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Pathological variants of hepatocellular carcinoma on MRI: emphasis on histopathologic correlation

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Abstract

Hepatocellular carcinoma (HCC) is a unique tumor because it is one of the few cancers which can be treated based on imaging alone. Magnetic resonance imaging (MRI) carries higher sensitivity and specificity for the diagnosis of HCC than either computed tomography (CT) or ultrasound. MRI is imaging modality of choice for the evaluation of complex liver lesions and HCC because of its inherent ability to depict cellularity, fat, and hepatocyte composition with high soft tissue contrast. The imaging features of progressed HCC are well described. However, many HCC tumors do not demonstrate classical imaging features, posing a diagnostic dilemma to radiologists. Some of these can be attributed to variations in tumor biology and histology, which result in radiological features that differ from the typical progressed HCC. This pictorial review seeks to demonstrate the appearance of different variants of HCC on MRI imaging, in relation to their histopathologic features.

Key words: Hepatocellular carcinoma—Atypical—MRI—Histopathology

Hepatocellular carcinoma (HCC) is the fifth most common adult cancer and the second leading cause of cancer-related death globally [1]. In Asia, the incidence of HCC is higher than the global average due to the increased prevalence of Hepatitis B and to some extent, Hepatitis C [2].

HCC is one of the few cancers that can be diagnosed on imaging and treated without the need for histological confirmation. The unique enhancement features of HCC have been attributed to the tumor having a large proportion of its volume composed of vascular spaces [3], its arterial supply coming from an unpaired hepatic artery and lacking portal venous supply. Several working groups and societies have developed consensus statements to define the criteria for the imaging diagnosis of HCC. As per the guidelines by the American Association for the Study of Liver Diseases (AASLD), the diagnosis of HCC can only be made in at-risk patients (patients with liver cirrhosis and chronic hepatitis B or C) if the nodule is greater than 1 cm in size, and shows arterial phase hyperenhancement and washout appearance in either the portal venous phase or delayed phase [4]. Once these criteria have been met, treatment for the tumor can commence without the need for histological confirmation. The rationale for this is because the findings of concomitant arterial hyperenhancement and washout appearance of a nodule in at-risk patients yield sufficiently high specificity for the diagnosis of HCC with a high positive predictive value close to 100%, as well as a low negative predictive value, particularly in the setting of liver transplant prioritization [5, 6].

Several other working groups have developed guidelines, and these are usually influenced by factors related to the prevalence of HCC in their community or local healthcare delivery systems [7–11]. The highest age-adjusted incidence rates of HCC (> 20/100,000) are seen in East Asia and sub-Saharan Africa [12]. Approximately 75% of liver cancers occur in Asia [13]. As such, diagnostic guidelines in Asia are tailored to be more sensitive in the detection of HCC. For example, the Asian Pacific Association for the Study of the Liver (APASL) 2017 guidelines for the diagnosis of HCC states that typical HCCs can be diagnosed on imaging regardless of size, so long as the typical vascular pattern (arterial hyperenhancement and portal venous phase washout appearance) is observed. The guidelines also recommend the routine use of Gadoxetic Acid (Primovist, Bayer) enhanced MRI in the work-up of liver nodules detected on ultrasound. Furthermore, the APASL guidelines state

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that arterially hyperenhancing lesions which demonstrate a defect in the hepatobiliary phase can be diagnosed as HCC on imaging, even if the washout appearance is absent [14]. This contrasts with guidelines in the western hemisphere such as the Liver Imaging Reporting and Data System (LI-RADS) where hepatobiliary phase hypointensity is not considered a major criterion in the diagnosis of HCC.

With the increased use of hepatobiliary specific MRI contrast agents and multiparametric MRI sequences, MRI of the liver has become the modality of choice in the evaluation of patients suspected to have HCC in many centers around the world. However, the surge in MRI use has not completely ameliorated the limitations of diagnosis with imaging. 87% of well-differentiated lesions and 41%–62% of lesions smaller than 2 cm showed either absence of arterial hypervascularity, venous washout, or both [15]. Furthermore, unique histological subtypes present with atypical morphological and enhancement features. This article aims to show the imaging features of pathological variants of HCC and correlate these non-classic lesions to their histological features.

Progressed HCC

Imaging features

Progressed HCCs demonstrate the classical pattern of arterial phase hyperenhancement and washout appearance during the portal venous and delayed phases which most radiologists are familiar with (Fig. 1). 'Arterial hyperenhancement' is defined as either part of, or the entire tumor showing increased signal intensity compared to the surrounding liver parenchyma during the late arterial phase. 'Washout appearance' is defined as part of, or the entire tumor showing temporal reduction in enhancement from an earlier to later phase, with reduced signal intensity compared to the surrounding liver parenchyma during extracellular phases. Another feature that is frequently seen in progressed HCC is the presence of an enhancing 'capsule' appearance. This is described in LI-RADS as a smooth, uniform, sharp border around most, or all of a lesion, is unequivocally thicker or more conspicuous than fibrotic tissue around background nodules, and is visible as an enhancing rim in the portal venous, delayed, or transitional phases [16]. In a recent study evaluating the performance of major and ancillary features of LI-RADS in 275 observations, the 'capsule' appearance was shown to have a high specificity (98.8%) and positive predictive value (97.1%) for HCC [17].

Histopathological features

HCC is believed to develop via stepwise carcinogenesis within the cirrhotic liver. Low-grade dysplastic nodules (LGDN) within the liver contain intra-tumoral portal tracts which comprise each of a hepatic arteriole and a portal venule. These are termed 'paired hepatic arterioles.' Progressive carcinogenesis within LGDNs results in transformation into a high-grade dysplastic nodule (HGDN) and eventually into nodules of progressed HCC [18–21].

As cellular atypia develops within the dysplastic nodule, there is gradual loss of the intra-tumoral portal tracts and increased formation of unpaired hepatic arterioles from the hepatic artery [22]. This process of neovascularisation causes an increase in the proportion of the intra-vascular space and corresponding decrease in

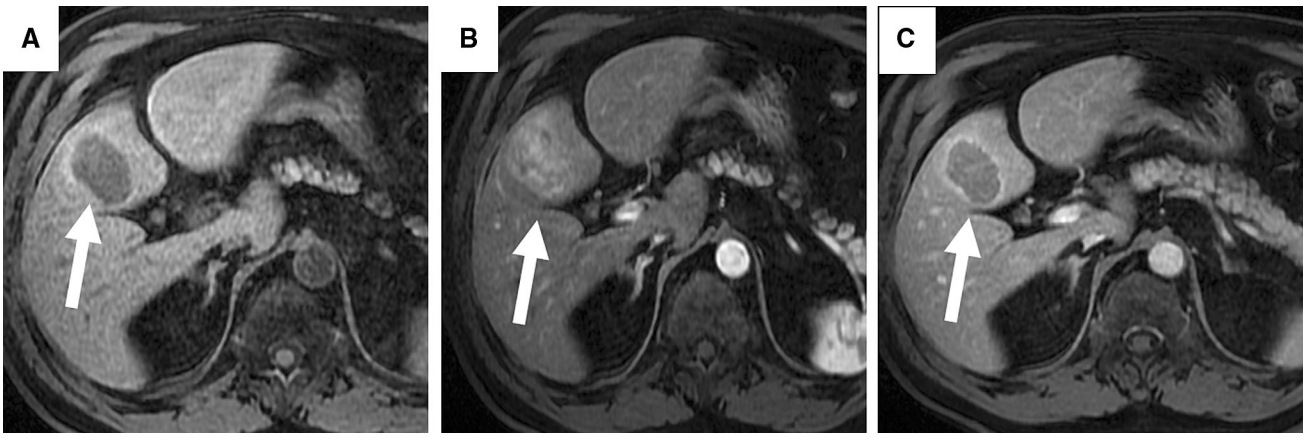

Fig. 1. Large T1 hypointense mass (arrowed) on the pre-contrast phase (**A**) with characteristic arterial phase hyperenhancement (**B**), washout appearance in the equilibrium phase (**C**) in a patient with chronic hepatitis B. These findings have become *sine qua non* for radiological diagnosis for HCC. Arterial phase hyperenhancement and washout appearance in distinctly nodular lesions are referred to as "progressed HCC" by the International Consensus Group for Hepatocellular Neoplasms. Histology revealed moderately differentiated HCC. Note also the presence of an enhancing 'capsule' appearance that is well seen in the equilibrium phase. The 'capsule' appearance is highly specific for progressed HCC.

