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Liver haemangioma: common and uncommon findings and how to improve the differential diagnosis

Received: 31 January 2006
Revised: 15 September 2006
Accepted: 12 October 2006
Published online: 27 January 2007
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Abstract Haemangiomas are common focal liver lesions, generally detected in the work-up of asymptomatic patients. From the pathological point of view, they can be classified as small (capillary) or large, with cavernous vascular spaces that may show thrombosis, calcifications and hyalinisation. The polymorphic imaging appearance of haemangiomas depends on their histological features and flow pattern. The widespread use of cross-sectional imaging has allowed an increased detection rate and a better characterisation of this benign

tumour. Recent developments of ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) providing high spatial and temporal resolution, together with the use of new contrast agents and/or pulse sequences has broadened the spectrum of imaging findings, contributing to diagnostic refinement in difficult cases. The scope of the present article is to provide an overview of the range of appearances of haemangiomas, explored with recent cross-sectional imaging modalities, emphasising its atypical findings as explored by temporally resolved contrast-enhanced imaging.

Keywords Ultrasound · Computed tomography · X-ray computed · Magnetic resonance imaging · Liver · Neoplasms · Haemangioma · Contrast agents

Introduction

Currently, the widespread use of modern cross-sectional imaging methods has led to an increased fortuitous detection of focal liver lesions in all patients, including the asymptomatic and oncologic groups. Since imaging techniques can now provide high spatial resolution, small liver nodules are easily depicted, posing the problem of the characterisation of the so-called incidental lesions. Recent papers based on helical computed tomography (CT) or on necropsy studies showed that liver tumours are more

frequent than it was previously accepted [1]. Among those, the majority correspond to cysts, haemangiomas, focal nodular hyperplasia, adenomas and pseudolesions, such as focal fatty infiltration and focal fatty sparing [2]. It has been demonstrated that the majority of incidental focal liver lesions discovered during any abdominal imaging work-up is, in fact, benign and devoided of particular clinical significance, even in oncologic patients [3, 4].

The characterisation of benignancy, when dealing with a focal liver lesion, assumes special importance, since it leads to cost reduction concerning further imaging work-up

and spares the patient from anxiety. Several factors are implicated on the confidence level assigned to characterise a focal liver lesion, such as their typical or atypical imaging findings, the previous existence of an oncologic disease, de novo appearance or modification of the imaging features as seen on follow-up studies. Diminutive size is one of the major constraints to achieving a proper characterisation and even the state-of-the-art imaging techniques may fail to provide the diagnosis in such cases, ultimately leading to other diagnostic tests, possibly even invasive methods [5].

The scope of this paper is to review the atypical features of liver haemangiomas and to show how to improve the diagnostic confidence in their characterisation by using state-of-the-art cross-sectional imaging techniques.

General considerations

Haemangiomas have an estimated prevalence of 0.4% to 20%, according to several autopsy studies. Being devoid of malignant potential, they are, in general, fortuitously

discovered during any abdominal imaging work-up, mostly being discovered between the fourth and fifth decades of life [5–7]. They are multiple in more than 50% of cases and show a clear female predilection (ratio of 2–5:1).

Pathological examination (Fig. 1a) reveals a focal tender mass formed by multiple vascular channels limited by a single layer of endothelial cells within a thin fibrous stroma. In general, the blood circulation within these tumour vessels is slow. Morphologically, it is a well-defined lesion, possessing round or lobulated margins. Although it may occur anywhere in the liver parenchyma, it is more commonly seen at peripheral and sub-capsular locations, mostly in the posterior segments of the right lobe [5, 6, 8]. Their size usually remains stable and can vary from a few millimetres to more than 20 cm, a feature that has been used for its classification into small (<15 mm), medium (15–50 mm) and large haemangiomas (>50 mm) [6]. Large haemangiomas may give rise to complications in 4.5% to 19.7% of cases, consisting of bleeding, compressive effect on adjacent structures such as the bowel and torsion if pedunculated [6, 7, 9, 10].

Fig. 1 a–d Usual findings in haemangiomas. **a** Histological feature depicting the large vascular spaces of a well-defined non-capsulated tumour. **b** On ultrasound (US), the tumour is homogeneously hyperechoic with lobulated contours. **c** On computed tomography (CT), centripetal, progressive enhancement is seen on the arterial phase of the dynamic liver study. **d** Magnetic resonance imaging (MRI) shows a homogeneous lesion with intensity similar to cerebrospinal fluid (CSF) on T2-w fatsat

