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● *Review Article*

WFUMB POSITION PAPER—INCIDENTAL FINDINGS, HOW TO MANAGE: SPLEEN

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Abstract—The World Federation for Ultrasound in Medicine and Biology (WFUMB) is addressing the issue of incidental findings (IFs) with a series of publications entitled "Incidental Imaging Findings—The Role of Medical Ultrasound." IFs are less commonly encountered in the spleen than in many other abdominal organs but remain a frequent dilemma in clinical practice. A histological diagnosis is rarely necessary for patient management. Many IFs, such as secondary spleens and splenic cysts, are harmless and do not require any further investigation. The diagnosis of many other focal splenic lesions is, however, often problematic. The following overview is intended to illustrate a variety of incidentally detected spleen pathologies such as size variants, shape variants, secondary spleens, focal splenic lesions and splenic calcifications. It should aid the examiner in establishing the diagnosis. Moreover, it should help the ultrasound practitioner decide which pathologies need no further investigation, those requiring interval imaging and cases in which immediate further diagnostic procedures are required.•In patients with splenomegaly (>13 × 6 cm), an imaging, clinical and laboratory evaluation is usually required to determine the underlying cause.•Most congenital variants of the spleen, and accessory spleens, have characteristic ultrasound appearances and do not require further evaluation or follow-up.•The use of ultrasound contrast microbubbles (contrast-enhanced ultrasound) is of particular value in ultrasound imaging of the spleen when an indeterminate incidental finding is encountered.•Splenosis can be confidently diagnosed with contrast-enhanced ultrasound and usually requires no additional imaging or follow-up.•The cause of an inhomogeneous splenic parenchyma must be clarified, especially to exclude sarcoidosis or lymphomatous infiltration.• Incidental indeterminate focal splenic lesions (with the exception of simple cysts) are often best managed by an interval follow-up examination (initially after 3 months) unless there clearly malignant clinical or sonographic features.•For splenic calcifications, including the "starry sky" spleen, no follow-up is necessary. (E-mail: c.f.dietrich@googlemail.com)

SUMMARY STATEMENTS

Introduction and definition

The World Federation for Ultrasound in Medicine and Biology (WFUMB) is dedicated to advancing ultrasound (US) by encouraging research, promoting international cooperation, disseminating scientific information and improving communication and understanding in the world community using US in medicine and biology. Therefore, the mission of WFUMB is to bring sustainable US programs to the underserved areas of the world to improve global health care through collaboration, communication and education (www.wfumb.org).

The WFUMB is addressing the issue of incidental findings (IFs) with a series of publications "Incidental Imaging Findings—The Role of Medical Ultrasound" (Dietrich et al. 2020a, 2020d). Each WFUMB position paper on IFs will follow the same template and accordingly be uniformly structured to help readers interpret the key messages (Dietrich et al. 2020a).

The WFUMB position paper on splenic incidentalomas will:

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1 Describe the definition, prevalence and imaging features of incidental findings,
2 Define red flag features of IFs,
3 Explain strategies for work-up and follow-up, and
4 Conclude with recommendations related to the role of US techniques.

SPLENIC INCIDENTALOMA

Prevalence, epidemiology

IFs on imaging studies are asymptomatic and unexpected pathologies, unrelated to the presenting illness (Scharitzer et al. 2017; Dietrich et al. 2020d). Increasing use of imaging, particularly computed tomography (CT), magnetic resonance imaging (MRI) and US, results in large numbers of IFs. Most are not of clinical significance, and therefore, it is important to define criteria for further management to minimise patient anxiety and avoid unnecessary diagnostic or biopsy procedures (Scharitzer et al. 2017). The largest number of IFs is detected in CT examinations of the abdomen and pelvis (≤61%); however, in only 1% of patients, without a history of malignant tumours, are these associated with malignancy (Ekeh et al. 2010; Scharitzer et al. 2017). In comparison with many other abdominal organs, focal splenic lesions (FSLs) are uncommon although they are usually clinically silent and discovered incidentally. In two retrospective reviews of abdominal CT scans in the setting of trauma and one in suspected appendicitis, incidental splenic findings were detected in only 1%−3% of cases, and with the majority considered to be either normal variants or benign lesions not requiring further work-up (Paluska et al. 2007; Ekeh et al. 2010; Ozao-Choy et al. 2011). Incidental splenic findings are even more uncommon in abdominal US examinations.

In one large unpublished series from a University Internal Medicine Ultrasound Centre, 550 FSLs were identified in 200,000 examinations (0.27%). The pathologies comprised 33% lymphomas, 15% infarcts, 11% metastases, 9% cysts, 7% ruptures, 5% haemangiomas, 2% abscesses, 5% other and 8% uncertain; approximately 25% of these 550 lesions were observed incidentally (personal communication from Trenker and Görg, 2020).

Recommendations for managing incidental splenic findings discovered on CT or MRI have been published by the American College of Radiology (Heller et al. 2013); the likelihood of malignancy in an incidentally discovered asymptomatic indeterminate splenic mass is, however, so small in a patient with no history of cancer and no symptoms (fever, weight loss, pain in the upper left quadrant and epigastrium) that the benefit of further characterization and follow-up is debatable (Siewert et al. 2018).

Atypical location, size and shape variations

The spleen has a bean-like shape and is located in the left upper quadrant of the abdomen. Clinical examination is insensitive in detecting splenic enlargement; US provides a simple and reliable method for determining spleen size, which is typically $11 \times 4 \times 7$cm (Sienz et al. 2011). Normal splenic size, however, varies significantly between individuals, depending on the patient age, height, surface area, weight and sex (DeLand 1970; Sienz et al. 2010, 2012; Chow et al. 2016). The spleen also increases in pregnancy (Maymon et al. 2006) and after trauma (Goodman and Aprahamian 1990). Spleen size in children is most closely correlated with body weight (Safak et al. 2005), but is also correlated with age, height and body surface area (Megremis et al. 2004). In routine US practice, spleen size is usually measured in one or two planes. A single measurement of splenic length provides a clinically useful indication of true splenic size (length, volume and weight) (Loftus et al. 1999); splenic width provides similar or greater degrees of accuracy (Lamb et al. 2002). Size determination may be highly clinically relevant, and the causes of abnormal splenic size are multifarious (Curovic Rotbain et al. 2017).

Splenomegaly

Although some patients with splenomegaly present with constitutional or left upper quadrant symptoms, it is frequently an asymptomatic IF. It is difficult to recommend a single measurement for the upper limit of normal splenic size because of the wide variation between different demographic groups. A length of more than 12 cm has previously been recommended to define significant splenomegaly but many normal patients have larger spleens, particularly tall men (Hosey et al. 2006; Chow et al. 2016). Longitudinal measurements of between 11 and 14 cm have also been used to define splenomegaly. As a guide in adult patients, a length of more than 13 cm should be considered abnormal (Pozo et al. 2009; Sienz et al. 2011). US practitioners must, however, use their judgement, incorporating patient factors when interpreting measurements of splenic size.

