the HBP of EOB-MRI [33], but they also demonstrate enhancement on the arterial phase. Some RNs and low-grade DNs may show hyperintensity on HBP without enhancement on the arterial phase, and their differentiation from the doughnut nodules in this study is difficult when the size of the nodule is small. However, the differentiation between low-grade DN and LRN is difficult or impossible even by the specialised pathologists [17]. There might be significant overlap between RNs, LRNs, low-grade DNs, and the doughnut nodules in this study in cirrhotic livers, but we think that the precise distinction among them is not clinically important.

As HBP-doughnut nodules without APHE, probable multiacinar cirrhotic nodules, are common, it is important for radiologists to know about this entity for correct image interpretation.

Our study had some limitations. First, pathological diagnosis was available in only a limited number of cases. However, there was convincing evidence of benignity on the basis of follow-up imaging and clinical findings. Second, there was patient selection bias. We enrolled patients who underwent EOB-MRI, dynamic CT, CTAP, and CTHA, but this cohort was far from representative of the normal population. This was for the purpose of elucidating the vascular structure of HBP-doughnut nodules without APHE.

In conclusion, HBP-doughnut nodules without APHE in cirrhotic liver were not infrequently seen in our study. We found that they were supplied by portal venous flow and showed no malignant transformation. Thus, we considered these nodules could be accurately named ‘multiacinar cirrhotic nodules’.

Acknowledgements We thank Cathel Kerr, Ph.D., and Libby Cone, M.D., M.A., from Edanz Group (www.edanzediting.com/ac) for editing drafts of this manuscript.

Funding This study has not received any funding.

Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Toshifumi Gabata, M.D., Ph.D.

Conflict of interest The authors declare that they have no competing interests.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Approval was obtained from the Institutional Review Board of Kanazawa University Graduate School of Medical Sciences, Japan.

Methodology
• retrospective
• observational
• performed at one institution

References

1. Tanimoto A, Kuwatsuru R, Kadoya M et al (1999) Evaluation of gadobenate dimeglumine in hepatocellular carcinoma: results from phase II and phase III clinical trials in Japan. J Magn Reson Imaging 10:450–460
2. Motosugi U, Ichikawa T, Sou H et al (2009) Liver parenchymal enhancement of hepatocyte-phase images in Gd-EOB-DTPA-enhanced MR imaging: which biological markers of the liver function affect the enhancement? J Magn Reson Imaging 30:1042–1046
3. Goodwin MD, Dobson JE, Sirlin CB, Lim BG, Stella DL (2011) Diagnostic challenges and pitfalls in MR imaging with hepatocyte-specific contrast agents. Radiographics 31:1547–1568
4. Suh YJ, Kim MJ, Choi JY, Park YN, Park MS, Kim KW (2011) Differentiation of hepatic hyperintense lesions seen on gadoxetic acid-enhanced hepatobiliary phase MRI. AJR Am J Roentgenol 197:W44–W52
5. Fujiwara H, Sekine S, Onaya H, Shimada K, Mikata R, Arai Y (2011) Ring-like enhancement of focal nodular hyperplasia with hepatobiliary-phase Gd-EOB-DTPA-enhanced magnetic resonance imaging: radiological-pathological correlation. Jpn J Radiol 29:739–743
6. Kobayashi S, Matsui O, Gabata T et al (2012) Intranodular signal intensity analysis of hypovascular high-risk borderline lesions of HCC that illustrate multi-step hepatocarcinogenesis within the nodule on Gd-EOB-DTPA-enhanced MRI. Eur J Radiol 81:3839–3845
7. Kitao A, Matsui O, Yoneda N et al (2011) The uptake transporter OATP8 expression decreases during multistep hepatocarcinogenesis: correlation with gadoxetic acid enhanced MR imaging. Eur Radiol 21:2056–2066
8. Yoneda N, Matsui O, Kitao A et al (2012) Beta-catenin-activated hepatocellular adenoma showing hyperintensity on hepatobiliary-phase gadoxetic-enhanced magnetic resonance imaging and overexpression of OATP8. Jpn J Radiol 30:777–782
9. Fukusato T, Soejima Y, Kondo F et al (2015) Preserved or enhanced OATP1B3 expression in hepatocellular adenoma subtypes with nuclear accumulation of β-catenin. Hepatol Res 45:E32–E42
10. Gentilucci UV, Gallo P, Perrone G et al (2011) Non-cirrhotic portal hypertension with large regenerative nodules: a diagnostic challenge. World J Gastroenterol 17:2580–2584
11. Hayano S, Naganuma A, Okano Y et al (2016) A case of idiopathic portal hypertension associated with nodular regenerative hyperplasia-like nodule of the liver and mixed connective tissue disease. Nihon Shokakibyo Gakkai Zasshi 113:828–836
12. Sugimori K, Numata K, Okada M et al (2017) Central vascular structures as a characteristic finding of regenerative nodules using hepatobiliary phase gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid-enhanced MRI and arterial dominant phase contrast-enhanced US. J Med Ultrason (2001) 44:89–100
13. Di Martino M, Anzidei M, Zaccagna F et al (2016) Qualitative analysis of small (</=2 cm) regenerative nodules, dysplastic nodules and well-differentiated HCCs with gadoxetic acid MRI. BMC Med Imaging 16:62
14. International Working Party (1995) Terminology of nodular hepatocellular lesions. Hepatology 22:983–993
15. Kitao A, Zen Y, Matsui O, Gabata T, Nakanuma Y (2009) Hepatocarcinogenesis: multistep changes of drainage vessels at CT during arterial portography and hepatic arteriography-radiologic-pathologic correlation. Radiology 252:605–614
16. Mohajer K, Frydrychowicz A, Robbins JB, Loeffler AG, Reed TD, Reeder SB (2012) characterisation of hepatic adenoma and focal nodular hyperplasia with gadoxetic acid. J Magn Reson Imaging 36:686–696
17. International Consensus Group for Hepatocellular Neoplasia (2009) Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia. Hepatology 49:658–664
18. Ferrell LD, Kakar S, Terracciano LM, Wee A (2017) Chap 13. Tumours and tumour-like lesions of the liver, 7 edn. Elsevier
19. Watanabe A, Ramalho M, AlObaidy M, Kim HJ, Velloni FG, Semelka RC (2015) Magnetic resonance imaging of the cirrhotic liver: an update. World J Hepatol 7:468–487
20. Krinsky GA, Lee VS (2000) MR imaging of cirrhotic nodules. Abdom Imaging 25:471–482