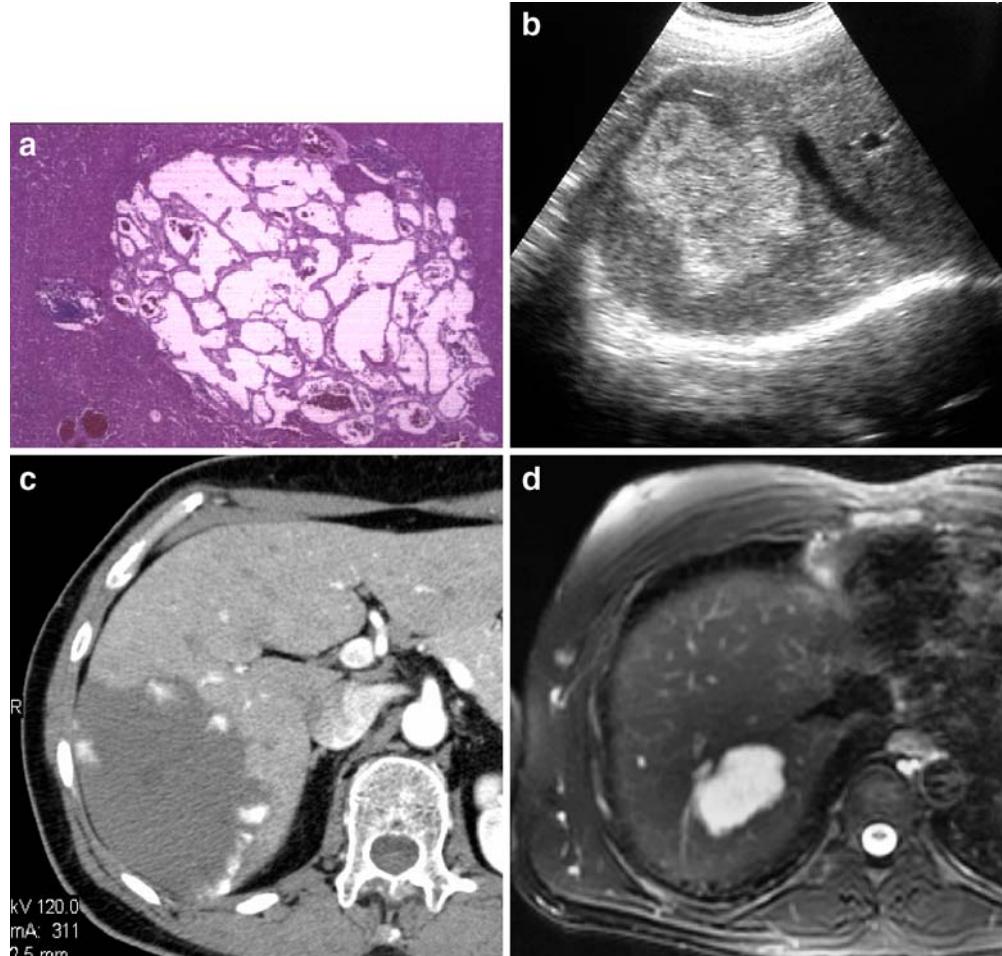
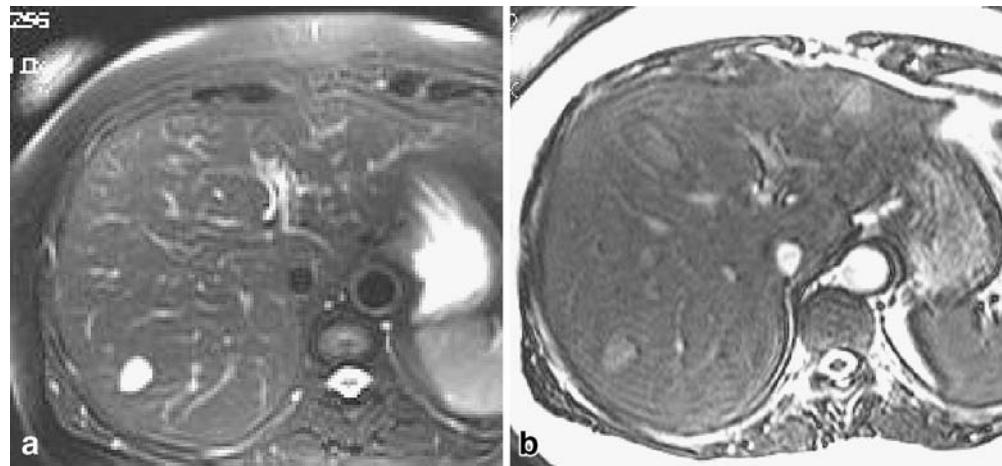


Fig. 2 a, b A case illustrating the possibility of differentiating non-invasively haemangiomas from cysts using plain MRI. Compared to the T2-w fatsat fast spin echo (FSE) sequence (a), the haemangioma shows a considerable signal intensity loss on the steady-state free precession (SSFP) images (TrueFISP) (b). Contrarily, biliary cysts retain high signal intensity on both sequences



Common imaging findings

The most common sonographic pattern of haemangiomas (Fig. 1b) consists of the demonstration of a homogeneous hyperechoic liver nodule, with discrete posterior acoustic enhancement, devoided of Doppler signal both on colour-coded and spectral examination [11].

CT features (Fig. 1c) usually shows a hypodense well-defined lesion, with an internal density similar to the vessels. Dynamic studies performed after the administration of non-specific extracellular iodine compounds exhibits early nodular peripheral enhancement (puddling), since its feeding vessels originate from the hepatic artery. Subsequent phases of liver enhancement reveal a progressive slow centripetal fill-in, with iso- or even slight hyperdensity on delayed phase as compared to the normal liver parenchyma. This classical presentation is diagnostic

with a high level of confidence [5, 6]. Late intra-tumoural accumulation of contrast can be explained by the slow flowing blood within its vascular channels determining iso-/hyperdensity and absence of noticeable washout on the latter phases of the dynamic study [5, 7, 12, 13]. However, delayed homogeneity due to complete contrast filling of the tumour should not be regularly expected, especially for large tumours, and, thus, should not be used as mandatory diagnostic criteria. Small haemangiomas may appear to enhance to a lesser extent but this may result from partial volume averaging [5, 12].

Currently, magnetic resonance imaging (MRI) is the imaging method of choice to diagnose haemangiomas (Fig. 1d) [5, 6]. On T1-weighted (-w) images, haemangiomas display low signal intensity and on T2-w, they are strikingly homogeneous, clearly demarcated from the adjacent parenchyma, with very high signal intensity,

