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Pictorial Review

Hepatic alveolar hydatid disease (*Echinococcus multilocularis*), a mimic of liver malignancy: a review for the radiologist in non-endemic areas

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Alveolar hydatid disease or alveolar echinococcosis (AE) is caused by the parasite *Echinococcus multilocularis* and is increasingly seen as an imported disease in non-endemic areas such as the UK. It is rare compared to cystic echinococcosis (CE), but like CE commonly affects the liver. AE does have imaging features that can aid in diagnosis, but is often initially misdiagnosed as liver malignancy. It is usually fatal if untreated, underscoring the importance of early diagnosis. This review highlights the role of imaging in AE diagnosis with the broader objective of increasing radiologists' awareness of this unusual, but increasingly prevalent disease.

Introduction

Alveolar hydatid disease or alveolar echinococcosis (AE) is a zoonotic infection with the metacestode (larval) form of the tapeworm *Echinococcus multilocularis*. Compared with its "cystic" counterpart *Echinococcus granulosus* or cystic echinococcosis (CE), AE is rare, but it is a growing public health concern with progressive spread to non-endemic areas in Northern Europe.[1,2] Infection usually takes place through direct or indirect ingestion (via contaminated food) of parasite eggs from faeces of foxes and dogs. Once ingested, eggs hatch and larvae penetrate the gut mucosa to reach the liver via the splanchnic circulation or lymphatics, before spreading to other organs either by direct invasion or metastatic spread.[3,4] AE is invariably fatal if untreated, can be difficult to treat once diagnosed, and once initiated treatment response is difficult to assess. Clinical, serological and imaging features all assist with diagnosis, but radiologists have an essential role in early diagnosis, driving timely referral to specialist care, and imaging follow-up;[5] however, imaging features of AE are variable and can often be confused with alternative diagnoses, so that initial misdiagnosis is common,[6–9] particularly in non-endemic areas such as the UK. The purpose of this review is therefore to provide an overview of AE and its imaging features in order to increase radiologists' awareness of this rare but increasingly prevalent disease.

Epidemiology

AE is only seen in the northern hemisphere (unlike CE that occurs worldwide). It is more common in Russia, China,

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and parts of North America. AE is more prevalent amongst individuals who have extended exposure to dogs (particularly those that roam outdoors) and foxes (e.g. farmers and gardeners). European incidence, particularly in Central and Northern regions has more than doubled in recent years. No cases have been reported as having been acquired in the UK, but increasing numbers of patients with AE are being diagnosed and managed in the UK as a result of northward migration of the disease and population migration from endemic areas.[1,2,9,10]

Radiological pathology

There is a 5–15 year asymptomatic incubation period and development of a primary AE liver lesion is slow.[11]

Hepatic disease: lesional

An important pathological distinction between AE and CE is the lack of formation of "cysts" (Table 1). Despite this, AE lesions often have a "cystic" appearance on imaging, which can be a useful radiological descriptor, but when used in this review does not imply histological formation of a cyst.

Early phase infection is typically characterised by an irregular multi-loculate hepatic mass, containing multiple vesicles (ranging from <1 to 30 mm in size), of irregular shape and size. Each vesicle contains a semi-solid (rather than fluid) protein-rich matrix, with ill-defined margins consisting of a thin non-cellular laminated membrane and an inner nucleated germinal layer.[11–13] Budding begins from the peripheral germinal layer causing infiltration at the lesion margin into surrounding parenchymal (and extra-parenchymal) tissues.[11]

As the lesion increases in size, there is central hypovascularity and secondary central necrosis. This can result in superimposed bacterial infection and central abscess development. Chronic central inflammation eventually results in fibrosis that can result in central calcification.[14]

Table 1
Summary of pathological and imaging differences between AE and CE.