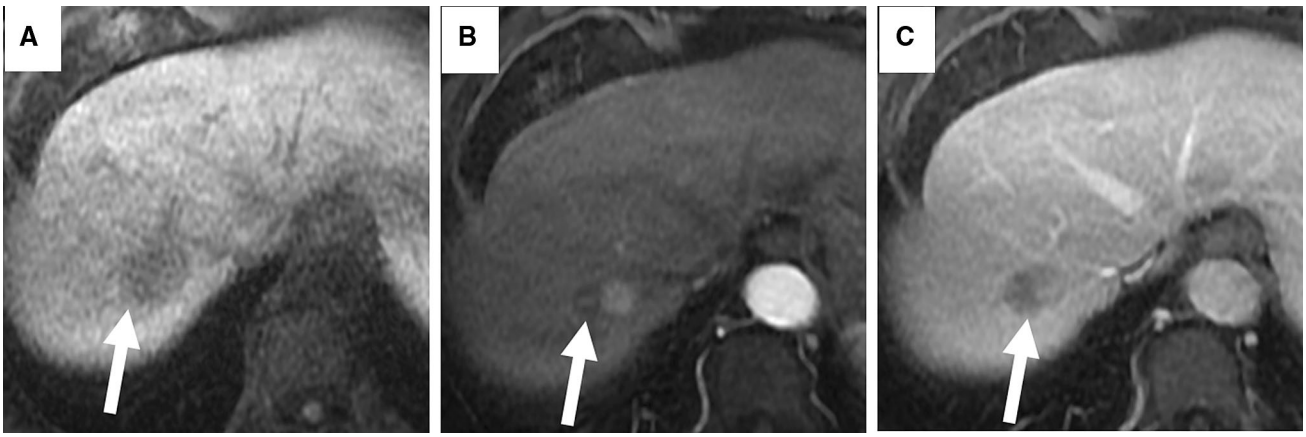

Fig. 2. **A** MRI depicts a T1 hypointense lesion in segment 7 of the liver in a Hepatitis B carrier. The nodular, medial component of lesion (arrowed) demonstrated arterial enhancement (**B**), washout appearance (**C**). The lateral component of the lesion remained hypointense without typical enhancement. This appearance has been termed as the 'nodule-within-nodule' appearance, where part of a dysplastic nodule undergoes malignant transformation into HCC, thereafter showing typical imaging features.

interstitial space within the nodule when compared with the background liver tissues [3], hence accounting for the phenomenon of arterial hyperenhancement. Conversely, the progressive loss of portal venules within the nodule during hepatocarcinogenesis accounts for the washout appearance in the portal venous and delayed phases [22]. Histologically, low-grade dysplastic nodules resemble cirrhotic nodules in that the hepatocytes do not show cellular atypia or architectural distortion [18, 22] in contrary to progressed HCCs, which demonstrate cellular atypia, stromal invasion, and vascular invasion.

The aforementioned 'capsule' appearance is a histopathologic feature of progressed HCC with expansile growth. The 'capsule' appearance does not necessarily refer to the presence of a true fibrous capsule, but may comprise fibrous tissue, prominent sinusoids, or compressed liver parenchyma [16].

Clinical significance

As highlighted earlier, the pathogenesis of HCC follows a stepwise process of malignant transformation, where regenerative nodules in a cirrhotic liver undergo progressive transformation into LGDN, HGDN, and eventually nodules of HCC. Most dysplastic nodules or well-differentiated HCC may show increased T1-weighted signal due to the presence of paramagnetic substances such as copper, zinc, and other metalloproteins [23]. Dysplastic nodules do not show arterial hyperenhancement. Furthermore, not all well-differentiated HCC nodules show arterial enhancement. Indeed, a study by Li et al. showed that only 47% of well-differentiated HCCs showed hyperenhancement in the arterial phase [24]. Hence, in the context of the cirrhotic liver, nodules which do not show enhancement should still be carefully observed on follow-up imaging as these nodules may represent dysplastic nodules or well-differentiated HCC which could eventually develop into a progressed HCC.

Occasionally, part of a dysplastic nodule may undergo malignant transformation into a HCC. This results in a 'nodule within a nodule' appearance on imaging, when only a component of the nodule shows arterial hyperenhancement and washout appearance while the rest of the nodule shows features of a dysplastic nodule (Fig. 2).

MRI imaging with hepatobiliary contrast agents

Hepatocyte-specific, gadolinium-based (hepatobiliary) contrast agents are increasingly being used in MRI studies of the liver. These agents are taken up and excreted by the hepatocytes of the liver via the Organic Anion-Transporting Polypeptide (OATP) group of molecules (in particular, OATP8) and Multidrug resistance-associated proteins (MRP)-2, respectively [25, 26]. The hepatobiliary phase is obtained 10–20 min after contrast injection with gadoxetic acid (Gd-EOB-DTPA, Primovist in Europe and Asia; Eovist in the USA, Bayer) or between 60 and 120 min in the case of gadolinium ethoxybenzyl dimeglumine (MultiHance, Bracco). This phase depicts maximal enhancement of the liver parenchyma before the contrast agent is fully excreted out into the biliary tract.

In the hepatobiliary phase, malignant lesions which do not contain normal, functioning hepatocytes such as metastases, cholangiocarcinomas, and HCC (Fig. 3), are not expected to take up the contrast agent and will therefore show up as a hypointense defect against a background of hyperintense liver parenchyma.

Unfortunately, this technique lacks specificity in that benign lesions such as haemangiomas, liver cysts, and

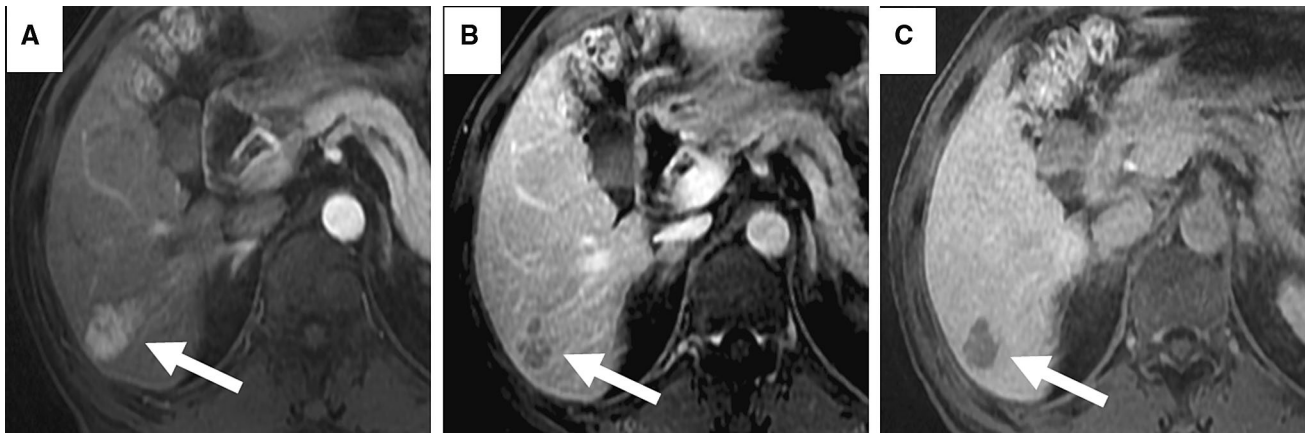

Fig. 3. Mass in segment 6 of the liver (arrowed) of this patient with Hepatitis B shows arterial hyperenhancement (**A**) and washout appearance in the portal venous phase (**B**). Intravenous Multihance was used as a contrast agent for this study and the hepatobiliary phase (**C**) taken at 90-min post-contrast injection showed a corresponding defect where tumor is located. Note that rest of liver shows hyperintensity due to uptake of contrast agent by normal, functioning hepatocytes. Histology confirmed HCC.

certain types of hepatic adenomas (Fig. 4) will also show up as a defect during the hepatobiliary phase as these lesions do not contain any normal, functioning hepatocytes. Conversely, other benign lesions such as focal nodular hyperplasia (FNH) or nodular regenerative hyperplasia (NRH) contain normal functioning hepatocytes and will present as hyperintense lesions during the hepatobiliary phase (Fig. 5). Note, however, that benign lesions such as FNH or hepatic adenomas are rare occurrences in the cirrhotic liver and that they remain a diagnosis of exclusion in at-risk patients because their imaging features can overlap with HCC.

Expression of OATP8 molecules is low in progressed HCCs [26–29]. Occasionally, moderately differentiated and even less frequently, well-differentiated HCCs tumors show uptake of contrast during the hepatobiliary phase which can pose a conundrum to radiologists (Fig. 6) [22, 30]. It has been variably reported that 9%–20% of HCCs gadoxetic acid [31–34], likely due to overexpression of OATP8. It is postulated that the overexpression of OATP8 in these tumors may be due to a different cell of origin or genomic alterations during hepatocarcinogenesis [27, 35–37]. In a more recent study by Kim et al. [30], in the presence of gadoxetic acid uptake in liver nodules, the washout appearance on PV phase remains indicative of HCC. A smooth hypointense rim on the hepatobiliary phase, that corresponds to the region of 'capsule' enhancement on the portal venous and transitional phase, further increases sensitivity while preserving specificity (Fig. 6) [38].

Early HCC

Imaging features

An international consensus in 2009 defined small HCCs as nodules of HCC which are smaller than 2 cm in size [18]. Small HCCs can be further divided into either early HCC and progressed HCC. Small early HCCs usually have a vaguely nodular appearance and are often well differentiated. Conversely, small progressed HCCs are distinctly nodular, mostly moderately differentiated, and shows microvascular invasion [18].