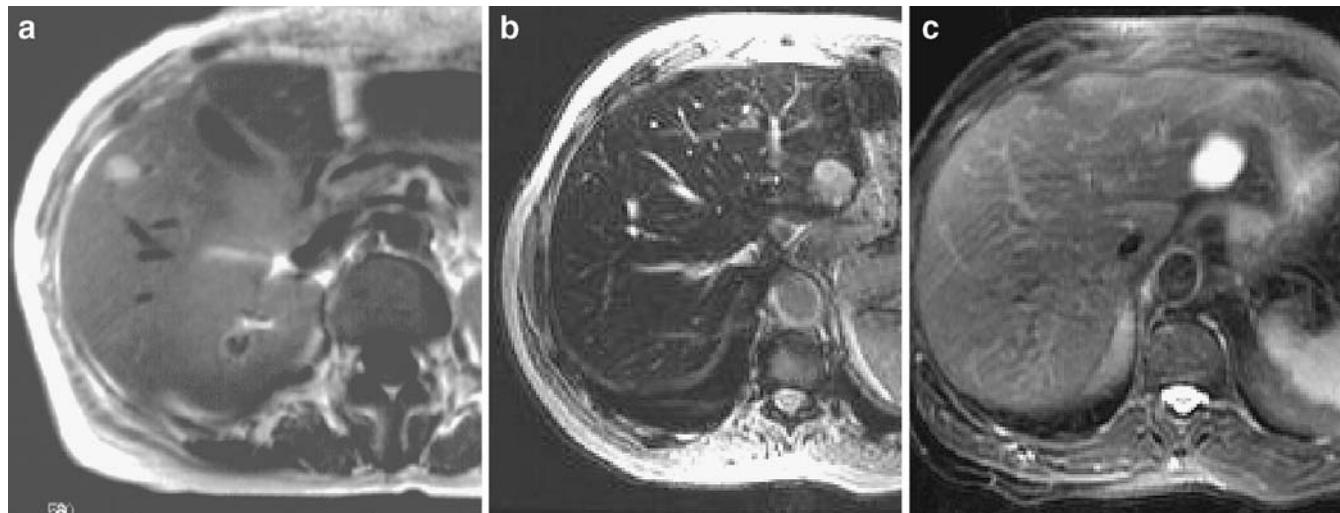


Fig. 3 a–c Haemangiomas and iron-oxide enhanced MRI. **a** Iron-oxide enhanced T1-w images obtained in the late retention phase. The small haemangioma of the right liver lobe becomes hyperintense, which can be explained by the T1-effect exerted by the

intra-tumoural circulating iron oxide particles. Another case showing signal intensity loss on the retention phase of the post-contrast GRE T2-w image (**b**) compared to the plain T2-w fatsat image (**c**)

Fig. 4 **a** Isoechoic haemangioma with a hyperechoic border; this is a common atypical appearance that has been associated with internal necrosis, scarring or myxomatous changes. **b** Pathological specimen of a cavernous haemangioma with a central area of myxomatous degeneration (arrow). **c** Haemangioma on a T2-w image displaying lobulated contours and a hyperintense central scar. **d** MRI features of a giant cavernous haemangioma; the tumour is heterogeneous, displaying internal septations, lobulated contours and a CSF-like signal intensity on this FSE T2-w image

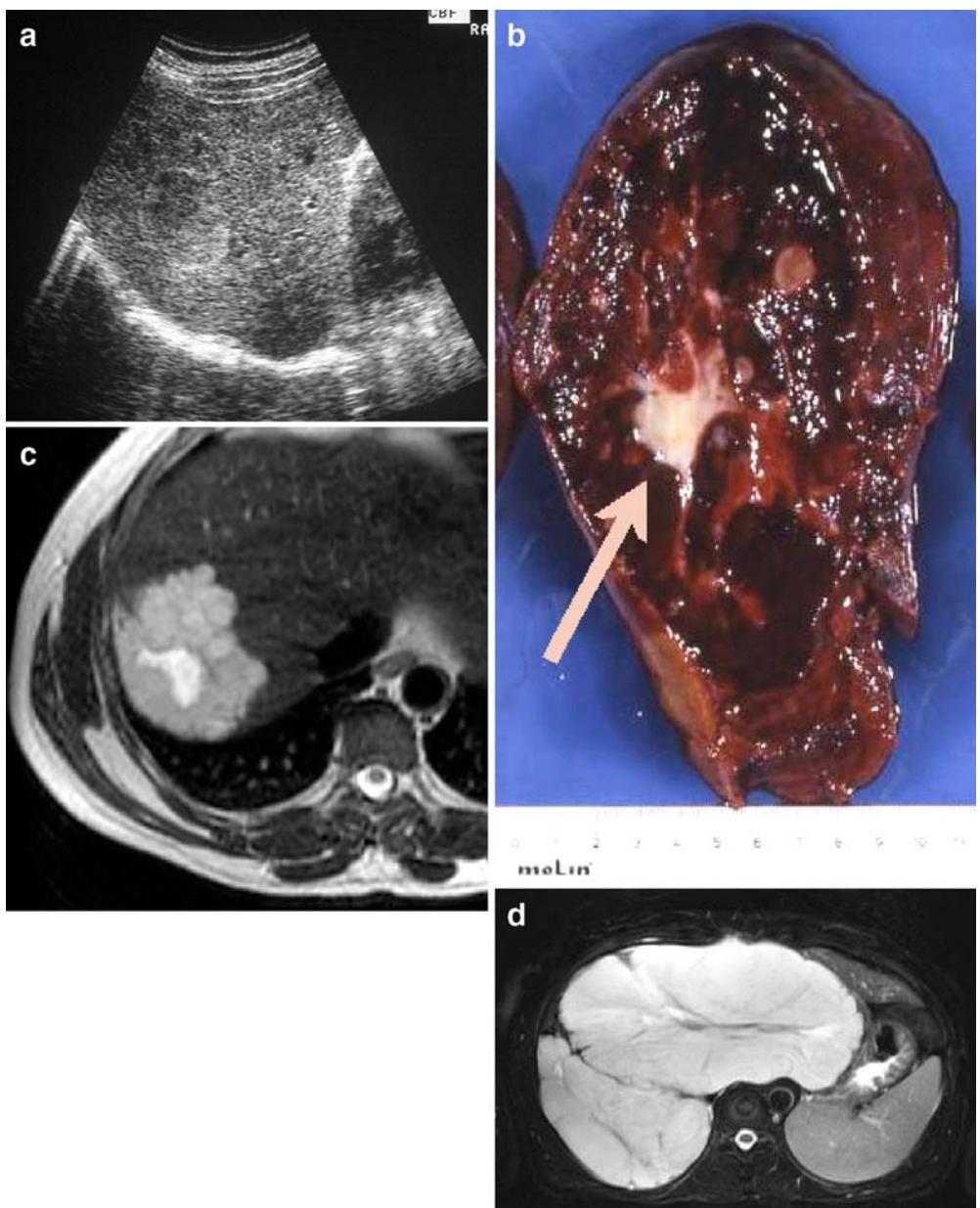


Fig. 5 **a** T2-w image of a peripheral haemangioma of the right liver lobe displaying capsular retraction. Signal intensity on the T2-w images and the contrast enhancement pattern (not shown) were sufficient to warrant the diagnosis. **b** Coronal volume-rendered (VR) image of a contrast-enhanced multi-detector computed tomography (MDCT) study showing a large pedunculated haemangioma originating in the left liver lobe