	Alveolar echinococcosis	Cystic echinococcosis
Lesion margin	• Infiltrating, irregular margins	• Well-defined, marginated
Central mass	• Solid/small cystic[a] components • Irregular central necrosis	• Large cystic/ multicystic • Solid inactive lesions
Contrast enhancement	• None/slight marginal enhancement	• None
Membranes	• Can have irregular septa within necrotic cavities	• Can have detached membranes
Calcification	• Scattered, irregular	• Marginal/septal
Metabolic activity	• Perilesional or negative	• Usually negative

[a] AE lesions do not form "cysts", but cyst-like morphology is used as a radiological descriptor.

Hepatic disease: perilesional

Early-stage infection triggers an exuberant host-driven granulomatous reaction around each multivesicular mass.[6] This causes an inflammatory response in the perilesional soft tissues, which over time becomes fibrotic and may calcify. Although the larvae themselves have the potential to invade biliary and vascular structures directly, it is the host-driven inflammatory and fibrous response that typically involves biliary and vascular structures, causing compression and distortion of these both at the acinar and macroscopic structural level. This can then cause parenchymal atrophy and capsular retraction.[6,11,14]

Extrahepatic disease

Extrahepatic primary disease is extremely rare, the most common site of extrahepatic primary disease being the spleen. Immune compromise is a risk factor for hepatic and extra-hepatic metastatic disease progression and pregnancy is thought to be a risk factor for neurological involvement.[15] Most extra-hepatic disease occurs secondary to direct invasion from the liver (e.g., transdiaphragmatic pulmonary involvement, renal, peripancreatic/pancreatic, splenic, retroperitoneal, upper abdominal nodal, and spinal involvement). The lungs and brain are the two most common distant sites of metastatic disease, with haematogenous and lymphatic spread are recognised as routes of dissemination.[16] Pathophysiology is similar to hepatic disease, with perilesional involvement of adjacent anatomical structures specific to the organ involved.[3,6,8,17]

Clinical features

Initial infection is asymptomatic with symptoms developing after a 5–15 year incubation period. Slowly developing primary liver lesions are detected incidentally on imaging in more than one-third of patients. Symptoms are usually related to internal organ involvement during later stages of infection.[11]

Initial clinical features are non-specific and include malaise, weight loss, and right upper quadrant pain (secondary to either hepatomegaly or capsular involvement). Biliary involvement can lead to complications such as obstructive jaundice, cholangitis, and eventual secondary biliary cirrhosis. Portal venous and hepatic venous compromise, either from inflammation-related thrombus or direct invasion is common, resulting in portal venous collaterals, portal hypertension, and/or Budd–Chiari syndrome.[18]

Pulmonary involvement is usually asymptomatic, but can also be associated with haemoptysis, productive cough, chest pain, and shortness of breath, particularly if there is associated pulmonary embolism or airway compromise.[19,20] Intracranial metastatic disease can result in symptoms of raised intracranial pressure, seizures and reduced levels of

consciousness, with focal neurology dependent on lesion location.[19]

Diagnosing AE

Non-specific clinical symptoms and imaging features contribute to the diagnostic challenge, which relies on a combination of clinical history, imaging, serology, and histopathology. Consensus guidelines advocate supportive evidence in all four of these areas for formal diagnosis;[3] however, verified diagnoses can be made with at least two of[21]: (i) the presence of positive serology, (ii) supportive lesion location and imaging features, (iii) supportive histopathological features, and (iv) the presence of polymerase chain reaction (PCR)-detected *E. multilocularis* nucleic acid within a clinical specimen.

Although eosinophilia is rare, hypergammaglobulinaemia is common.[22] Serology for AE is more sensitive than for CE, and selective assays for antigens such as Em2 and Em2^{+} have reported sensitivity and specificity levels exceeding 90%.[6,22,23]

Image-guided aspiration/biopsy

Samples can be obtained at the time of surgery, but more commonly, ultrasound (US)/computed tomography (CT)-guided biopsies/aspiration are used for histopathological/polymerase chain reaction (PCR) diagnosis. In addition to the standard risks of targeted liver biopsy, there is also the theoretical risk of anaphylaxis and seeding of the disease, but data are limited and a small retrospective case series did not report any instances of these complications.[24] Biopsy cores are required for immunostaining, but aspirates or fragments of tissue can be used for PCR analysis.[3]

Imaging of hepatic disease

Imaging features are an essential non-invasive component of the diagnostic criteria, with the potential to reach diagnosis prior to, or even in the absence of biopsy. The changes that occur with AE in the liver are described for US, CT, magnetic resonance imaging (MRI) and 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography (PET).