Small early HCCs are considered a precursor to progressed HCCs [39]. As would be expected, small early HCCs have an ill-defined appearance with indistinct margins. A tumor capsule is absent. In terms of enhancement kinetics, small progressed HCCs show arterial phase hyperenhancement. Small early HCCs do not show arterial hyperenhancement or washout appearance as they lie within the earlier stages of neoangiogenesis.

As such, early HCCs are usually hypovascular, showing either hypoenhancement or isoenhancement relative to the liver parenchyma during the arterial phase (Fig. 7). Nonetheless, these early HCCs present as hypointense lesions during the hepatobiliary phase, postulated to be secondary from earlier loss of expression of OATP receptors in relation to rise in unpaired arterioles [40]. In addition, early HCCs may also show signal loss in the opposed-phase images due to small amounts of fat [41].

Histopathological features

Histologically, stromal invasion is seen in early HCCs, as opposed to high-grade dysplastic nodules where this feature is distinctly absent. However, early HCCs lack the vascular invasion which is seen in progressed HCC. Small progressed HCCs are usually moderately differentiated HCCs and consequently show arterial hyperenhancement because they have a high density of unpaired hepatic arterioles. However, as mentioned above, small early HCCs do not show arterial hyperen-

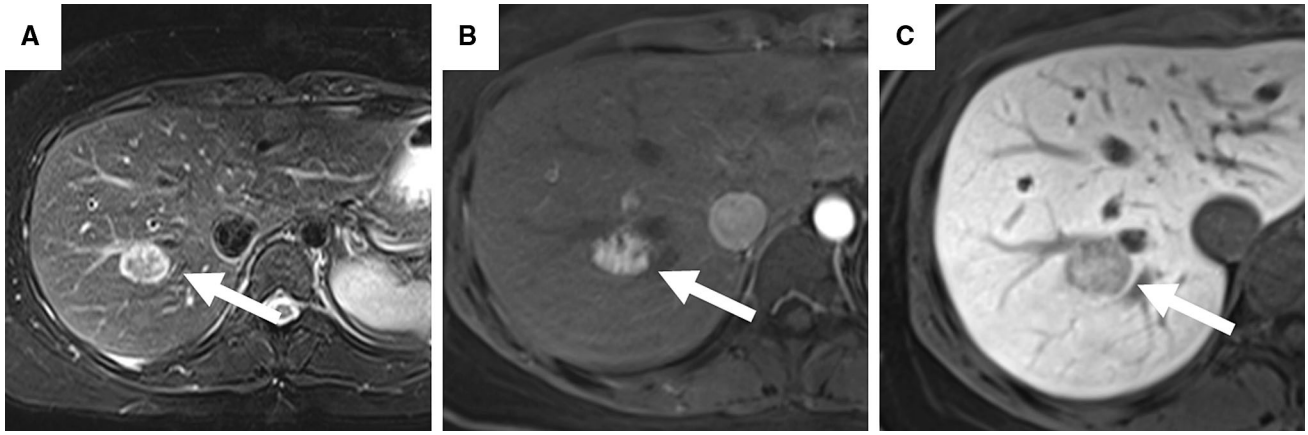

Fig. 4. Contrast-enhanced MRI with gadoxetic acid (Primovist) performed on a 30-year-old female patient with no risk factors for HCC development showed a mass in segment 7 of the liver (arrowed). The mass showed intense T2 hyperintensity (**A**). Note that the mass showed intense, heterogeneous arterial enhancement (**B**) and washout appearance in the transitional phase (not shown). The mass appeared hypointense on hepatobiliary phase, indicating the absence of functioning hepatocytes (**C**). Biopsy revealed hepatic adenoma. The profound T2 hyperintensity suggests an inflammatory subtype.

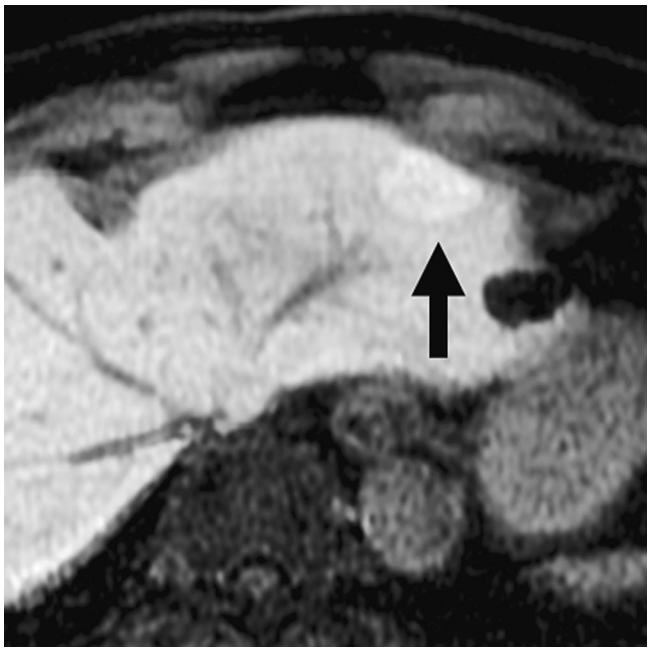

Fig. 5. Contrast-enhanced MRI with gadoxetic acid (Primovist) demonstrates a nodule (arrow) in segment 3/4A of the liver which shows persistent uptake of during the hepatobiliary phase in a patient with Hepatitis B. Histology confirmed focal nodular hyperplasia.

hancement as they are in the earlier stages of neoangiogenesis.

Conversely, small early HCCs are hypovascular, primarily because of the reduced density of both paired and unpaired hepatic arterioles during the initial stages of hepatocarcinogenesis [42]. Early HCC do not usually take up gadoxetic acid during the hepatobiliary phase because reduced OATP expression takes place prior to arterial neovascularisation from the unpaired hepatic arteriole [22, 27, 28].

Clinical significance

Early HCCs have excellent prognosis and vascular invasion is exceptionally rare. As alluded to earlier, small early HCCs are hypovascular during the arterial phase. As such, these lesions may be dismissed as a dysplastic nodule by the inexperienced radiologist. However, in the at-risk patient, nodules which are hypointense on hepatobiliary phase should be carefully scrutinized with meticulous analysis of other MRI sequences. Hypovascular lesions between 1 and 2 cm which show increased T2 signal and restricted diffusion should raise suspicion for small, early HCC. Intra-voxel fat can be present, but this finding is not specific as it can also be found in dysplastic nodules. Importantly, early HCC are usually hypointense in the hepatobiliary phase while dysplastic nodules are usually isointense or slightly hypointense.

Infiltrative HCC

Imaging features

Macroscopically, most HCC present as discrete nodules or masses. However, innumerable nodules of HCC may be seen to spread throughout the hepatic lobe or the entire liver. This appearance has been termed as 'infiltrative HCC.' As the name suggests, this form of HCC can potentially have a geographic, ill-defined appearance, rather than present as a rounded mass. At times, the tumors may also appear to have a segmental appearance (Fig. 8). Infiltrative HCC accounts for 7%–20% of HCC cases. It has also been described as diffuse HCC, cirrhoto-mimetic HCC, or cirrhosis-like HCC [43].

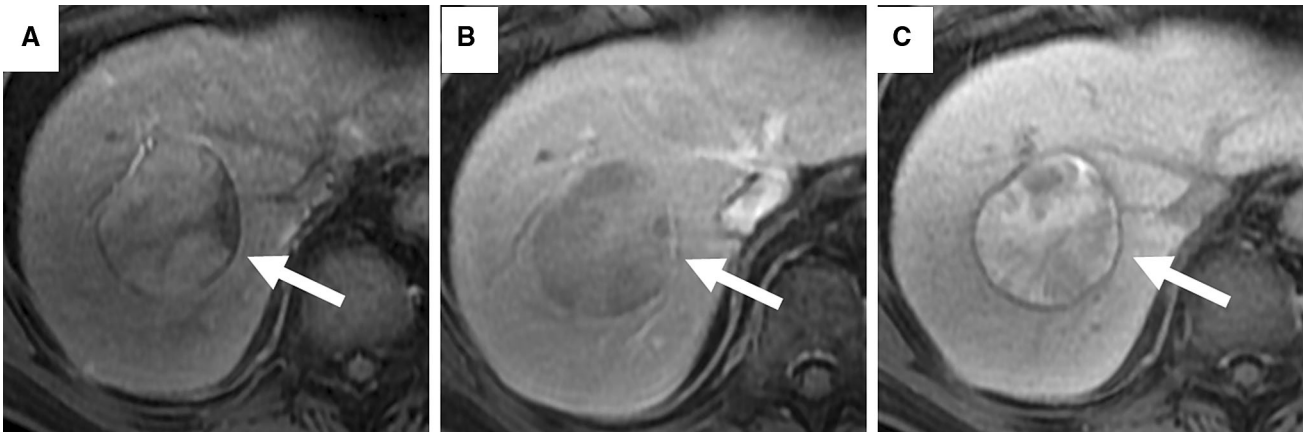

Fig. 6. Contrast-enhanced MRI with gadoxetic acid (Primovist) in a patient with Child's A liver cirrhosis. Mass (arrows) with characteristic enhancement features of HCC in the arterial (**A**) and portal venous phases (**B**). Hepatobiliary phase uptake (**C**) is atypical for HCC. Nevertheless, arterial phase enhancement and portal venous washout appearance are diagnostic. Radiologically guided percutaneous biopsy of the tumor confirmed well-differentiated HCC. Note also the presence of a hypointense rim around the tumor in the hepatobiliary phase which corresponds to the location of the capsule appearance seen in the portal venous phase.