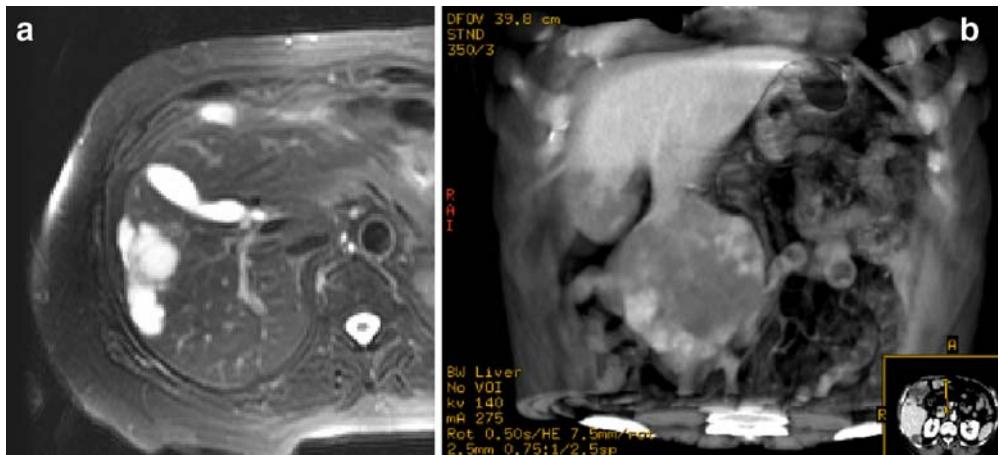


Fig. 6 a, b Asymptomatic haemangioma causing bile duct dilatation. **a** Contrast-enhanced CT study depicting a segment IV haemangioma. **b** Slice obtained at an upper level revealing upstream bile duct dilatation caused by extrinsic compression. This finding should not preclude the diagnosis. In this case, imaging findings remain stable 4 years after the initial diagnosis



similar to cerebrospinal fluid (CSF), due to the long T2 relaxation time of its blood-filled vascular channels, a feature that has been coined as the bulb-light sign [5–7, 10]. In the past, calculation of the T2 relaxation time was deemed useful for its differential diagnosis with other focal liver lesions, since a relaxation value of at least 112 ms could differentiate it from metastases with a 92–97% accuracy [5, 6, 12, 14–16]. Other MRI approaches may include a double-echo heavily T2-w sequence [17, 18], a fluid-attenuated inversion recovery (FLAIR) or the use of the balanced steady-state free precession (SSFP) sequence [19, 20], which can discriminate between haemangiomas and simple liver cysts without the need for contrast injection (Fig. 2). More recently, a diffusion-weighted echo-planar technique has demonstrated usefulness in distinguishing benign from malignant liver tumours, based on their different magnetic properties at a microscopic level [21].

The high spatial and temporal resolution provided by state-of-the-art MRI equipment is currently used to acquire fast gradient-echo imaging (GRE) within the time frame of a single breath-hold, allowing contrast-enhanced dynamic liver imaging using gadolinium chelates. Characterisation of focal liver lesions are, thus, being progressively obtained by the combined information conveyed by static and dynamic imaging, with haemangiomas displaying similar dynamic MRI features as seen on CT. Liver MRI can also be performed with dedicated cell-specific contrast agents, such as iron-oxide particles (SPIO), which are captured by the Kupffer cells of the reticulo-endothelial system. Using the most recent iron-oxide contrast agents, compatible with a bolus-injection of small volumes, haemangiomas can display T1-w enhancement, due to the initial extra-cellular distribution of the SPIO agent, similar to that observed with gadolinium chelates. In the late retention phase, haemangiomas can also show peculiar imaging features consisting of discrete hyperintensity on T1-w images (Fig. 3a). This is due to the slow intra-tumoural blood flow carrying iron-oxide particles which, at very low concentrations, produce shortening of the tumour T1 relaxation time. On T2-w sequences, which are more prone to be disturbed by

magnetic susceptibility effects caused by the iron-oxide particles, the haemangioma may show negative enhancement and, consequently, signal loss, which may pose an additional difficulty for its characterisation [6, 22, 23] (Fig. 3b,c). Since haemangiomas do not contain hepatocytes, enhancement should not be expected with other specific paramagnetic contrast agents and their imaging features are basically unremarkable when compared to other hepatocyte-devoided liver tumours [6].

Recently, pulse-inversion ultrasound (US) after administration of the second-generation contrast agents replicates the characteristic puddling and progressive centripetal fill-in of haemangiomas, contributing to a diagnostic refinement for undetermined cases seen on the baseline B-mode US [24–26].