Diagnostic work-up and follow-up strategy. Patients with incidentally discovered diffuse splenomegaly will usually require a full clinical, haematological, biochemical, microbiological and immunological assessment. Imaging studies may identify features of chronic liver disease/portal hypertension or may reveal multisystem disease—particularly lymphadenopathy (Trenker et al. 2020a, 2020b), primary or secondary malignancy or granulomatous disease—suggesting the underlying pathology (Pozo et al. 2009). In the absence

of focal splenic abnormality, the cause of isolated splenomegaly frequently cannot be determined with imaging studies alone. Haematological disease is the most frequent cause; congestion caused by liver cirrhosis and infective causes are also common, and rare causes such as amyloidosis should be considered (Barreiros et al. 2009). US should be extended to examine the liver and portal venous system (e.g., flow direction, flow velocity, collaterals, thrombosis) and to search for abdominal and retroperitoneal lymphadenopathy (Trenker et al. 2018). Shear-wave elastography has been found to be useful in predicting the etiology of splenomegaly (Batur et al. 2019; Yalcin and Demir 2021). However, in a significant number of cases, the root cause cannot be identified, even after a complete diagnostic workup (Curovic Rotbain et al. 2017).

The imaging follow-up of splenomegaly depends on the cause.

Hyposplenia

Spleens smaller than $6-7 \times 3$ cm are defined as hyposplenia (Gorg et al. 2003; Dietrich et al. 1999, 2015; Allgayer and Dietrich 2008; Trenker et al. 2019). Hyposplenia can occur as a normal variant and, in older patients, is almost always an incidental finding. Functional hyposplenism (FH) is the clinical condition characterised by a defective immune response to infectious agents and thrombocytosis, increasing the risk of thromboembolic events; it has a wide variety of causes including sickle cell anemia, stem cell transplantation and celiac sprue (Gorg et al. 2003; Sienz et al. 2011; Kirkineska et al. 2014). Patients with FH are at risk of developing overwhelming sepsis, particularly from streptococcus pneumonia; immunisation and antibiotic prophylaxis are recommended (Kirkineska et al. 2014).

Diagnostic work-up and follow-up strategy. Diagnosis is based on haematological abnormalities and functional nuclear medicine examinations (William et al. 2007). Patients with small spleens should be suspected of having FH, particularly where there is reduced or absent parenchymal blood flow on colour Doppler US (Gorg 2007); abnormal contrast-enhanced ultrasound (CEUS) patterns may also frequently be seen (Trenker et al. 2019).

Routine imaging follow-up is not usually required but will depend on the underlying cause.

Variants of shape

The spleen develops from multiple lobules that fuse before birth. Remnants of these lobules may persist as splenic lobulation, clefts and septa; occasionally complete septations with several splenic hila may be seen. Theses normal variants may be misinterpreted as splenic laceration in the setting of trauma (Gayer et al. 2006) or as chronic splenic infarction.

Diagnostic work-up and follow-up strategy. Depending on the clinical situation and history, CEUS may be used to diagnose or exclude splenic laceration or splenic infarction (Sidhu et al. 2018).

No follow-up is necessary.

Accessory spleen and splenosis

Accessory spleen (AS, splenunculus) has a prevalence of 10%−30% in autopsy series (Dietrich et al. 1998; Gayer et al. 2006; Sienz et al. 2011) and is a frequent incidental finding on imaging studies, reported in 16% of patients undergoing contrast-enhanced abdominal CT (Mortele et al. 2004). A recent meta-analysis of data from 81 studies including more than 22,0000 subjects reported an overall pooled prevalence of 14.5% (and 11.5% in healthy subjects). Considering only imaging studies (7080 cases in 18 studies), the prevalence of AS was 16.6% (Vikse et al. 2017) (Fig. 1).

On US, AS is usually isoechoic with adjacent splenic parenchyma, solitary, round, well-defined and <2 cm in diameter. They are typically located close to the spleen (Mortele et al. 2004); 62.1 % are found in the splenic hilum and 5.2% above or below the hilum (Vikse et al. 2017). Demonstration of a vascular supply from the splenic vessels is frequently possible with colour Doppler US and is a diagnostic feature (Subramanyam et al. 1984). Occasionally, accessory spleens may be multiple (19.6% of cases with ≥ 1 AS, 3.4% with ≥ 3 ASs) and located away from the spleen (see European Federation of Societies for Ultrasound in Medicine and Biology [EFSUMB] case of the month, http://www.efsumb.org/blog/archives/2545) (Vikse et al. 2017). Although sonographic diagnosis is not usually problematic, it can sometimes be difficult to differentiate accessory spleens from pathological masses, particularly in patients with a history of malignancy, and they may mimic adrenal or peritoneal masses or enlarged lymph nodes (Dietrich et al. 2020). Accessory spleens are located in the pancreatic tail in a significant minority of cases (5.5%) and can be particularly diagnostically challenging, with a high risk of misdiagnosis as hypervascular pancreatic tumours (Spencer et al. 2010; Osher et al. 2016; Vikse et al. 2017; Ding et al. 2018) leading to unnecessary biopsy procedures or surgery. Interobserver disagreement for diagnosis of intrapancreatic AS was found to be substantial with endoscopic US (Kim et al. 2019). In particular, for diagnosis of AS in atypical locations (endoscopic), US-guided fine-needle aspiration biopsy

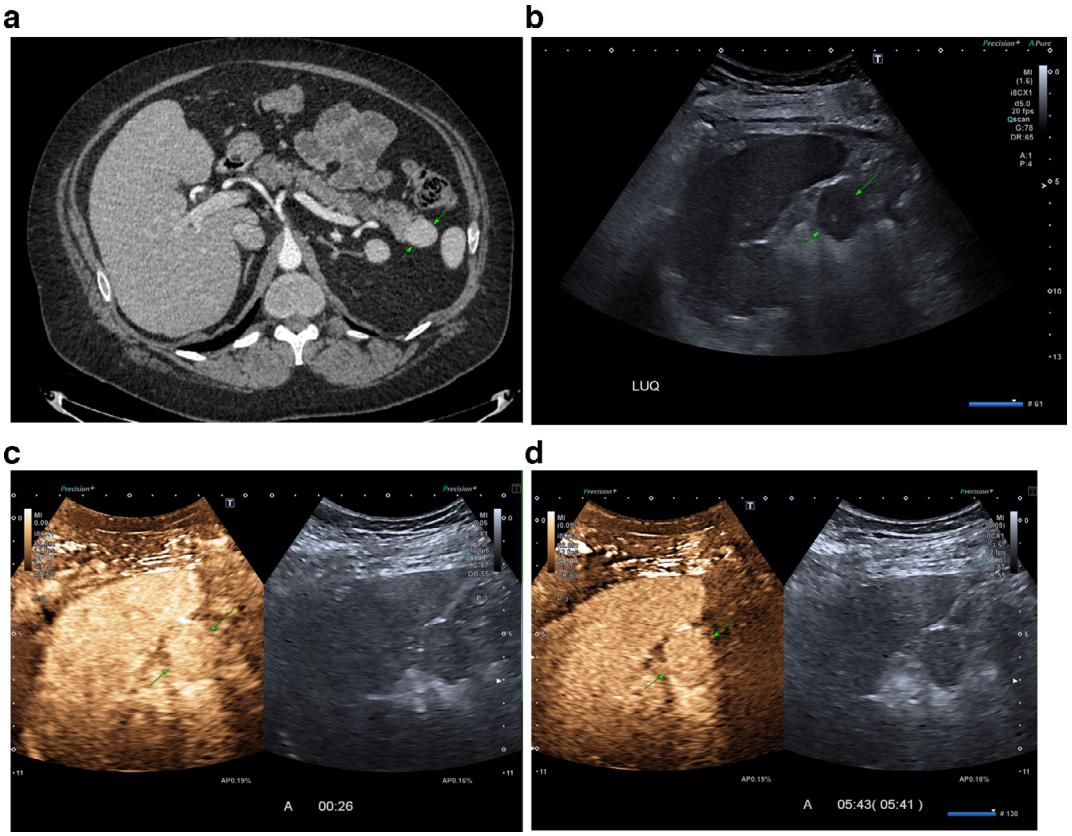

Fig. 1. Pancreatic tail splenunculus. Image from a CT urogram examination in a 56 year old man undergoing investigation for visible haematuria. A small incidentally discovered hypervascular mass is present in the pancreatic tail (a, arrows). The mass is visible on ultrasound with echogenicity identical to the adjacent spleen (b, arrows). Following injection of ultrasound contrast microbubbles the mass enhances in an identical manner to adjacent splenic parenchyma in the arterial (c, arrows) and late phases (5 minutes 41 seconds post injection, arrows (d)). Equivalent enhancement to splenic parenchyma and persistent late phase enhancement are characteristic features of ectopic splenic tissue.