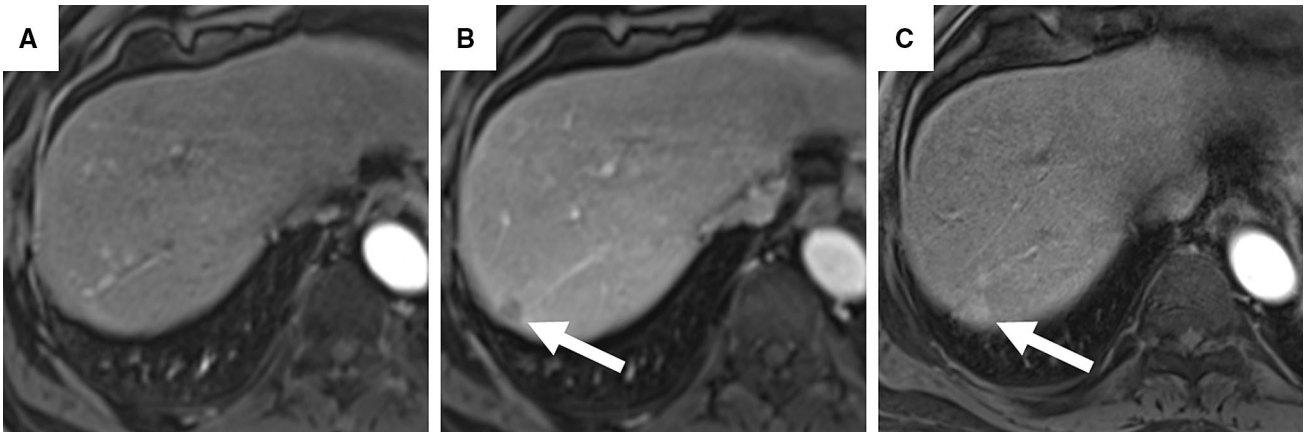

Fig. 7. Multiphasic MRI performed for this patient with Hepatitis B shows a subcapsular nodule in the hepatic dome (arrowed) that showed no arterial enhancement (**A**), but did demonstrate a washout appearance (**B**). Two years later, the nodule developed arterial enhancement (**C**) with persistent washout appearance (not shown). This was resected and proven to be HCC on histology. On retrospect, the nodule 2 years earlier may have been a small early HCC.

Arterial hyperenhancement of such lesions is less conspicuous and consistent. Consequently, other sequences such as T2 and DWI are more helpful in making the diagnosis [43]. Furthermore, 60% to 100% of these lesions present with portal vein thrombosis and the ensuing anomalous vascular supply could account for the lack of arterial hyperenhancement [43–46]. The tumor thrombus also shows enhancement characteristics similar to the primary tumor.

Histopathological features

To the pathologists, infiltrative HCC represents an extensive nodular HCC, characterized by the spread of minute tumor nodules throughout a hepatic lobe or the entire liver [43], rather than a separate histopathologic entity.

Clinical significance

The geographic, segmental appearance of infiltrative HCC can mimic other processes such as infection or granulomatous inflammation, resulting in an incorrect diagnosis (Fig. 9). Nonetheless, the presence of a tumor thrombus has similar imaging characteristics to the primary tumor, is highly suggestive of infiltrative HCC, and allows a confident diagnosis to be made. Infiltrative HCC also carries a worse prognosis compared to conventional HCC because of frequent vascular invasion and aggressive biological behavior [47].

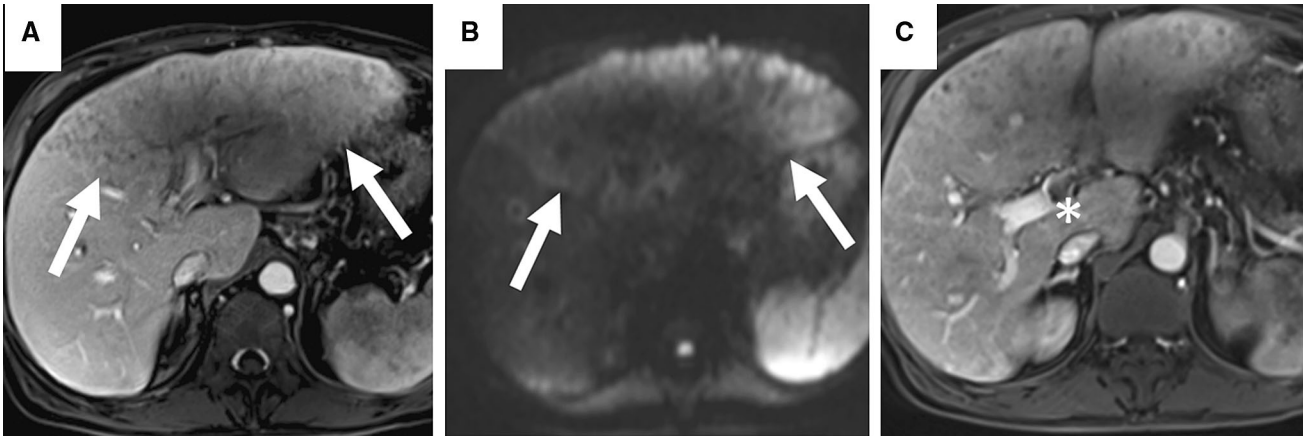

Fig. 8. Geographic area of signal abnormality (arrows) involving segments 2, 3, and 4 which shows equivocal arterial enhancement (**A**). However, DWI shows restricted diffusion (**B**) in the abnormal areas which turned out to be an infiltrative form HCC on resection. Note also tumor thrombus within the right portal vein (asterisk, **C**).

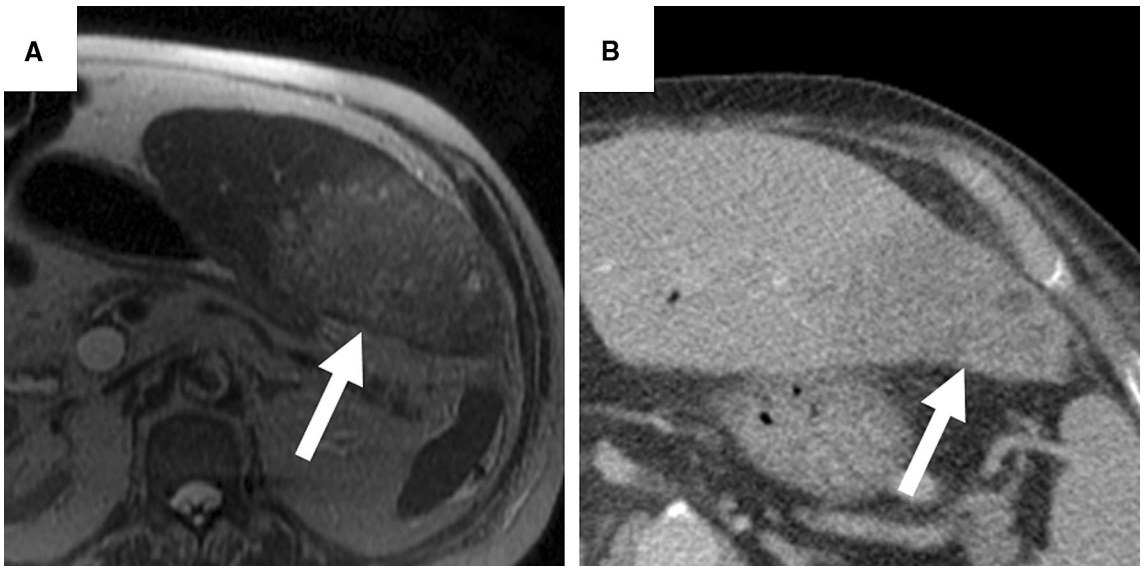

Fig. 9. Patient with hepatitis B underwent a right hepatectomy several years prior for HCC. She was presented subsequently with symptoms of sepsis and MRI revealed a geographic, infiltrative area of signal abnormality in the left lobe of the liver (**A**, arrow). In view of the history of hepatitis B infection, the possibility of an underlying infiltrative HCC was raised. However, a follow-up scan 1 month later after a course of antibiotics showed the region of signal abnormality to have reduced in size (**B**, arrow). It was eventually deemed to be due to infection rather than infiltrative HCC.