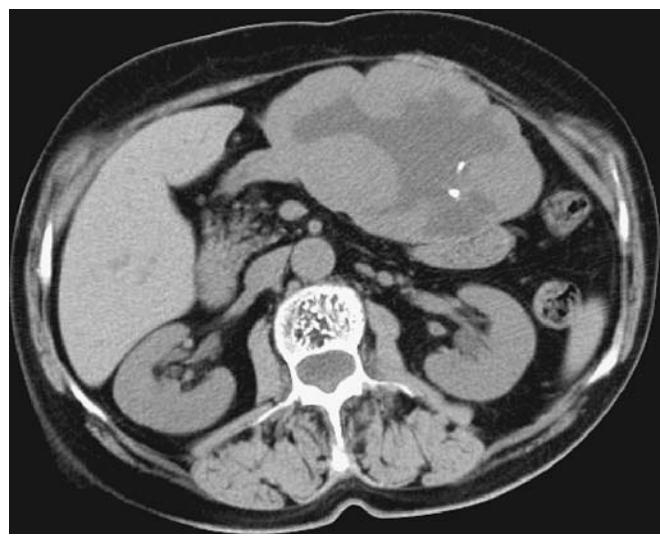
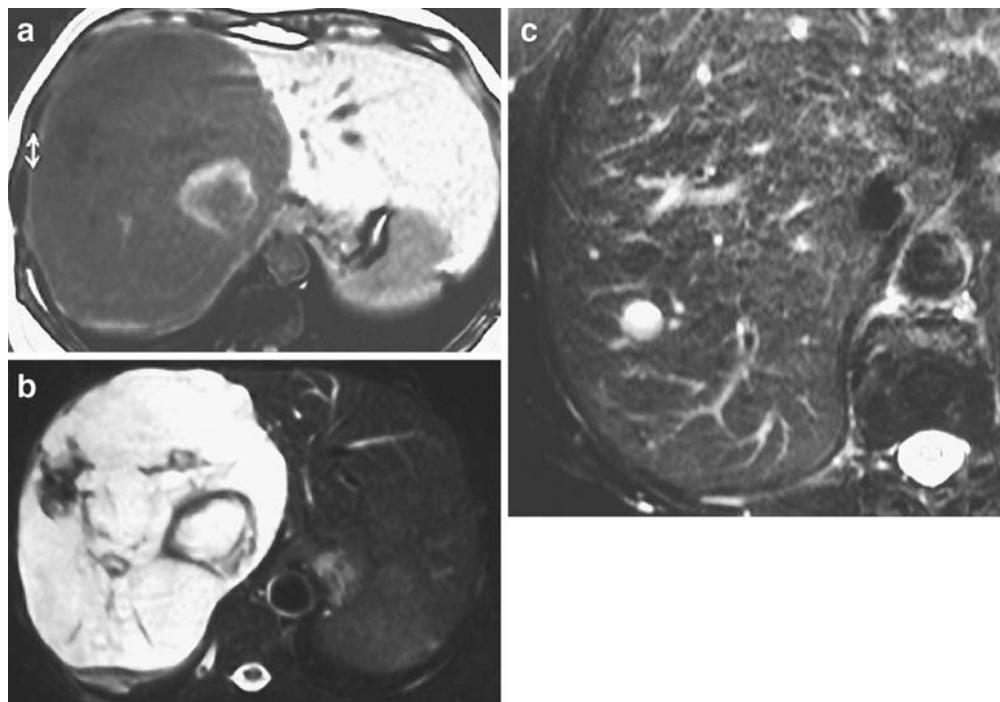


Fig. 7 Plain CT of a cavernous haemangioma showing punctate calcifications. In general, calcifications are due to intra-lesional phlebolites but may be the end result of fibrosis and dystrophic changes

Fig. 8 **a, b** Haemorrhagic haemangioma seen on MRI. **a** T1-w FSE image disclosing an internal hyperintense area. **b** On the corresponding T2-w FSE image, the haemorrhagic area is hypointense, which is due to the susceptibility effects caused by the methaemoglobin content. Other areas of scarring and fibrosis are also apparent, exhibiting low signal intensity on both sequences. **c** T2-w fatsat image of a haemangioma with a fluid–fluid level. Very rarely, haemangiomas can display an internal fluid–fluid level traducing different blood flow velocities within the haemangioma, with layering of red blood cells on the dependent portion



Uncommon presentations of haemangiomas

The diagnostic management of haemangiomas depend both on the clinical context and the imaging features of the tumour. In patients with a known malignancy, and with previous normal examinations, or in cases of atypical imaging presentation, the diagnosis needs to be confirmed by other means beyond US, ultimately leading to the use of invasive techniques [11]. Less typical imaging findings of haemangiomas can result from three main causes: altered morphology or structure, unusual flow patterns or associated liver abnormalities. Although these aspects do not preclude in all instances the correct diagnosis, they may be misleading and, therefore, should be known by radiologists in order to avoid other potentially more invasive diagnostic tests. Whenever the diagnosis is doubtful, especially in oncologic patients, even after a multimodality imaging approach, a percutaneous biopsy could be sought, with considerable evidence concerning its safety [27].

Uncommon morphology/structure

On grey-scale US, atypical haemangiomas can show an internal *iso-/hypoechoic texture* with a *peripheral hyperechoic border* (Fig. 4a), which has been associated with internal thrombosis or scarring [7]. Large haemangiomas are frequently heterogeneous and may display a *central scar* (Fig. 4b,c), which does not enhance on the late interstitial phases of the dynamic studies. On pathology, the scar is formed by myxomatous degeneration, thrombosis,

fibrosis or necrosis [6]. The T2-w images are frequently unable to determine its exact composition, as seen on pathological studies, because a central fluid-like hyper-



Fig. 9 Flash-filling haemangioma on dynamic contrast-enhanced CT showing intense homogeneous blush on the arterial phase. Isodensity was observed on the delayed image (not shown)

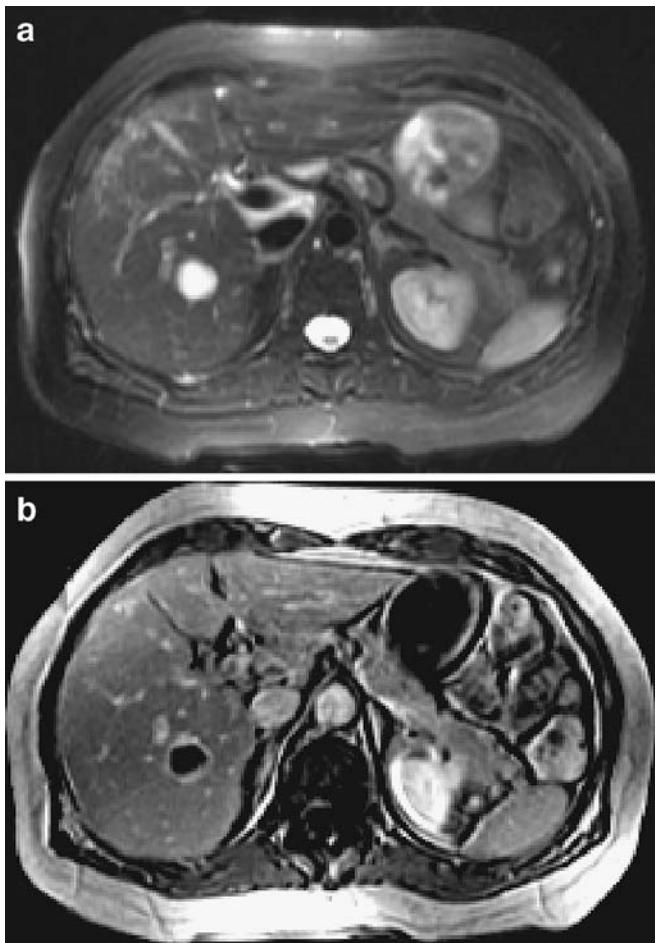


Fig. 10 **a, b** Hypodynamic haemangioma with a late-filling pattern on MRI. **a** Plain T2-w image showing high signal intensity and homogeneous pattern. **b** Dynamic imaging showing peripheral enhancement on the portal phase of the dynamic study. Thirty minutes after contrast injection, the fill-in pattern and persistent enhancement were seen (not shown), thus, enabling the correct diagnosis

intensity can be displayed, even in cases of myxomatous degeneration. Other atypical morphological features consist of the presence of *internal septations* (Fig. 4d), exhibiting low signal intensity on T1- and T2-w images related to the presence of a fibrotic component.