(FNAB) may be useful (Tatsas et al. 2012; Hocke et al. 2013, 2017; Gilani et al. 2020).

Splenosis refers to autotransplantation of normal splenic tissue following trauma or surgery, usually within the abdomen or pelvis (Lake et al. 2012). The splenic deposits are usually asymptomatic and discovered as IFs on imaging studies. Splenosis masses are frequently misinterpreted as a pathological finding, particularly when the history of splenectomy or trauma is not appreciated, and may lead to unnecessary biopsy or surgical procedures (Tasci et al. 2005; Sarraf et al. 2006).

Diagnostic work-up and follow-up strategy. Management algorithms have been proposed to reduce the risk of unnecessary resection (Osher et al. 2016; Baugh et al. 2019). Although scintigraphy, using labelled denatured red blood cells, has frequently been used to detect and diagnose ectopic splenic tissue (Ekmekci et al. 2015), CEUS is also ideally suited to diagnosis of accessory splenic tissue, which will have the same arterial and parenchymal enhancement patterns as normal spleen. Persistent late-phase enhancement is a particularly valuable feature because of the characteristic sequestration of contrast microbubbles by normal splenic tissue (Lim et al. 2004) extending far beyond the washout of bubbles from pathological tissue (Catalano et al. 2006; Rogers et al. 2011; Kruger and Freeman 2019). Characterisation of suspected accessory spleens and splenosis is an indication for CEUS as recommended by EFSUMB guidelines (Sidhu et al. 2018). No follow-up is necessary.

Inhomogeneous splenic parenchyma

Splenic parenchyma is usually characterized by a homogeneous echogenicity. An inhomogeneous parenchymal echotexture, without clearly defined focal lesions, may also be regularly encountered on US (Sienz et al. 2011). Whilst this can represent an incidental normal variant, it may also indicate the presence of underlying disease including infarction, congestion,

infection, granulomatous disease (Tana et al. 2014b, 2019) and malignancy and may cause diagnostic difficulty.

Diagnostic work-up and follow-up strategy. When an inhomogeneous splenic parenchyma is identified, CEUS is recommended to improve the detection of any focal abnormalities (Gorg et al. 2006; Sidhu et al. 2018) with diagnostic performance equivalent to that of CT or MRI (Schwarze et al. 2019). Splenic infarction is not always symptomatic and is a particular diagnostic consideration for patients with an inhomogeneous splenic parenchyma; CEUS is usually diagnostic.

Follow-up will be determined by the result of CEUS and clinical findings.

Splenic cysts

Although the most common incidental splenic lesions, splenic cysts are observed in less than 0.1% of routine abdominal US examinations (Gorg et al. 2014). They are usually asymptomatic but may cause pressure symptoms if large. Cysts may be broadly categorised as congenital, pseudocysts or cystic masses secondary to infection/inflammation or neoplasia. The majority of splenic cysts are pseudocysts secondary to trauma (Dawes and Malangoni 1986; Ahmed et al. 2011; Sangiorgio and Arber 2021).

Diagnostic work-up and follow-up strategy. US frequently cannot determine the nature of a cyst but, if entirely sonographically simple, then it is almost certainly benign and, as an incidental finding, does not require further investigation or follow-up. Some benign cysts may manifest minor complexity with internal septation or intra-cystic echoes caused by cholesterol crystals or hemorrhage; absence of enhancement on CEUS is reassuring that the cyst is an incidental benign finding (Catalano et al. 2006; Yu et al. 2012). Thick peripheral calcification in an otherwise simple cyst is a feature of some benign post-traumatic pseudocysts and is not of concern (Heller et al. 2013). Colour Doppler US should always be employed to exclude (intrasplenic) pseudoaneurysm (Ignee et al. 2014; Tana et al. 2014a). Although abscess formation must be considered in any patient with a cystic splenic lesion, the absence of leukocytosis, fever, abdominal pain and nausea/vomiting makes a pyogenic splenic abscess unlikely (Tung et al. 2006); however, occasionally abscess formation may be occult, particularly if the patient is immunocompromised. CEUS in splenic abscess formation will typically manifest a thickened enhancing rim and sometimes enhancing septation (Catalano et al. 2004). When there is concern over abscess formation, diagnostic aspiration can usually be performed safely (Chou et al. 1998). Multiple incidental complex splenic nodules in an immunocompromised patient should also raise the possibility of fungal (candida) infection, and several sonographic patterns may be seen (Pastakia et al. 1988). Parasitic infection with *Echinococcus granulosus* (hydatid disease) is usually asymptomatic. The spleen is the third most common site for hydatic cysts, and therefore, in some geographical regions *E. granulosus* is among the most common etiologies of splenic cystic lesions (Akbulut et al. 2013; Rasheed et al. 2013; Brunetti et al. 2018). Patient history and geographical origin, results of serological examinations and characteristic sonographic appearances (World Health Organization Informal Working Group 2003) should be included in diagnostic assessment. With CEUS, the wall, septa or contents of hydatid cysts never show contrast enhancement (Schwarze et al. 2018; Dietrich et al. 2020b, 2020c).

Other splenic pathologies may result in more complex splenic masses with a cystic component, including haematoma, infarction, metastases, and primary splenic malignancy. Splenic lymphangioma is a rare benign splenic tumour typically having a well-defined multilocular US appearance (Peddu et al. 2004). Further management in these cases will depend on imaging features and clinical assessment.

Follow-up is not usually required for incidentally detected splenic cysts that are sonographically simple or cysts showing no enhancement on CEUS.

Solid FSLs

Solid FSLs are uncommon, usually asymptomatic and present as IFs on imaging studies. Benign lesions are slightly more common than malignant lesions (Goerg et al. 1991). Haemangiomas are the most common benign tumours of the spleen (Giovagnoni et al. 2005) and are often classified with hamartomas (splenomas) as benign vascular tumours (Gorg et al. 2003; Sangiorgio and Arber 2021) (Fig. 2). Other incidentally discovered rarer benign splenic tumours usually do not have characteristic grey-scale US features and include littoral cell angiomas (Cui et al. 2013), extramedullary haematopoiesis, myolipomas, sclerosing angiomatoid nodular transformation of the spleen and pseudotumours (Gorg et al. 2003; Sangiorgio and Arber 2021). Benign lesions may be associated with malignancy elsewhere. Non-neoplastic conditions such as splenic abscesses and infarctions may also present as incidentally discovered splenic masses.