21. Hanna RF, Aguirre DA, Kased N, Emery SC, Peterson MR, Sirlin CB (2008) Cirrhosis-associated hepatocellular nodules: correlation of histopathologic and MR imaging features. Radiographics 28: 747–769
22. Shimamatsu K, Kage M, Nakashima O, Kojiro M (1994) Pathomorphological study of HCV antibody-positive liver cirrhosis. J Gastroenterol Hepatol 9:624–630
23. Husainy MA, Sayyed F, Peddu P (2017) Typical and atypical benign liver lesions: a review. Clin Imaging 44:79–91
24. Yamamoto T, Sugimoto H, Takahashi N, Isobe Y (2006) Hepatic hyperplastic nodules showing stains by portal blood flow: hemodynamics revealed by CTAP and CTHA. Abdom Imaging 31:65–68
25. Yoneda N, Matsui O, Kitao A et al (2016) Benign hepatocellular nodules: hepatobiliary phase of gadoxetic acid-enhanced MR imaging based on molecular background. Radiographics 36:2010–2027
26. Wanless IR, Solt LC, Kortan P, Deck JH, Gardiner GW, Prokipchuk EJ (1981) Nodular regenerative hyperplasia of the liver associated with macroglobulinemia. A clue to the pathogenesis. Am J Med 70: 1203–1209
27. Yoneda N, Matsui O, Kitao A et al (2012) Hepatocyte transporter expression in FNH and FNH-like nodule: correlation with signal intensity on gadoxetic acid enhanced magnetic resonance images. Jpn J Radiol 30:499–508
28. Kitao A, Matsui O, Yoneda N et al (2015) Hepatocellular carcinoma with β-catenin mutation: imaging and pathologic characteristics. Radiology:141315
29. Kitao A, Matsui O, Yoneda N et al (2012) Hypervascular hepatocellular carcinoma: correlation between biologic features and signal intensity on gadoxetic acid-enhanced MR images. Radiology 265: 780–789
30. Kitao A, Zen Y, Matsui O et al (2010) Hepatocellular carcinoma: signal intensity at gadoxetic acid-enhanced MR imaging–correlation with molecular transporters and histopathologic features. Radiology 256:817–826
31. Kitao A, Matsui O, Yoneda N et al (2018) Differentiation between hepatocellular carcinoma showing hyperintensity on the hepatobiliary phase of gadoxetic acid–enhanced MRI and focal nodular hyperplasia by CT and MRI. AJR Am J Roentgenol 211:1–11
32. Galia M, Taibbi A, Marin D et al (2014) Focal lesions in cirrhotic liver: what else beyond hepatocellular carcinoma? Diagn Interv Radiol 20:222–228
33. Newerla C, Schaeffer F, Terracciano L, Hohmann J (2012) Multiple FNH-like lesions in a patient with chronic Budd-Chiari syndrome: Gd-EOB-enhanced MRI and BR1 CEUS findings. Case Rep Radiol 2012:685486