Liver capsule retraction is not a frequent finding, but it should not preclude the diagnosis, since it may be seen as secondary to peripheral fibrotic changes (Fig. 5a) [7, 28, 29]. In this case, other diagnoses should be ruled out, such as intra-hepatic cholangiocarcinoma, epithelioid haemangioendothelioma or, more rarely, metastases with a fibrotic component. *Pedunculated haemangiomas* are rare and, in general, its signal intensity and enhancement pattern is consistent with the diagnosis (Fig. 5b), except if they undergo torsion and infarction, when they can become symptomatic. Recognition of its hepatic origin is better accomplished using multiplanar images, allowing identification of the stalk [7, 30]. Sometimes, *bile duct dilatation* may occur because of large haemangiomas centrally located within the liver, especially around segment IV and near the liver hilum (Fig. 6). Therefore, this feature should not preclude the diagnosis [7, 30, 31].

Calcifications in haemangiomas can be found with a central or peripheral location, with multiple foci usually representing phlebolites. They are better depicted on CT as tiny dense nodules or as low signal intensity foci within the hyperintense tumour on T2-w images [7] (Fig. 7). MRI is useful for identifying *intra-tumoural haemorrhage*, displaying areas with high signal on T1-w images, best depicted on fat-suppression sequences (Fig. 8a,b). Blood signal intensity on T2-w images is variable, depending on the products of haemoglobin degradation. The spared non-haemorrhagic areas of the lesion usually maintain the same signal intensity and enhancement pattern of typical haemangiomas [7]. *Intra-peritoneal bleeding* is exceedingly rare but may be associated even with minor

Fig. 11 **a, b** Hyperdynamic haemangiomas seen on dynamic CT associated with an arterio-portal fistula. **a** Plain image disclosing four hypodense focal lesions at the right liver lobe. **b** The arterial phase of the dynamic CT study reveals two haemangiomas with the usual flow pattern and two other flash-filling, causing adjacent perfusion abnormalities. Early opacification of a segmental branch of the portal vein (arrow in **b**) can be recognised due to an associated arterio-portal fistula. An incidental liver cyst is seen at segment IV

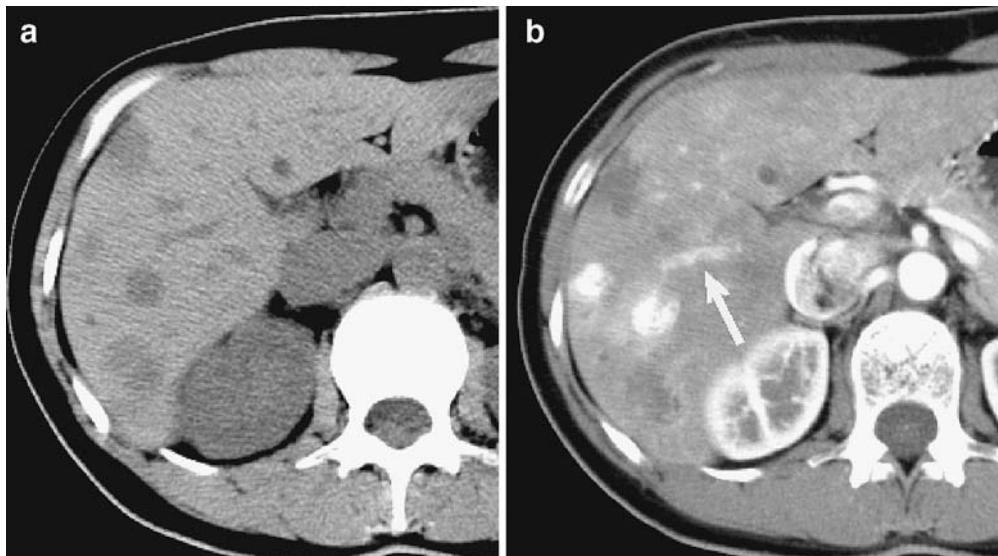


Fig. 12 a, b Other atypical enhancement patterns of haemangiomas seen on CT. **a** Arterial phase image of a dynamic CT study showing a triangular hyperdense area representing arterio-venous shunting. This area corresponds to a transient hepatic attenuation differences (THAD) that was no longer depicted in the portal venous phase (not shown). **b** Haemangioma showing an area of central enhancement