Lymphoma is the most common malignancy affecting the spleen and is almost always seen in disseminated disease, with primary splenic lymphoma occurring in only 1%−2% of cases at presentation (Bhatia et al. 2007) (Fig. 3). Non-lymphomatous metastases are unusual in the spleen (Lam and Tang 2000); most often seen in patients with widespread metastatic

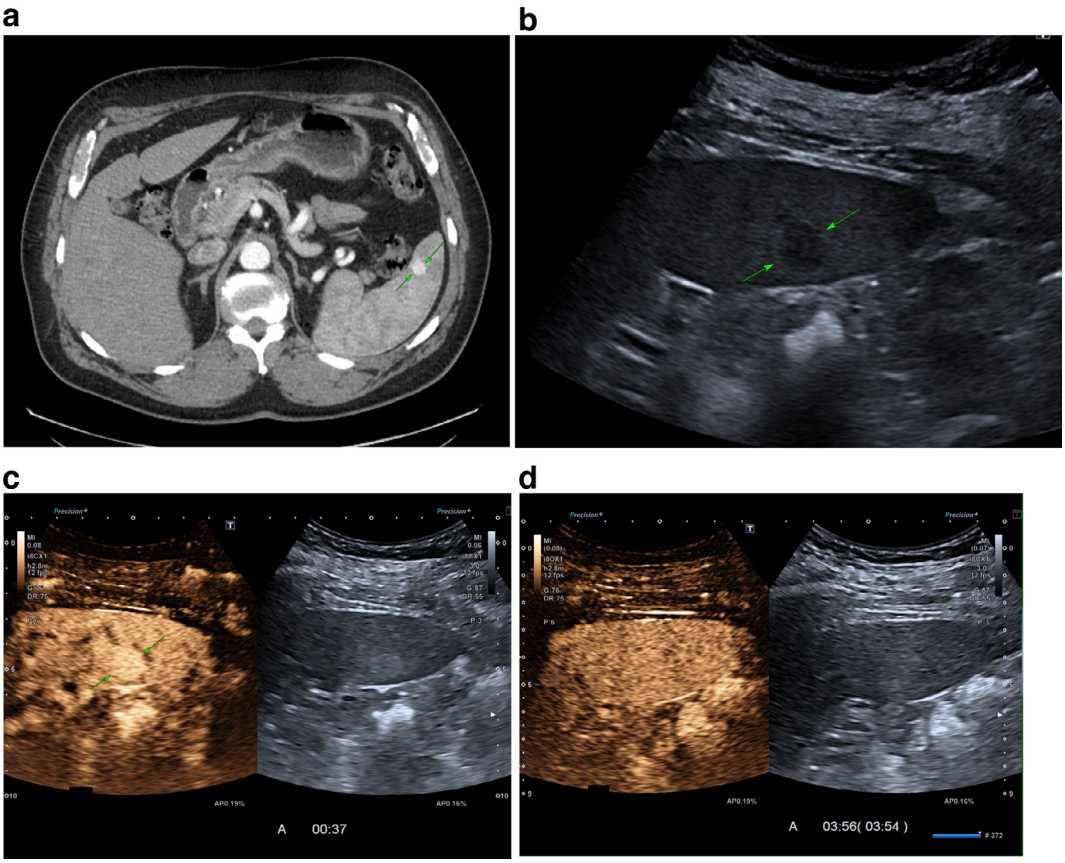

Fig. 2. Presumed atypical benign vascular tumor of the spleen. Image from a renal mass characterisation protocol CT in a 61 year old man being investigated for a mildly complex renal cyst (not shown). The CT shows a small incidentally discovered hypervascular splenic lesion (a, arrows). On ultrasound the mass is echo-poor and cannot be characterised (b, arrows). Following injection of ultrasound contrast microbubbles the mass is hypervascular in the arterial phase (c, arrows), in the late phase the mass is isoenhancing with adjacent spleen and difficult to identify (d). Although the grey scale morphology is unable to differentiate between a benign and malignant lesion, the ultrasound contrast appearances are characteristic of a benign lesion (likely benign vascular tumour). This case is suitable for ultrasound surveillance.

disease, they may have a variety of sonographic patterns. The presence of a known cancer is a significant predictor of a malignant splenic lesion (Jang et al. 2018). Primary non-lymphomatous splenic malignancy is exceptionally rare, and affected patients will usually be symptomatic at presentation (Falk et al. 1993; Thompson et al. 2005).

Diagnostic work-up and follow-up strategy. In comparison with many other abdominal organs, imaging has a limited ability to characterise solid splenic masses, and the appearances of benign and malignant masses frequently overlap (Heller et al. 2013). Correlation with laboratory tests, clinical examination and previous imaging is essential for accurate patient management (Ahmed et al. 2011; Gore and Ecanow 2015). Ill-defined margins and hypovascularity on contrast-enhanced CT and MRI are predictors of malignancy (Cao et al. 2018).

On US, solid splenic lesions can be divided into those that are echogenic and those that are echopoor. Most incidentally detected echogenic lesion are haemangiomas, which are usually solitary (but occasionally multiple), well defined and avascular on colour Doppler examination (Peddu et al. 2004). When these are small (<2 cm in diameter) in a patient with no cancer history, interval imaging to confirm stability is safe for further management (Willcox et al. 2000). Haemangiomas may, however, also have more atypical appearances that do not allow confident sonographic diagnosis with mixed or low echogenicity patterns, cystic change and calcification (Abbott et al. 2004; Peddu et al. 2004).

Echopoor splenic masses represent the greatest diagnostic challenge, and malignant, benign and non-neoplastic lesions may be echopoor (Gorg et al. 2003). Lymphoma deposits are almost always echopoor (Goerg et al. 1990), and a variety of sonographic patterns may be seen (Gorg et al. 1997). Granulomatous disease is also a frequent cause of echopoor FSLs (Tana et al. 2014b) (Fig. 4). Therefore, in most cases a

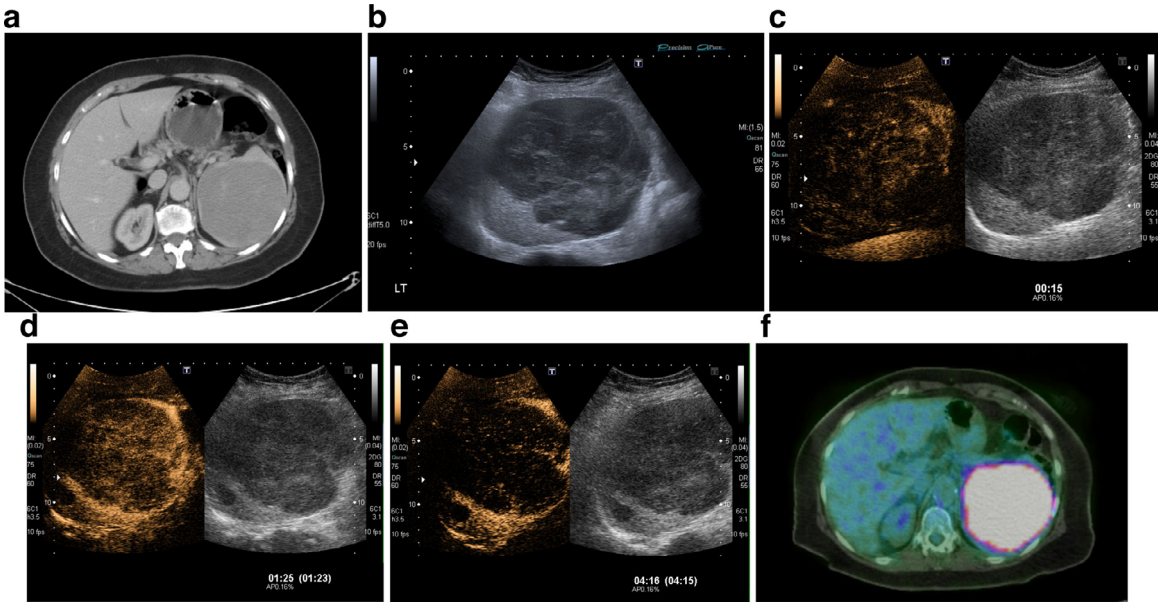

Fig. 3. Splenic Lymphoma. Imaging from a staging CT scan in a 77 year old man with a biopsy proven small oesophageal cancer (not shown). The CT image shows a large, but asymptomatic, mass in the spleen (a). Ultrasound shows that the mass is heterogeneous but predominantly very echo-poor (b) Following ultrasound contrast administration the mass is hypovascular but with visible internal vessels in the arterial phase (c), is hypovascular in the late portal phase (d) and shows microbubble washout in the late phase (Figure 3e). This enhancement pattern suggests a malignant lesion. On FDG PET CT the mass is highly FDG avid (f). The patient underwent oesophagectomy and splenectomy, histology revealed a previously undiagnosed lymphoma.

definitive diagnosis is not possible using US alone. Correlation with clinical, laboratory and other imaging investigations will usually allow for a short differential diagnosis.