US

US is a very useful screening tool for initial assessment before escalation to CT or MRI if a lesion is found. Although useful in the assessment of lesion relationships with vascular and biliary structures, it is less effective in providing comprehensive assessment and is comparatively less sensitive for smaller (<2 cm) lesions.[25]

Appearances include the "hailstorm" appearance of an indistinct irregular hyperechoic heterogeneous mass (often <10 cm) with possible foci of dense hyperechogenicity and/or acoustic shadowing secondary to intra-lesion calcification (Fig 1a). The other "pseudo-cystic" appearance refers to a large (often >10 cm) irregular lesion with central anechoic/hypoechoic portions and a hyperechoic irregular rind, possibly containing dense hyperechogenicity and/or acoustic shadowing secondary to peri-lesional calcification (Fig 1b).[5,6,25–27]

Rarely, "ossified" appearances (heavy peripheral hyperechogenicity with dense acoustic shadowing), "haemangioma-like" (more well defined than the hailstorm pattern and lacking macrocalcification) and "metastasis-like" (mostly ill-defined, mostly hypoechoic and heterogeneous echotexture) appearances have been described.[26–28]

CT

CT can provide comprehensive evaluation of the intra- and extra-hepatic disease burden. The presence and pattern of calcification, number, and size of lesions, the degree of vascular and potential biliary involvement and presence of secondary capsular retraction/focal hepatic atrophy can all be assessed. Lesion attenuation can vary, with areas of hypo-attenuation (particularly in the presence of necrosis) and mild post-contrast delayed phase enhancement of peripheral fibro-inflammatory tissue.[5,6,29] Although more ill-defined small-cystic lesions tend to be associated with early-stage disease, large internal cystic/necrotic

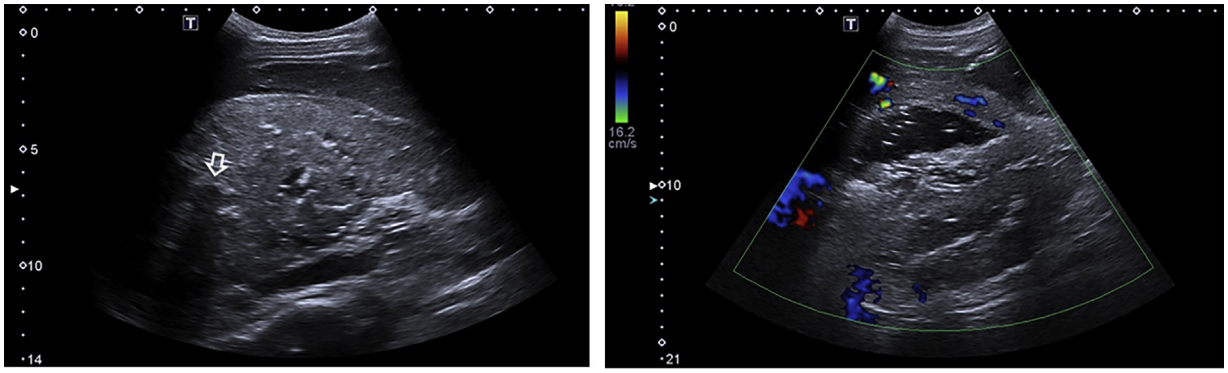

Figure 1 Sonographic appearances are broadly clustered into two main morphologies, those of a more (a) solid hyperechoic mass, often with indistinct margins and intralesional calcification (note internal acoustic shadowing (arrow) or more (b) pseudo-cystic with central hypoechogenic components, internal debris and irregular/relatively non-vascular peri-lesional tissue on Doppler US. Both images demonstrate lesions in the right hepatic lobe, obtained intercostally.