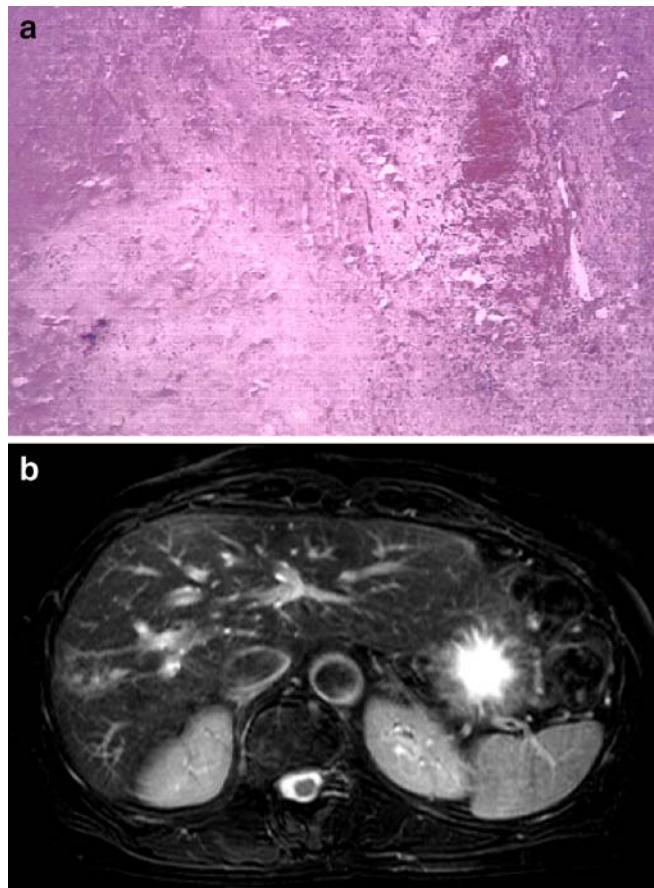
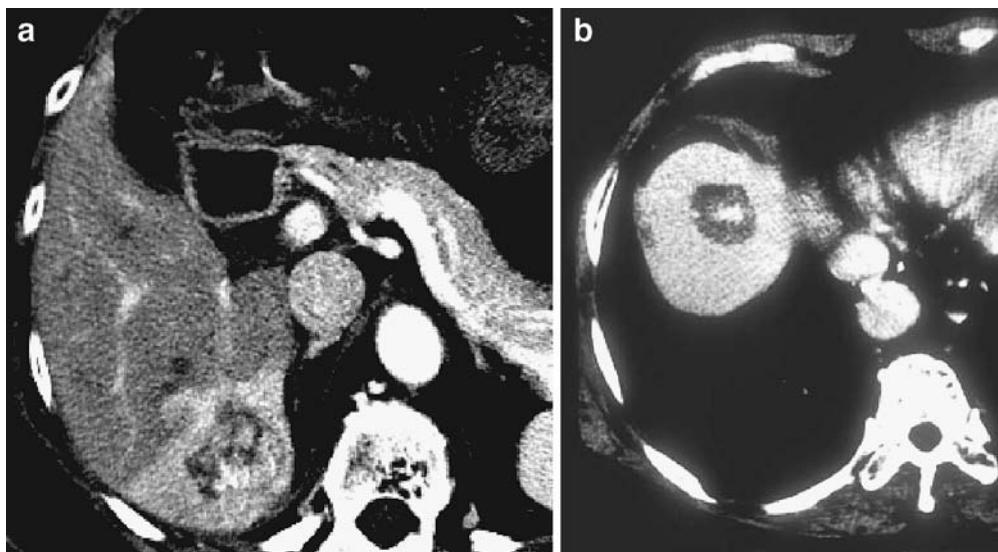


Fig. 13 a, b Sclerosed haemangioma. **a** Low-power magnification haematoxylin and eosin (H&E) staining showing complete obliteration of the vascular channels and replacement by fibrous tissue. **b** Corresponding heavily T2-w image disclosing loss of the typical light bulb intensity of the haemangioma (compare with the CSF signal)

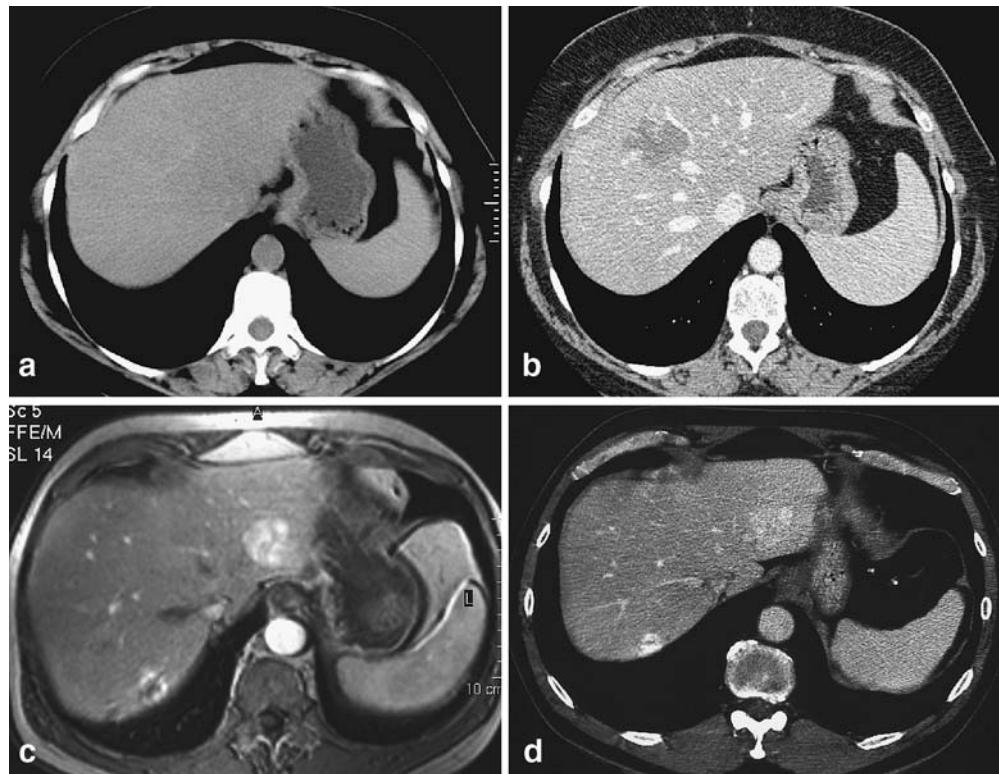
abdominal trauma in cases of large superficial tumours. *Cystic and multilocular haemangiomas* containing a large central cavity are extremely rare. On MRI, this atypical feature is represented by a single or multiple intra-tumoural cavities, possessing long T1 and T2 relaxation times related to thrombosis and old haemorrhage. Nevertheless, peripheral enhancement with puddling can still occur [7]. In rare instances, a *fluid–fluid level* may be depicted inside the haemangioma, which is thought to represent stagnant or slow flowing blood with sedimentation of red blood cells on the dependent portion [32]. The superior fluid layer consists of serum and the inferior layer contains unclotted sedimentary red blood cells [7, 32]. On CT, the superior layer shows fluid attenuation, while the inferior layer has higher attenuation due to the density of the packed cells. On MRI, T2-w sequences show high signal intensity on the upper layer and a less intense signal on the more cellular inferior layer (Fig. 8c). The fluid–fluid level is not specific of haemangiomas and has been reported in other lesions, such as complicated cysts, ciliated foregut cysts, chronic haematomas, biliary cystadenomas, tumours with liquefactive necrosis or haemorrhage, and necrotic metastases [33]. In general, histopathologic correlation is necessary to confidently establish the diagnosis [7, 32–34].