The spleen is ideally suited for CEUS evaluation because of its high vascularity and property of sequestrating contrast microbubbles, resulting in persistent, long-lasting enhancement (Figs. 5 and 6). The use of CEUS for identification and characterisation of solid splenic masses is recommended (Ignee et al. 2014; Sidhu et al. 2018). In CEUS, two distinct patterns can be distinguished in incidental hypo-echoic splenic masses:

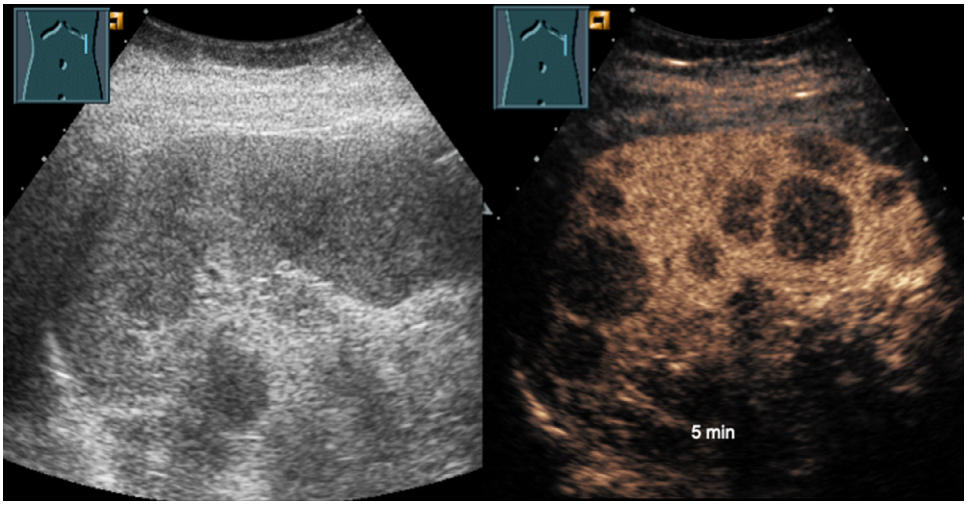

Fig. 4. A patient with granulomatous spleen infiltration in sarcoid disease. Inhomogeneous splenic parenchyma in the B-mode ultrasound (left). In the parenchymal phase of CEUS (5 min) the lesions present a hypoenhancement.

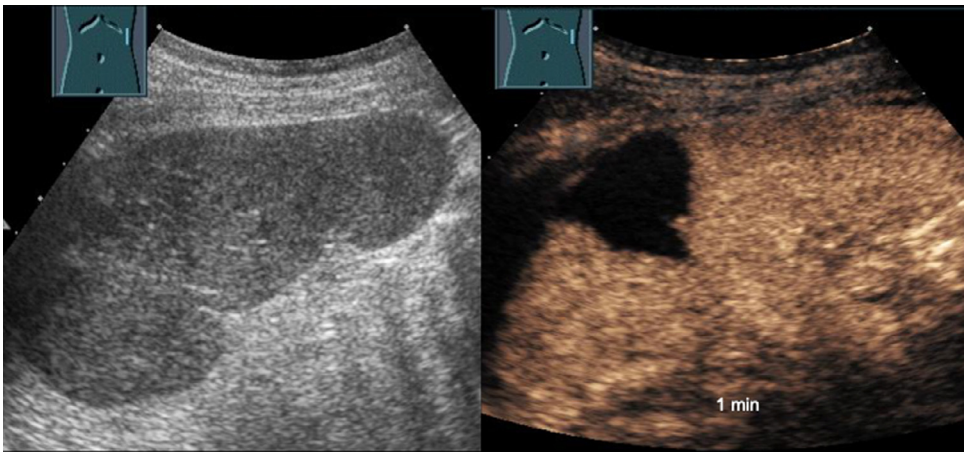

Fig. 5. Flat, hypoechoic, wedge-shaped area in the spleen (left) as incidental finding. In the CEUS (right) there is no contrast media uptake appropriate to a splenic infarction in this area.

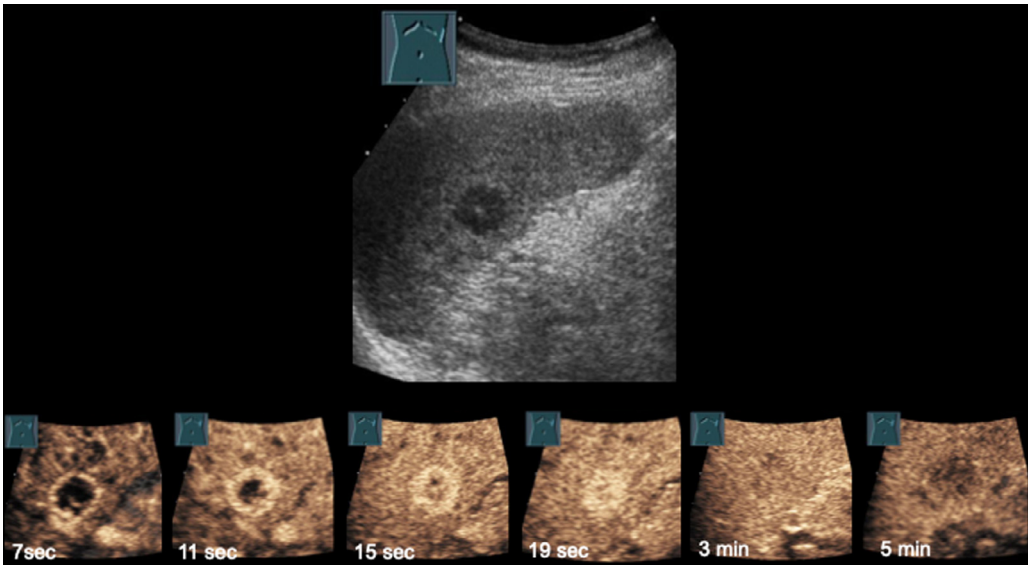

Fig. 6. Hypoechoic, accidentally detected focal splenic lesion in B-mode ultrasound. In CEUS, the lesion shows an early arterial-peripherally beginning, enhancement ("high flow" pattern). Parenchymal the lesion shows a long-lasting enhancement with hypoenhancement in the parenchymal phase. This finding is indicative of a hemangioma or splenoma.

lesions may manifest arterial iso- to hypo-enhancement with late-phase (parenchymal) hypo-enhancement (washout) (Gorg 2007; Bert et al. 2010; Ignee et al. 2014). This pattern is non-specific and unhelpful for differentiating a malignant from a benign lesion; although this is the most common pattern in malignant lesions, it is also seen in benign conditions such as granulomatous disease and therefore lacks specificity (Gorg et al. 2014; Tana et al. 2014b, 2019). Alternatively, lesions may present a strong early-arterial enhancement—starting peripherally or centrally—-with rapid arterial filling (Caremani et al. 2013) and, in the parenchymal phase, may retain the contrast medium or manifest slight hypo-enhancement (Gorg 2007; Gorg et al. 2014). This finding is useful as this pattern is associated with a benign etiology.