Scirrhous HCC

Imaging features

Scirrhous HCC (S-HCC) is a subtype of HCC which is characterized by the abundance of fibrosis along the sinusoids and varying degrees of atrophy of the tumor trabeculae (Fig. 10). It comprises approximately 4.6% of cases of HCC [48]. In a study conducted by Lee et al. [49], it was found that such tumors have less apparent arterial enhancement and are more likely to demonstrate persistent enhancement during the portal venous and delayed phases.

Indeed, in a recent study by Choi et al. comparing the gadoxetic acid-enhanced MRI features of S-HCC and intrahepatic cholangiocarcinomas showed that only 31.3% (30/96) of S-HCCs showed typical arterial enhancement and washout appearance. Interestingly, 94.8% (91/96) of S-HCC did not show central T2 hyperintensity, a feature which is closely associated with progressed HCCs [50]. In the same study, 79.2% (76/96) S-HCCs showed a targetoid appearance in the hepatobiliary phase, whereby the tumor showed peripheral hypointensity compared to uptake of contrast centrally. In the same manner, 47.9% (46/96) of S-HCCs showed a

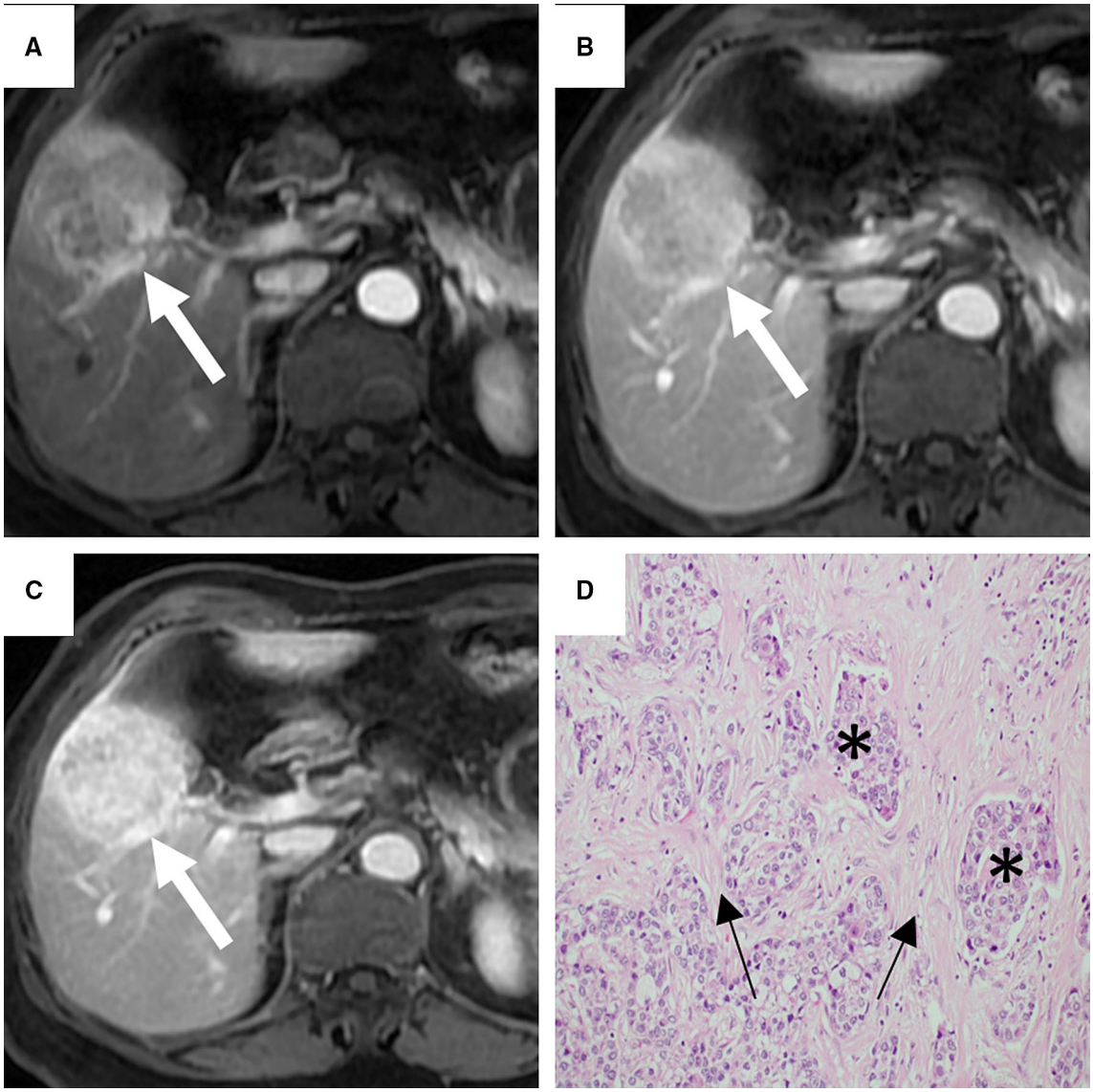

Fig. 10. Mass in the right lobe of the liver (white arrows) shows progressive enhancement during the arterial (**A**), portal venous (**B**), and equilibrium phases (**C**) rather than washout, which is a feature of tumors with dense fibrotic component and large degree of interstitial space. Cholangiocarcinomas and adenocarcinomas are also examples of tumors with such characteristics. Histology (**D**) of the mass showed fibrous stroma (black arrows) interspersed among nests of HCC cells (black asterisk), in keeping with a scirrhous form of HCC.

target appearance on DWI where there was peripheral hyperintensity compared to the central part of the tumor [50].

S-HCCs and intrahepatic cholangiocarcinomas share similar imaging characteristics such as rim-enhancement and targetoid appearance on DWI and the hepatobiliary phase. The proportion of arterial hyperenhancement of 20% or more of the tumor diameter was postulated to be a helping distinguishing feature by Park et al. [51, 52].

Histopathological features

Typically, HCC do not contain prominent areas of fibrotic tumor stroma. However, prominent fibrotic changes are seen across the section of S-HCC on histology. The stroma is said to comprise approximately 50% of the area of largest slice of tumor, or 50% of the area of the fields of microscopic sections [53]. It has been hypothesized that the presence of fibrous stroma within the tumor results in greater uptake of contrast during the portal venous and delayed phases which would account for less discernible washout appearance, but instead progressive enhancement [49].

Clinical significance

Because of the prolonged enhancement during the later phases, these tumors are frequently misdiagnosed as

cholangiocarcinomas. That said, the study by Choi et al. postulated that the ancillary features of a capsule, septum, and central T2 hypointensity (that favor S-HCC) could be used in conjunction with conventional enhancement patterns on gadoxetic acid-enhanced MRI to differentiate between S-HCC and ICC [50].

Lee et al. showed that patients with S-HCCs have reduced prevalence of hepatitis B infection and lower levels of serum AFP, albeit with outcomes and prognosis similar to patients with conventional HCC [49]. One caveat is that small HCCs frequently show atypical enhancement. Therefore, the absence of washout appearance in a small HCC does not necessarily imply a scirrhous variant.

HCC with granulomatous inflammation

Imaging Features

Development of HCC with granulomatous inflammation is very rare, and usually associated with patients with hepatic sarcoidosis. These lesions may demonstrate atypical imaging features on MRI such as arterial enhancement with the absence of washout appearance (Fig. 11). Arai et al. reported a solitary hypervascular liver tumor in a patient, who apart from having sarcoidosis, had no known risk factors for HCC development. The tumor showed no washout appearance and no uptake of gadoxetic acid [54]. The subsequent histology showed a hepatocellular carcinoma with areas of non-necrotising granulomas scattered in and around the tumor.

Histopathological features

Histological evaluation of such lesions usually demonstrates tumor cells associated with non-caseating granulomas. A review of past literature by the authors showed four other case reports which described patients diagnosed with HCC associated with sarcoidosis [54–57], out of which, three of the reports described histological evidence of granulomas associated with the tumor.