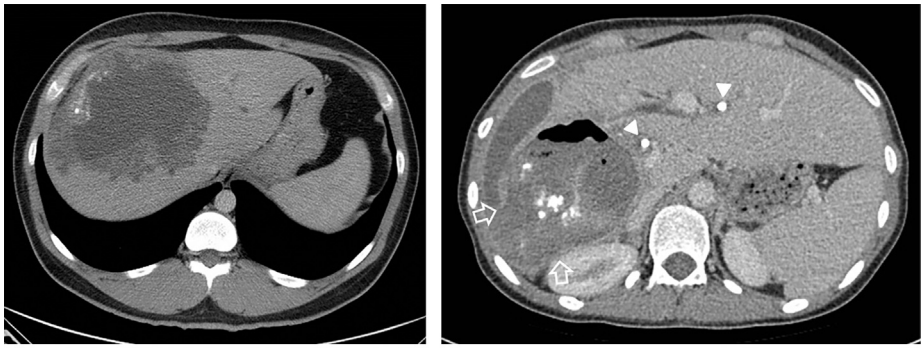

Figure 2 CT as a useful tool to identify and evaluate patterns of (a) peripheral and (b) central lesional calcification. Note how in (b) CT demonstrates extension through the hepatic capsule (white arrows) and formation of a perihepatic collection. Intra-ductal high density (white triangles) consistent with biliary drainage tubing. There is slight irregular marginal enhancement.

components are associated with evolved disease and complete calcification reflects inactive lesions.[26] The link between patterns of calcification (i.e., central/peripheral, punctate/diffuse) and AE pathogenesis remains unclear (Fig 2).[29]

MRI

MRI is an especially useful tool in the evaluation of AE, with lesion T1/T2-weighted signal changes, post-contrast imaging for the assessment of enhancement and relationships with vessels, MRI cholangiopancreatography (MRCP) sequences for the assessment of biliary involvement and quantitative methods, such as diffusion-weighted imaging (DWI), for aiding lesion characterisation. MRI is also sensitive for small lesions (<2 cm) and can assess perihepatic soft tissue and upper abdominal visceral invasion.[5,6,26]

AE lesions tend to be heterogeneous with irregular and occasionally poorly defined margins at MRI. Biliary and/or vascular involvement can result in upstream biliary dilatation (best evaluated using MRCP sequences, Fig 3a), portal and hepatic venous thrombus formation (Fig 3b), and secondary hepatic atrophy and local capsular retraction. Characterisation relies on assessment of cystic and solid components within the lesion, with the most widely accepted MRI-based classification system proposed by Kodama *et al.*,[30] stratifying lesions into five types. Types 1–3 are thought to represent sequential stages of lesion evolution of progressively increasing size: type 1, multiple small round vesicles without solid components (Fig 4a); type 2, multiple small round cystic lesions with a central solid component; and type 3, a large/irregular cystic structure with a rind of solid tissue containing small vesicles (Fig 4b). Type 4 lesions are solid masses, and represent type 2-stage lesions without the peripheral multivesicular component; whereas type 5 lesions represent type 3-stage lesions without any solid and/or peripheral small cystic components. Solid–cystic types 2 and 3 are the most commonly seen (>80%).[30]

T2-weighted imaging is useful in the evaluation of cystic components: multiple small vesicles (<1 cm) clustered