Malignant splenic lesions typically manifest variably arterial enhancement and parenchymal phase microbubble washout; benign lesions typically either manifest no contrast enhancement in any phase or retain microbubbles in the late phase (Catalano et al. 2006; Gorg 2007; von Herbay et al. 2010; Neesse et al. 2010; Yu et al. 2012; Caremani et al. 2013; Li et al. 2020). Intralesional vessels, heterogeneous enhancement, necrotic regions and a dotted enhancement pattern are also features suggesting malignancy. As a rule, lesions with hyperenhancement during all phases, including the

very late phases, are with a high probability benign (Ignee et al. 2014). Arterial phase hyper- or iso-enhancement has also been reported to be an independent predictor of benign lesions and is a feature of some benign vascular tumours (Stang et al. 2011; Yu et al. 2012).

In a meta-analysis of eight studies, CEUS was reported to be more sensitive and specific than conventional US in diagnosing splenic lesions (Li et al. 2020). In a recent single-centre study, the diagnostic performance of CEUS for FSLs was found to be non-inferior to that of CT and MRI (Schwarze et al. 2019). Therefore, CEUS can be a powerful tool for triage of incidental indeterminate splenic lesions (Ignee et al. 2014) into those that are likely to be benign and can be managed by imaging surveillance, and those that are more worrying for malignancy and for which further work-up and biopsy may be required.

[^{18}F]Flurodeoxyglucose-positron emission tomography/computed tomography (PET-CT) may also be valuable in triage of indeterminate splenic masses having a high negative-predictive value for malignancy (Metser et al. 2005; Metser and Even-Sapir 2006).

As an IF in an asymptomatic patient with no history of cancer, an indeterminate FSL is usually benign (Siewert et al. 2018). Where there are no clearly malignant imaging features, surveillance is an attractive management strategy. However, there are no generally accepted recommendations for surveillance interval and duration. MRI has been recommended for this purpose at 6 and 12 mo (Heller et al. 2013; Thut et al. 2017). US is well suited to surveillance of splenic masses; in a single-centre study, follow-up was undertaken at three monthly intervals for the first year and then annually for at least 5 y; 85% of masses remained unchanged (Bert et al. 2010). When there is size progression on surveillance, further work-up and biopsy may be required (Bert et al. 2010; Ignee et al. 2014).

In conclusion, and in accordance with an algorithm of the American College of Radiology for managing CT- or MRI-detected incidental splenic findings (Heller et al. 2013), no follow-up is recommended for solid FSLs manifesting definitive benign features on US and CEUS, contrast-enhanced CT, MRI or PET-CT. In patients with no history of cancer with incidentally discovered indeterminate splenic lesions, imaging surveillance is recommended. If surveillance is done with US, the first follow-up should be at 3 mo, following which annual scans are recommended according to expert opinions. In patients with a history of cancer or suspicious imaging features or in whom the mass manifests increasing size on interval imaging, a full clinical and laboratory work-up is required. Whole-body CT or PET-CT may identify sites of occult disease elsewhere, MRI may provide more information on lesion morphology and PET-CT may help to determine the risk of malignancy. Biopsy may then be indicated.

Splenic calcification

Splenic calcifications are harmless, may be focal or diffuse and are almost invariably observed as IFs (Dietrich et al. 2020b, 2020d). In homozygous sickle-cell anemia, the spleen may shrink in size and may be visualized only as a calcified sickle-shaped organ. Rarely, this pattern can also be observed in autoimmune diseases. Focal calcifications may be seen as the residua of infectious (granulomatous) diseases after cyst treatment with sclerotherapy or splenic abscesses. In some cases, the pathogenesis of the calcification remains uncertain. After perisplenic infections (persplenitis), splenic capsular calcification can be observed.

Calcification within a splenic mass may be seen with benign and malignant tumours. Calcification may occur in non-lymphomatous metastases, as in the liver, particularly secondary to neuroendocrine or colorectal tumours.

Diagnostic work-up and follow-up strategy. Splenic calcifications without an associated mass do not require follow-up.

"Starry sky" spleen

The "starry sky" spleen describes a special form of small nodular diffuse calcifications and can be also found in other parenchymal organs (testes, pancreas, liver, kidney). The cause of this incidental finding is often uncertain although frequently attributed to infectious diseases such as tuberculosis and candidiasis. This IF has no consequences, and further investigation is not required.

Diagnostic work-up and follow-up strategy. No follow-up is necessary.

IS THE IF MALIGNANT?

Primary malignant lesions of the spleen are extremely rare and include primary malignant non-Hodgkin's lymphoma (NHL) of the spleen, primary splenic Hodgkin's disease (HD) and splenic haemangiosarcoma (Gorg 2007).

The most frequent malignancies of the spleen are secondary to hematological diseases. The spleen is involved in 30%−40% of cases of systemic lymphoma (HD: 33%, NHLs: 50%), while primary lymphoma of the spleen has an incidence of only 1% (Caremani et al. 2013). Haematological malignancy accounts for 15.6% of FSLs (Goerg et al. 1991; Comperat et al. 2007); lymphoma deposits are invariably echopoor on US. Homogeneous mild to moderate splenic

enlargement (without FSLs) is also frequently seen in both HD and NHLs, is commonly reactive in etiology and does not always indicate lymphomatous infiltration (Bhatia et al. 2007). Usually, marked splenomegaly indicates an underlying hematological disorder (leukemia, lymphoma), and massive splenomegaly suggests myelofibrosis. In many cases, associated lymphadenopathy can be also seen on US. Positive diagnosis is completed by other imaging and laboratory investigations.

Non-lymphomatous splenic metastases are rare and represent a late appearance in the evolution of malignant disease. Usually, the site or primary tumour is known (Rousselot and Stein 1953; Lam and Tang 2000; Schon et al. 2006; Comperat et al. 2007; Kaza et al. 2010). Neesse et al. (2010) reported an incidence of 32 metastases in 50,000 US examinations in 5 y. They are almost always a sign of advanced disease and often do not influence the patient's overall prognosis. However, not all FSLs associated with malignancy are metastases.

There are no data suggesting that benign FSLs may be at risk for malignant transformation. A sudden, unexpected increase in splenic size in patients with known non-malignant diffuse splenomegaly may, however, suggest that a malignant process has developed, particularly in the context of hepatitis C infection, where there is a known association with NHL (Iliescu et al. 2018); increasing splenic size and appearance of FSLs may be the first signs of lymphomatous disease.

The role of contrast-enhanced techniques

CEUS is recommended for triage of FSLs. A lesion that is constantly non-enhanced or iso-enhanced with adjacent splenic parenchyma in the parenchymal phase is invariably benign, and only periodic imaging follow-up is necessary, whereas a lesion manifesting progressive hypoenhancement is predictive of malignancy in 87% of cases (Stang et al. 2011; Caremani et al. 2013), and other investigations are necessary to exclude malignancy.