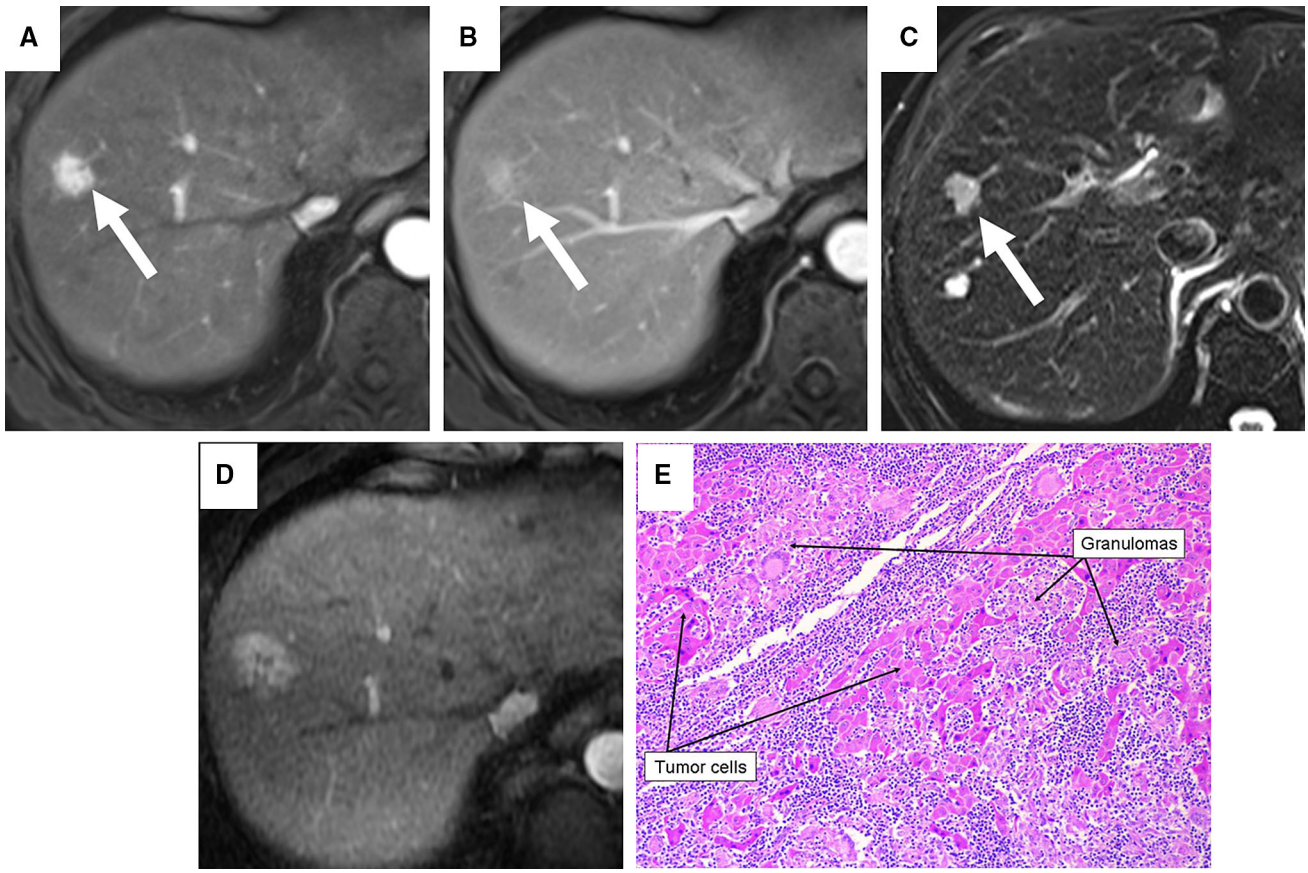

Fig. 11. Contrast-enhanced MRI of the liver was performed for this patient with Hepatitis B and Child's A liver cirrhosis. MRI revealed a nodule (arrowed) that showed arterial enhancement (**A**) and retention of contrast on the portal venous phase (**B**). The lesion also showed high T2 signal (**C**) and was initially mistaken to be a haemangioma. However, the nodule doubled in size after 2 years (**D**) and was resected. Histology (**E**) showed HCC containing areas of granulomatous inflammation. The presence of inflammation resulted in increased perfusion and lack of washout appearance.

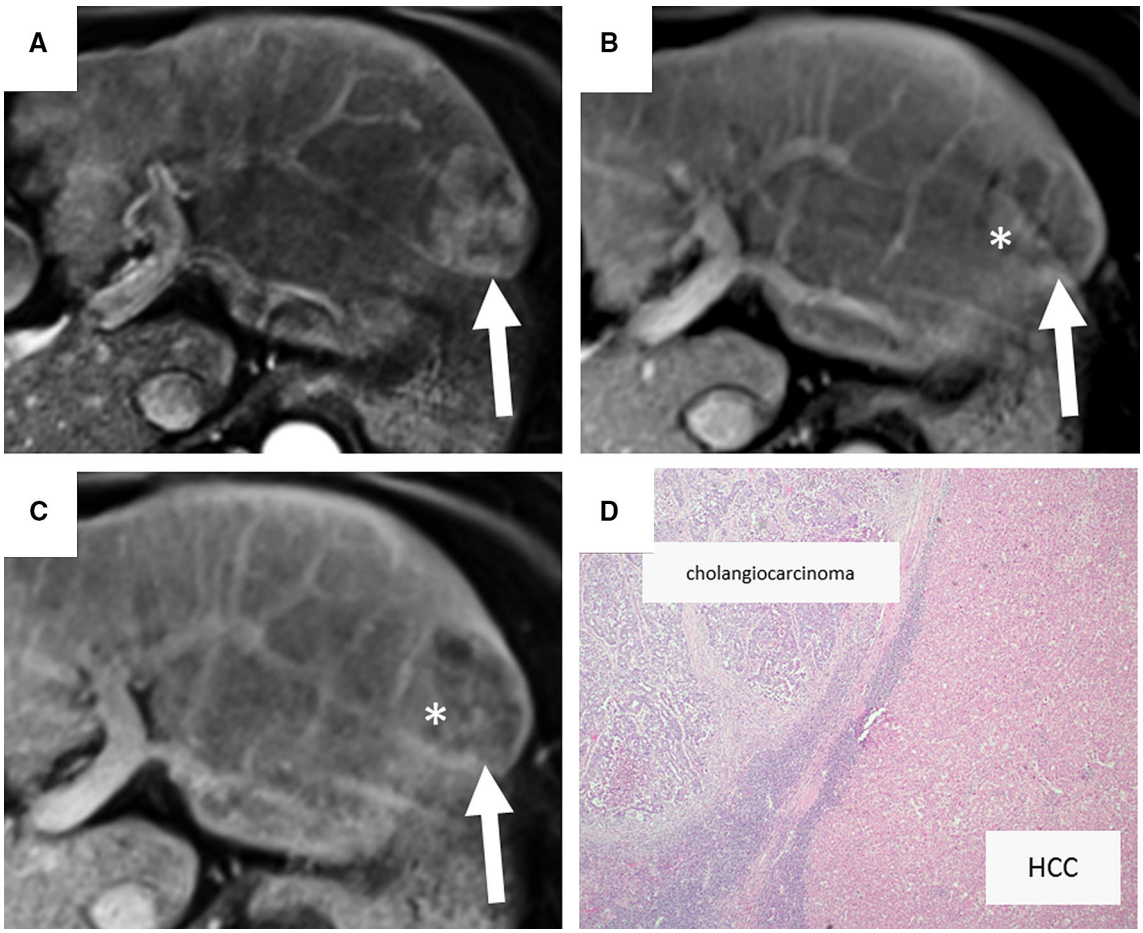

Fig. 12. In this patient who is positive for Hepatitis C infection and Child's A liver cirrhosis, a nodular, arterially enhancing lesion (**A**) is seen in the lateral segment of the liver (arrow). Thick nodular components are also seen, which do not show washout appearance in the portal venous and equilibrium phase (**B**, **C**), particularly along the medial aspect (asterisks). The lesion was surgically resected and histology (**D**) showed it to be a cHCC-ICC or hepatocholangiocarcinoma. A variable minority of tumors may present with typical arterial hyperenhancement and washout appearance, presumably in those with predominant HCC components.

Clinical significance

The relationship between sarcoidosis and malignancy was described in a Swedish retrospective study involving 472 patients with sarcoidosis from an incidence study between 1966 and 1980 and 8541 patients with sarcoidosis from the Swedish Inpatient Register from 1964 to 1994. An increased risk was found for liver cancer with a standardized incident ratio of 1.4% which increased to 1.9% after more than 10 years of follow-up [58]. Other studies on sarcoidosis patients have obtained varying results. A long-term follow-up study of 555 Danish patients showed no increased cancer risk in patients with sarcoidosis [59]. Authors have postulated that chronic inflammation and oxidative stress from sarcoidosis may result in an increased risk of malignancy and presumably HCC development.

In patients with no history of chronic liver disease or risk factors for HCC development, arterially enhancing lesions with no evidence of washout appearance would not allow for a diagnosis of HCC to be made. In the case of HCC with granulomatous inflammation, patients are often negative for Hepatitis B and C. Imaging with gadoxetic acid would be helpful to rule out FNH since FNH is usually hyper- or isointense in the hepatobiliary phase. Nonetheless, it should be kept in mind that HCC with granulomatous inflammation is a very rare entity and should be a diagnosis of exclusion. In patients with chronic granulomatous infection of the liver, a growing hypervascular tumor that does not have the specific imaging features of non-malignant tumors such as hemangiomas, FNH, or hepatic adenoma should be biopsied to exclude an underlying malignancy.