Interval growth has been reported in haemangiomas, although it is extremely rare. In this situation, the initial diagnosis should be questioned and biopsy studies performed on selected cases [9].

Uncommon enhancement patterns

The current use of state-of-the-art CT and MRI equipment with high temporal resolution increasingly reveals less known enhancing patterns of haemangiomas. The so-called *flash-filling pattern* is mostly seen in small tumours under

Fig. 14 Haemangioma and associated liver abnormalities.
a, b Haemangioma in fatty liver.
a Plain CT image disclosing a low liver density consistent with diffuse steatosis. The haemangioma is practically invisible.
b After contrast enhancement, the haemangioma is disclosed with the typical peripheral globular enhancement.
c, d Association of focal nodular hyperplasia (FNH) and haemangioma.
c Arterial phase of a dynamic MRI depicting the vigorous enhancement of an FNH at the left liver lobe and the peripheral puddling of contrast in the small haemangioma at segment VII.
d Portal venous phase of the same case on CT showing contrast retention within the haemangioma and a near-isodensity of the left lobe FNH



2 cm and show fast, intense and uniform enhancement on the arterial phase of the dynamic study, typically, paralleling aortic enhancement (Fig. 9) [35, 36]. Since these tumours may also display colour spots on Doppler examination, differentiation from other hypervascular tumours may be problematic. A key point resides on the evaluation of the late interstitial phase of the dynamic study, where flash-filling haemangiomas should not reveal contrast washout. In contrast to haemangiomas with this type of hyperdynamic status, on the other side of the spectrum, hypodynamic tumours with very slow internal flow may be seen, resulting in a *very delayed fill-in pattern*. These cases request prolonged examination times with ultra-delayed acquisitions, in order to be able to observe the centripetal enhancement and contrast retention within the tumour (Fig. 10). These haemodynamic differences are probably related to the size of the vascular channels composing the haemangioma, with slow flow in areas of large channels and hyperdynamic flow in those containing small-sized channels.

Peri-lesional enhancement is seen in 19–25% of cases and manifests itself as transient hepatic attenuation differences (THAD), corresponding to staining areas seen on the arterial phase of liver enhancement, fading away on the subsequent phases of the dynamic study [36, 37]. Pathological explanation resides in arterio-venous shunting related to their hyperdynamic status. Early opacification of a drainage vein may occur (Fig. 11) [36, 38]. Although

THAD is mostly seen in cases of small flash-filling haemangiomas, larger tumours can also show the same perfusion abnormalities due to portal vein compression and compensatory arterial inflow, determining a peri-tumoural area of parenchymal enhancement [36] (Fig. 12a). It must be stressed that peri-lesional THADs have been described in association with a variety of focal liver lesions, such as metastases, abscesses and hepatocellular carcinoma [38]. Haemangiomas presenting an *early central enhancement* evolving centrifugally are rare (Fig. 12b). According to Kim et al. [13], these lesions have a central area with multiple vascular spaces and peripheral regions with a dominant fibrous component. More frequently, central enhancement is simulated by the axial nature of the CT slices.

Hyalinised or sclerosed haemangioma is rather unusual and is believed to represent the end stage of a haemangioma involution. The replacement of the vascular spaces by hyalinised fibrotic tissue leads to marked modifications of its imaging features, with loss of the typical globular enhancement on contrast-enhanced studies and of its high signal intensity on T2-w images on MRI (Fig. 13). Since it is virtually impossible to propose a definitive diagnosis in such a case, pathologic proof may be necessary, which discloses extensive fibrotic tissue and obliteration of the vascular channels. Differential diagnosis should include hypovascular tumours, especially metastases [7, 39].

Associated liver abnormalities

Haemangioma in fatty liver may be difficult to diagnose on US and CT, due to the decreased liver–lesion contrast which, in severe steatosis, may even be reversed in both imaging modalities, with the haemangioma being hypoechoic and denser, respectively, when compared to the adjacent fatty liver (Fig. 14a,b). Although dynamic CT is able to show the characteristic enhancement pattern, MRI may be preferable in this setting, especially using in-phase and out-of-phase gradient-echo sequences. The high signal intensity on T2-w images and the enhancement features are preserved, thus, rendering the diagnosis relatively straightforward. Sometimes, in CT studies, a peripheral dense halo may be seen surrounding the haemangioma. This corresponds to spared non-fatty parenchyma, as a consequence of the preferential arterial inflow and/or decreased portal flow around the lesion due to compression phenomena [12].

Haemangioma in cirrhotic liver is rare, with an incidence estimated to be about 1.7% at pathologic examination and 0.6% at CT, which is clearly lower than the frequency in unselected autopsy series or at CT in non-cirrhotic patients [40, 41]. Despite the stiffening of the liver parenchyma, haemangiomas generally retain their characteristic findings, both on T2-w images and the enhancement pattern. In rare cases, however, mostly in advanced cirrhosis, they can lose their typical

imaging features due to the development of fibrosis, determining lower volume and lower signal intensity on T2-w images [12, 40, 42]. MRI seems to be superior to CT for characterising haemangiomas in cirrhosis, due to its intrinsic higher contrast resolution and the additional information conveyed by the T2-w sequences, which can also incorporate quantitative data as T2 relaxation value calculation and/or performance of sequences using very late echo times [40].

Haemangioma associated with focal nodular hyperplasia (FNH) (Fig. 14c,d) has been reported in approximately 20% of cases of patients having a concomitant FNH, a prevalence that is higher than that observed in the general population. A common physiopathological mechanism may explain this association, which is believed to result from a focal disturbance of the liver blood supply facilitating a hyperplastic response and subsequent development of these benign tumours [43, 44].

In conclusion, liver haemangiomas have specific imaging features, allowing its characterisation with cross-sectional imaging techniques. There is, however, a wide range of findings that fall out of the typical description, which are, essentially, due to modifications of the tumour structure or flow dynamics. Current state-of-the-art imaging techniques are more prone to demonstrating these findings, thus, increasing their diagnostic confidence level.

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