Some patterns of contrast enhancement can be indicative, on both CT and MRI for benign or malignant pathology. Early nodular centripetal enhancement and uniform enhancement at delayed imaging is characteristic of splenic hemangioma (Ramani et al. 1997) although this pattern of early-phase enhancement is much less frequently seen than in liver haemangiomas (Catalano et al. 2004). Arterial phase hyper- or isoenhancement has also been reported to be an independent predictor of benign lesions (Stang et al. 2011; Yu et al. 2012). Furthermore, a lesion that is iso- or hyper-enhancing to the spleen in the late phase is more likely to be benign, whereas lymphomatous nodules and splenic metastases present, in most cases, as hypoenhancing nodules in both venous and delayed phase (Rabushka et al. 1994). Splenic angiosarcoma is a heterogenous lesion with intense and multinodular enhancement with focal areas of non-enhancement similar to those of the liver (Thompson et al. 2005; Dong et al. 2016; Klinger et al. 2019).

Combined imaging criteria

PET-CT and positron emission tomography-magnetic resonance imaging are, in most cases undertaken for staging or follow-up of oncologic disease. Incidental finding of a splenic lesion on PET-CT is a rare event.

[^{18}F]Flurodeoxyglucose (^{18}F-FDG)-PET-CT can be used for characterization of an indeterminate splenic mass and has a high negative predictive value for malignancy (Metser et al. 2005). Malignant splenic lesions have, in the majority of cases, avid $^{18-}$F-FDG uptake, whereas the common benign lesions (such as splenic haemangiomas or hamartomas) exhibit no enhanced ^{18}F-FDG uptake. Some benign splenic diseases, such as granulomas and infections, can lead to ^{18}F-FDG uptake and false-positive results for malignancy (Metser and Even-Sapir 2006). In patients with known oncologic pathology, a standardized uptake value threshold of 2.3 can accurately differentiate between benign and malignant FSLs (Metser et al. 2005). PET-CT has very good sensitivity and specificity for diagnosing splenic involvement in lymphoma (de Jong et al. 2009).

Some authors advocate the use of PET-CT in the diagnostic management of an indeterminate splenic mass (Ahmed et al. 2011; Siewert et al. 2018). A splenic mass with no ^{18}F-FDG uptake can be confidently characterized as benign, whereas histologic sampling would be necessary for FDG-avid splenic masses, because of the risk of false-positive results (particularly in patients with no known malignancy) (Metser and Even-Sapir 2006). Care should be taken in the case of splenic metastases from non-FDG avid tumours, such as renal and thyroid cancers (Ahmed et al. 2011), where PET may be falsely negative. These cancers rarely metastasize to the spleen, and when they do, patients will usually are known to have a malignancy and/or CT/PET-CT signs of malignant disease elsewhere in the body. In this situation, splenic findings cannot be described as incidental.

Image-guided biopsy

Biopsy of the spleen is rarely performed, mainly because of the rarity of splenic disease and unjustified fears regarding haemorrhagic complications. When a tissue diagnosis is required in patients with multiple sites of disease, a non-splenic biopsy site is usually preferable, but splenic biopsy is both accurate and safe in most patients where the spleen is the only abnormal organ, or most accessible organ, for biopsy (McInnes et al. 2011). Splenic FNAB and core needle biopsy (CB) are both

well-established and safe techniques with high levels of diagnostic accuracy. Major complications are rare and lower than those for diagnostic splenectomy (McInnes et al. 2011). Diagnostic rates for FNAB and CB are comparable, except in lymphoma, where CB is superior (Civardi et al. 2001). When CB is performed, 18-gauge needles are recommended to maximize diagnostic rates and minimize bleeding complications (Liang et al. 2007; McInnes et al. 2011; Sidhu et al. 2015a, 2015b).

The most common indications for biopsy of FSLs are known or suspected lymphoma, extra-splenic malignancy, immunocompromise and pyrexia of unknown origin. Aspiration should also be considered in cystic lesions where there is a concern over malignancy or abscess. Ultrasound is the imaging modality of choice for most splenic biopsy procedures. Abnormal coagulation must be corrected, the patient must be sufficiently cooperative to be able to maintain suspended respiration and lesions close to the splenic hilum should be avoided (Sidhu et al. 2015a, 2015b). Endoscopic US-guided sampling has been suggested as an alternative to percutaneous image-guided biopsy because of its advantages of a shorter and safer needle path to some focal lesions and better access in cases of lung emphysema Jenssen et al. 2016a, 2016b. Experience is limited to small cohorts of patients, with no major complications reported so far (Fritscher-Ravens et al. 2003; Rana et al. 2017; Saab et al. 2018; Mosquera-Klinger et al. 2020).

Diagnostic work-up and follow-up strategy

Recommendations for follow-up of incidental splenic findings detected on CT or MRI examinations propose that clearly benign lesions or indeterminate lesions remaining constant in size over a period of 12 mo do not require further evaluation. For all other findings, especially in patient with tumour history, further investigation is recommended (Heller et al. 2013). For US, no official guidelines for incidental splenic lesions exist. Nevertheless, the EFSUMB guidelines recommend CEUS for characterization of indeterminate focal lesions (Sidhu et al. 2018). In general, IFs that are not in need of further investigation should always be documented and patients informed, to avoid unnecessary additional investigations and misinterpretation in subsequent illnesses. Patients should be reassured when a clearly harmless finding, such as calcification, is discovered as an IF.

Surgery and other treatment options

The complication rate, morbidity and mortality are higher for diagnostic splenectomy than for percutaneous biopsy procedures. Biopsy has a high accuracy level and is a safer alternative to diagnostic splenectomy (McInnes et al. 2011).

CLINICAL SCENARIOS AND ROLE OF ULTRASOUND

Detection of IFs by transabdominal ultrasound

With good resolution, accessibility and low cost, US is a very useful first-line imaging method for detection of splenic variations in shape and size. Splenomegaly can be easily detected on routine B-mode US. The method can also identify other features suggesting an underlying cause, such as chronic liver disease and lymphadenopathy. Usually, other investigations are necessary to establish the etiology of splenomegaly, but follow-up can be performed with US.

Splenic lesions are detected in 0.1%−0.6% of US examinations (Ekeh et al. 2010; Gorg et al. 2014; Vikse et al. 2017). Detection of FSLs is difficult for small lesions, especially when located under the diaphragm. There is evidence indicating that US imaging could identify 88% of splenic diseases detected at CT, but that US was unable to detect iso-echoic subdiaphragmatic and subcapsular lesions and particularly 50% of infarctions, 33.3% of metastases and 16.6% of lymphomas (Wan et al. 2000). One study with different inclusion criteria reported a much higher incidence of FSLs (10%) with a benign-to-malignant ratio of 1.6 and with a diagnostic accuracy for US that reached 87.2% (Caremani et al. 2013).

CEUS significantly improves detection of infarcted areas, with high sensitivity and specificity. In the detection of splenic metastases, CEUS is 38% more sensitive than grey-scale US and is recommended for detection of splenic metastases in oncologic patients or to monitor their response to therapy, where a tumour response can be seen earlier than on PET (Neesse et al. 2010).

CEUS proved to be very useful in detection of lymphoma nodules. There are studies that indicate a sensitivity of 90% and a specificity of 100%, in comparison to CT scan (Tafuto et al. 2006), and other studies that state a higher sensitivity of CEUS compared with CT or FDG-PET in the detection of nodules positive for lymphoma in patients with HD (Picardi et al. 2009).

Although CEUS significantly improves the detection of lymphoma infiltrations or metastases, the method cannot differentiate between these lesions and small fungal abscesses, which are a particular differential diagnostic concern in immunocompromised patients. Therefore, the differential diagnosis of FSLs detected in patients with lymphoma or malignancies is very important.