Combined hepatocellular carcinoma and cholangiocarcinoma

Imaging features

Combined hepatocellular carcinoma and cholangiocarcinoma (cHCC-CC) are lesions in which both HCC and

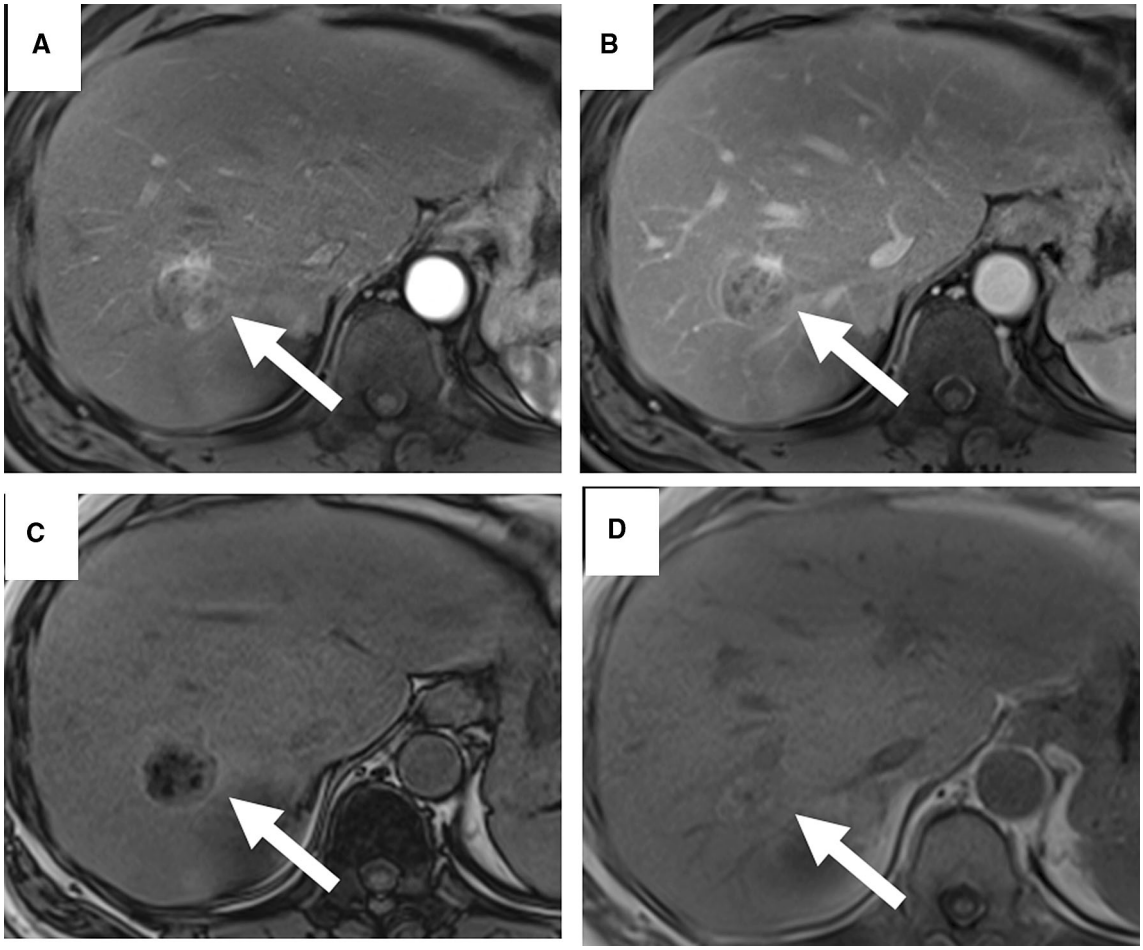

Fig. 13. Nodule seen in segment 7 of the liver in this patient with Hepatitis B shows arterial hyperenhancement (**A**) and washout appearance (**B**), typical of a progressed HCC. The nodule also demonstrates intralesional fat as shown by signal loss during the opposed-phase image (**C**) from the in-phase image (**D**). This finding is unusual as intralesional fat is not typically seen in progressed HCCs except for steatohepatitic HCC. Histological analysis of the nodule showed it to be an infarcted HCC. Hence, the deposition of prominent intralesional fat in this case could have been a response to the compromised vascular supply.

intrahepatic cholangiocarcinomas (ICC) are seen to coexist on histology. Theoretically, the tumor would show features of both HCC and ICC on imaging (Fig. 12). The HCC component of the tumor would demonstrate arterial enhancement and washout appearance. As per convention, the ICC component of the tumor would show peripheral and progressive enhancement in the arterial and delayed phases, respectively. Therefore, two distinctive enhancement patterns in the same tumor or peripheral enhancement of the tumor in cirrhotic liver raise concern for cHCC-CC.

Histopathological features

The tumor cells express both biliary and hepatocellular markers by immunohistochemistry and may also express progenitor cell and stem cell markers such as cytokeratin (CK) 19 or 7. It has been postulated that such tumors arise from liver progenitor cells or from dedifferentiation of mature hepatocytes [60, 61].

Clinical features

These tumors herald a poorer prognosis with overall median and 5-year survival rates markedly lower than those of HCC. They are also associated with high recurrence rates.

Furthermore, diagnosing a cHCC-CC prospectively on imaging is challenging due to the varied appearance of the tumor and the presence of overlapping features. Sammon et al. demonstrated that arterial phase hyperenhancement, washout appearance, washout and progression, intralesional fat, and hemorrhage were strongly associated with cHCC-CC. However, these features, except for washout and progression, are also features that favor HCC. Peripheral persistent enhancement and

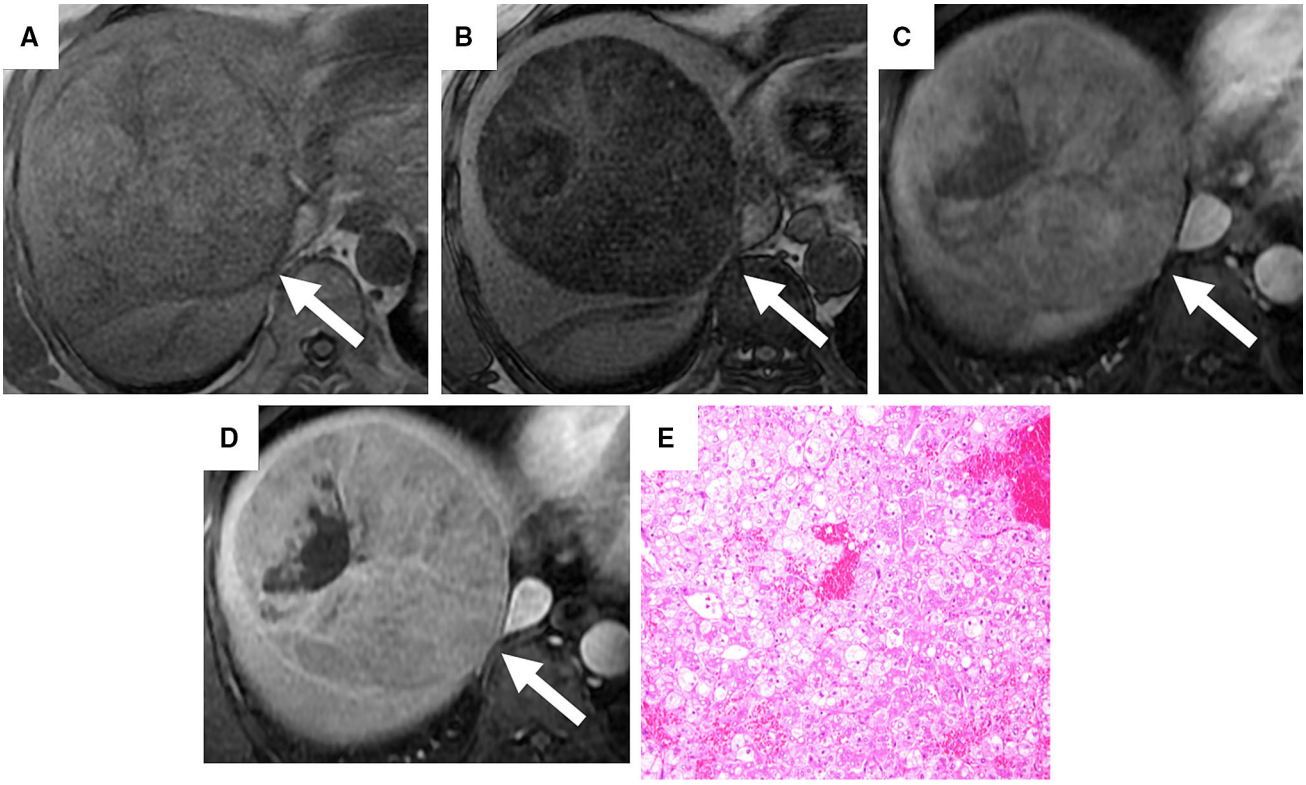

Fig. 14. MRI of patient with Hepatitis B shows a tumor in right lobe of liver (**A**, arrow) which demonstrates signal loss on opposed-phase images (**B**), indicative of intra-voxel fat. Minimal arterial enhancement is seen (**C**), although wash-out appearance is noted on the portal venous phase (**D**). Histologically, the tumor cells appeared swollen with cytoplasmic clearing due to lipid deposition (**E**).

heterogeneous hyperenhancement with washout were also the most common enhancement patterns in cHCC-CC in his study [62]. Similar overlapping enhancement patterns were also seen in the study by de Campos et al. [63].