Ultrasound, the only and best imaging method

US and CEUS can be used as the only imaging methods in diagnosis and follow-up of AS and splenosis, cysts or some benign FSLs.

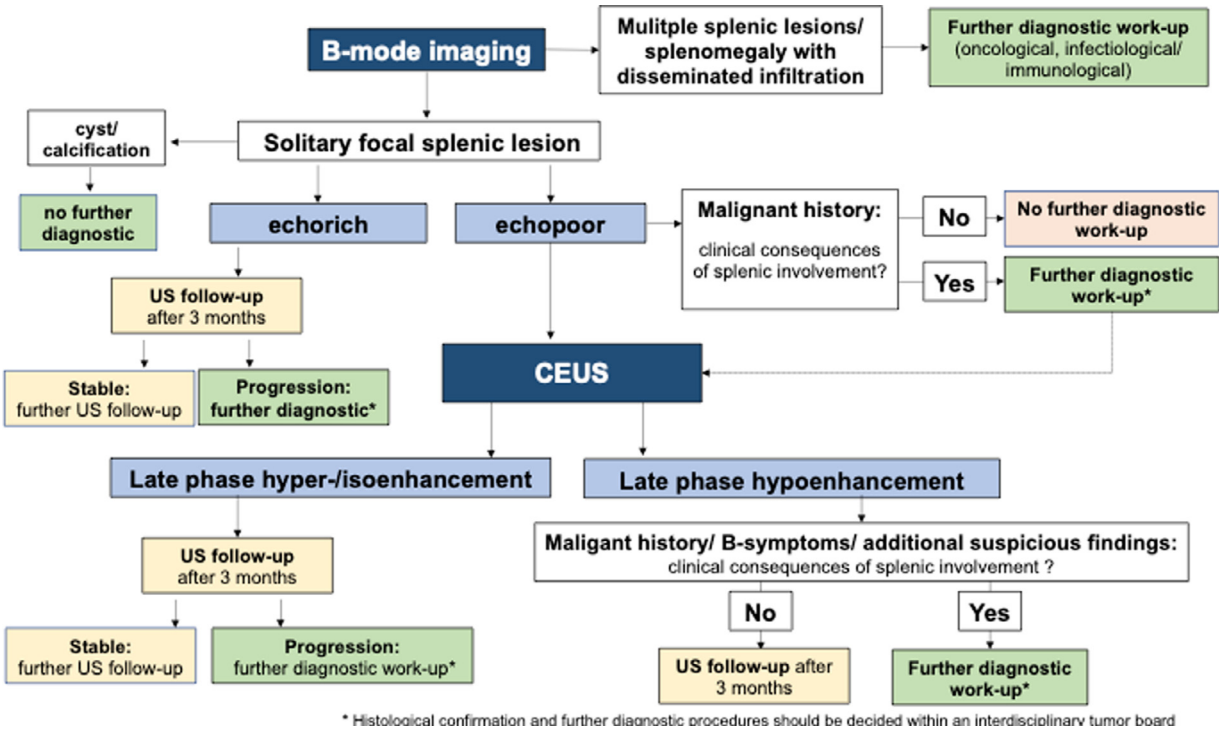

Fig. 7. Work up strategy in focal splenic lesions.

Limitations

Despite its advantages (accessibility, portability, lack of irradiation and lack of toxicity of contrast agents and recent technological advances), a single US study in isolation cannot be recommended as the only imaging method for incidental FSLs that are not anatomical variants or simple cysts. The main difficulty is the differential diagnosis between benign, malignant and infectious FSLs, as well as the difficulty of making a single diagnosis. In combination with clinical and laboratory tests, however, US is usually able to provide a short differential diagnosis and, particularly with the use of CEUS, triage patients into those requiring further investigation and those that can be safely managed by follow-up US imaging.

Detection of IF by cross-sectional imaging (CT, MRI)

Splenic lesions, similarly to lesions in other viscera such as the liver, adrenals and pancreas, are being detected at an increased rate on cross-sectional imaging because of advances in technology. The IFs of splenic lesions in patients who undergo abdominal CT is still uncommon, reported in 1% of cases (Paluska et al. 2007). Incidentally detected splenic lesions, in patients with no known malignancy, are rarely malignant. In a series of 205 incidental splenic lesions, in patients with no known malignancy, only 2 (1%) lesions proved to be malignant (Siewert et al. 2018). Both patients had other malignant lesions elsewhere in the body (diagnoses were established prospectively). In patients with a history of malignancy, it has been reported that 33.8% of FSLs represent metastases (Siewert et al. 2018).

Follow-up of incidentally found FSLs may be necessary because of the relatively low performance of CT in characterizing splenic masses and the significant overlap that exists between the imaging aspects of benign and malignant splenic lesions (Olpin 2017). The recommendations of the American College of Radiologists (ACR) are that incidentally found FSLs, greater than 1 cm and with no clear features of benignity (such as splenic cysts), should undergo either follow-up or further diagnostic work-up with MRI, PET-CT or even biopsy (Heller et al. 2013). The radiologist should classify the imaging features of the splenic lesion as either benign (no further follow-up or diagnostic work-up needed), indeterminate (follow-up needed) or suspicious (further diagnostic work-up needed). The suspicious imaging findings are considered to be heterogenous enhancement, irregular margins, necrosis and splenic parenchymal or vascular invasion. MRI can be used in addition to CT in the diagnosis of FSLs as it can characterize, as benign, some FSLs indeterminate after the CT examination, such as hemorrhagic cysts and hemangiomas. According to the recommendations of ACR (but not ours recommending US and CEUS), the preferred technique for follow-up should be MRI, to avoid unnecessary and potentially harmful irradiation of the patient (Heller et al. 2013). The ACR recommendations do not mention US

techniques for further characterization and follow-up of incidentally detected FSLs. As indicated above, EFSUMB recommends CEUS for characterization of FSLs and suggests a CEUS-based triage algorithm for FSLs with further diagnostic work-up (further imaging, biopsy) of FSLs with low-level arterial enhancement and progressive late-phase contrast washout and surveillance of FSL with benign enhancement characteristics (Sidhu et al. 2018).

Thut et al. (2017) proposed a diagnostic protocol for incidentally detected splenic lesions to avoid unnecessary follow-up. Lesions with indeterminate imaging features that are stable based on previous imaging studies have no need for further diagnostic work-up or follow-up. Furthermore, US follow-up could be applied in patients with an indeterminate splenic lesion after MRI of the upper abdomen (Thut et al. 2017).

Despite this evidence, follow-up of splenic IFs remains controversial because some benign splenic lesions, such as sclerosing angiomatoid nodular transformation of the spleen, can manifest an increase in size on serial examinations, and in such cases, follow-up may lead to unnecessary biopsy procedures or splenectomies in asymptomatic patients (Lewis et al. 2013). In a series of FSLs, followed by CT, 18 of 165 (10.9%) manifested a small increase in size on serial examination of less than 2 mm/y (Siewert et al. 2018). If a focal splenic lesion is stable in size over 1 y, no further follow-up is needed, regardless of the imaging features (Olpin 2017).

STRATEGY

The recommended work-up strategy is summarized in Figure 7. Criteria for this strategy include symptoms (yes, no), past medical history (malignancy, inflammatory disease), distribution (solitary, multiple) of solid or cystic Focal solid lesions and, in addition, the echogenicity (echorich, echopoor, echofree), contrast enhancement with or without washout and stable size or progression during follow-up.

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