In such a situation, adherence to the LI-RADS guidelines may help in preserving specificity for the diagnosis of HCC, while maintaining a high sensitivity for the detection of malignancy. This is because any observation which has a targetoid appearance is classified as an LR-M lesion, and a biopsy is mandated to exclude a non-HCC malignancy.

Nonetheless, false positives can still occur due to the heterogeneity of the tumor. A study by Horvat et al. showed that 4 cHCC-CC were misdiagnosed as HCC due to the presence of arterial hyperenhancement which led the radiologists to classify them as HCCs [64]. Potretzke et al. demonstrated similar findings with 6.5% of cHCC-CC cases diagnosed as HCC [60].

It is important to note that the risk factors for HCC are similar to cholangiocarcinoma, making it even more relevant that we accurately distinguish the two entities in diagnostic evaluation, particularly in the setting of orthotopic liver transplant evaluation. Concomitant elevated serum CA 19-9 and/or atypical patterns of spread to regional nodal stations by the primary tumor may allude to the diagnosis of cHCC-CC. A biopsy of the lesion should be performed if there is any doubt regarding the diagnosis of HCC.

Steatohepatitic HCC

Imaging features

Intralesional fat is typically seen as signal loss on opposed-phase images. A nodule which demonstrates such a finding in a patient with chronic liver disease is suspicious for an early HCC. It is unusual for progressed HCCs to show intralesional fat (Fig. 13) [65]. Steatohepatitic HCC is a variant of HCC which has prominent fatty deposits. Apart from the characteristic enhancement pattern of progressed HCC, these lesions show also prominent intra-tumoral fat. The background liver would also typically show features of steatosis.

Histopathological features

Histologically, steatohepatitic HCC is usually accompanied by steatotic malignant cells, ballooned hepatocytes, inflammation, and fibrosis, reminiscent of non-alcoholic steatohepatitis (NASH) in a non-neoplastic setting [65]

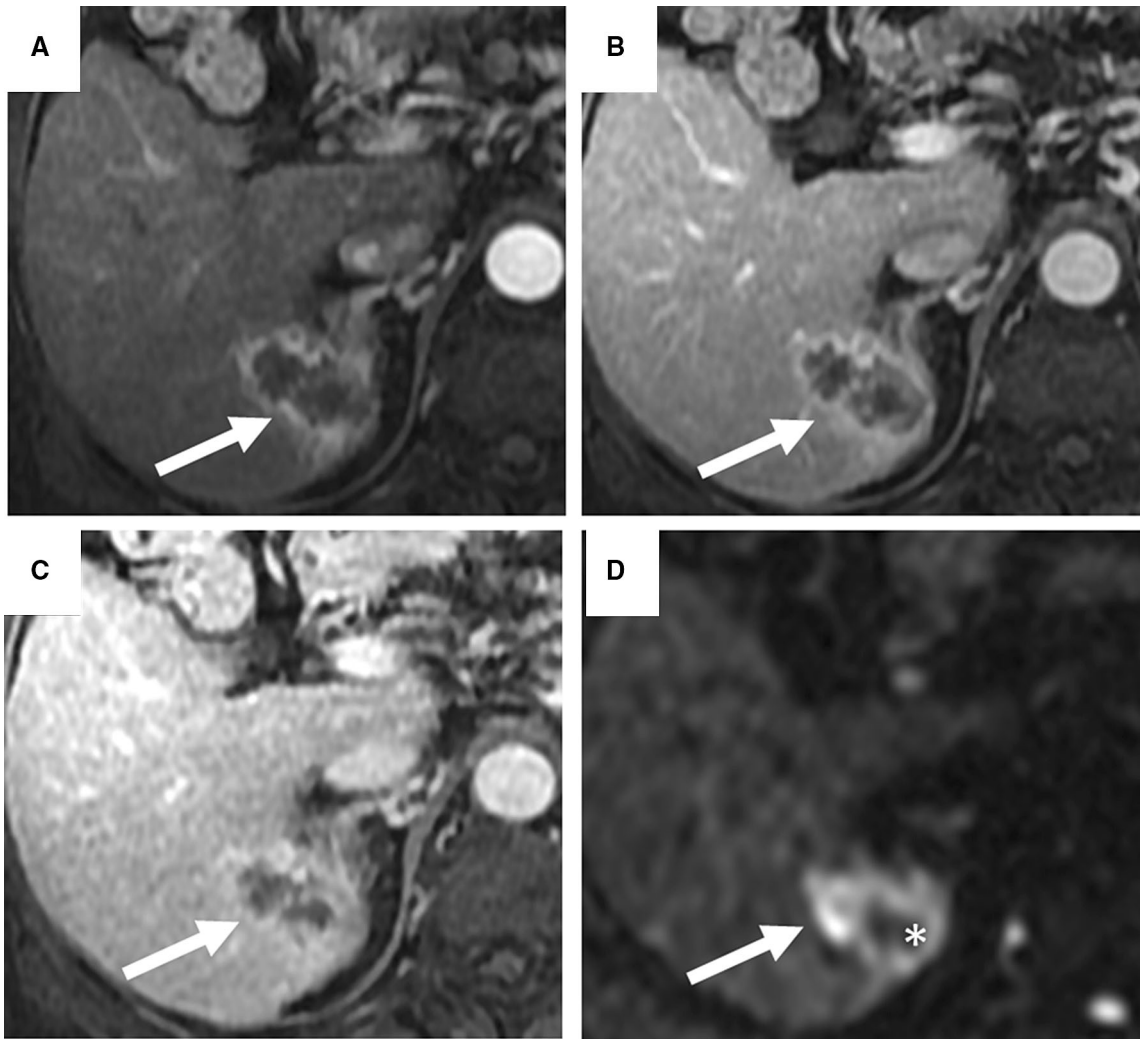

Fig. 15. As HCCs become more poorly differentiated, they may lose their characteristic enhancement patterns and become indistinguishable from other malignancies. This was a case of HCC with sarcomatoid change in a patient with alcoholic liver cirrhosis, showing aggressive features of ill-defined, peripheral, progressive enhancement, and central necrosis (**A**, **B**, and **C**). Note the peripheral rim of restricted diffusion surrounding the tumor (arrow in **D**) which indicates the presence of viable tumor tissue. Centrally, no restricted diffusion is seen due to the presence of necrosis (asterisk in **D**). The prognosis in this form of HCC tends to be much worse and this patient demised within a year.

(Fig. 14). Intralesional fat of HCC tends to occur in the early stage of hepatocarcinogenesis due to transient hypoxia from the lack of insufficient blood supply. In contrast, steatohepatitic HCC harbors higher grade tumor with abundant quantities of fat [65].

Clinical significance

Lesions are associated with background non-alcoholic fatty liver disease (NAFLD) and risk factors for metabolic syndrome. The incidence ranges from 13.5 to 18.8%. Salomao et al. have demonstrated that HCC with steatohepatitic features did not lower disease-free or overall survival [66].

With the growing incidence of NAFLD and NASH, steatohepatitic HCC may become more common. Indeed, a prevalence study reported that between 2002 and 2008, NAFLD and non-alcoholic steatohepatitis (NASH) were the most common underlying aetiologic risk factors for HCC development (at 59% of 4406 cases) identified in the United States [67]. A review article by Streba et al. postulated that diabetes, obesity, and NAFLD induce a chronic active inflammatory state through multiple hormonal and cytokine pathways that promotes hepatocarcinogenesis [68].

The differential signal intensities of tumors compared to non-tumor liver tissue can be confusing in the setting of severe hepatic steatosis, since fat-suppressed sequences are typically employed for multiphasic contrast-enhanced MRI. Also, steatohepatitic HCCs can mimic other fat-containing lesions in the liver such as angiomyolipomas or hepatic adenomas.

Other rare variants

HCCs that have a spindle cell component have been referred to as sarcomatoid HCCs (Fig. 15). The pathogenesis of sarcomatoid HCCs is still uncertain, although it is postulated to arise from dedifferentiation from an ordinary HCC. Immunohistochemical stains have also shown the spindle cell component of sarcomatoid HCC to be secondary to sarcomatous change in HCC rather than a true sarcoma [69, 70]. Due to the rarity of such tumors, the imaging features have not been well established. Honda et al. showed that sarcomatoid HCCs showed progressive, peripheral enhancement due to fibrous stroma interspersed within viable cancer cells [69, 71]. A literature search performed by Hung et al. also revealed 92.3% of sarcomatoid HCC to demonstrate central necrosis [72]. Patients with sarcomatoid HCCs have much poorer prognosis due to the high frequency of recurrence and extrahepatic metastases [72]. In contradistinction to ordinary HCCs, sarcomatoid HCCs tend to have normal or low AFP levels [69].

Conclusion

Pathological variants of HCC can be confusing due to their atypical morphology and enhancement characteristics. These imaging features can be attributed to their distinct histopathologic characteristics. Nevertheless, a high index of suspicion for HCC and its variants in high risk patients will ensure timely diagnosis through biopsy and appropriate treatment.

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Compliance with ethical standards

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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