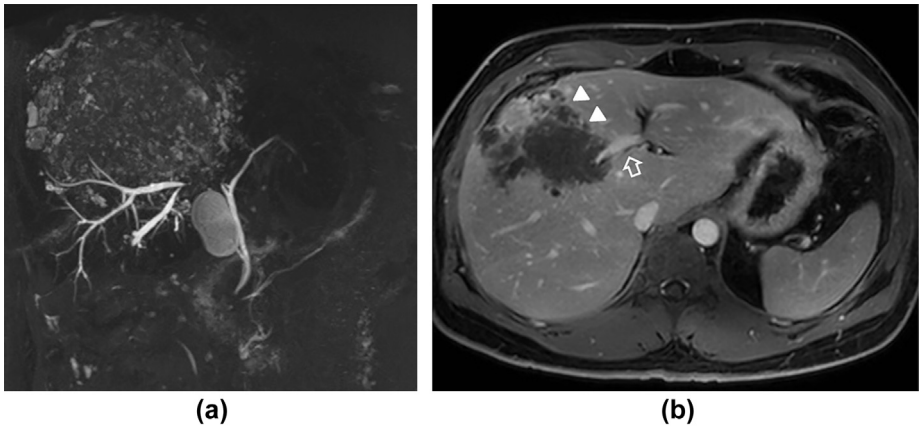

Figure 3 MRI as a useful tool for assessing the extent of (a) biliary and (b) vascular involvement. Both images have been obtained from the same patient demonstrating a large predominantly right hepatic cystic lesion with multiple small peripheral cystic areas. (a) On MRCP sequences, central occlusion of both right intrahepatic ductal systems is demonstrated with involvement of some of the anterior left segmental branches. (b) Following intravenous contrast medium administration, at the inferior margin of the lesion there is right main portal venous compromise (white arrow), with early extension into segment IV (two white triangles).

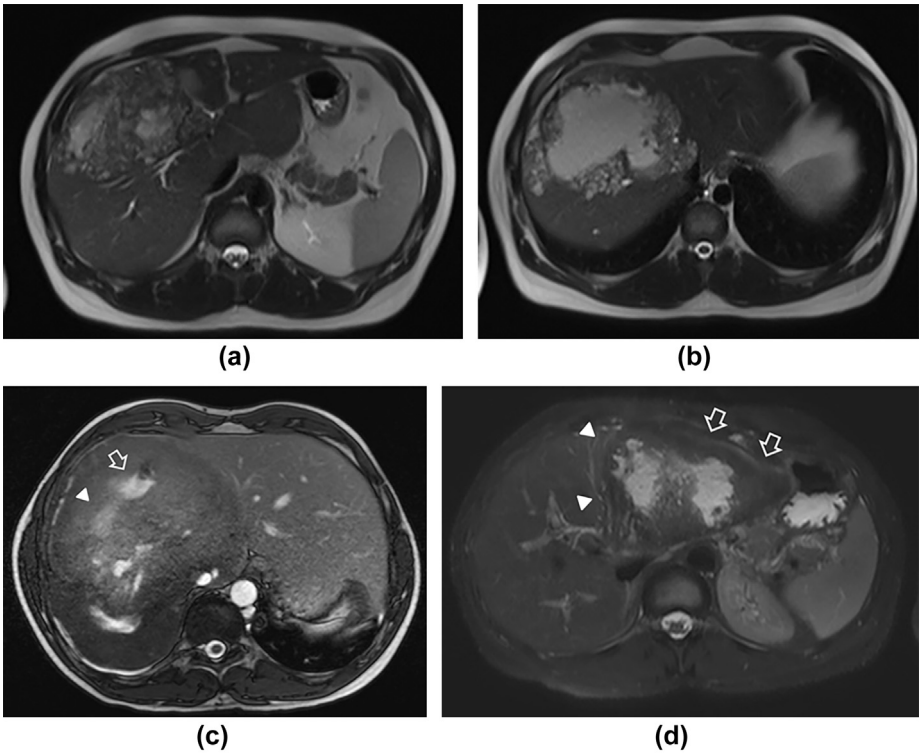

Figure 4 T2-weighted MRI in the evaluation of morphological and liquefactive components of AE lesions: (a) a sizeable complex of multiple small irregular cystic lesions are seen in a transitionary stage with additional early irregular central cystic components. (b) A Kodama type 3 lesion demonstrating a central cystic component with a rind of solid tissue containing multiple small peripheral vesicles. (c) A mature Kodama type 3 lesion with more well-demarcated margins with liquefactive (white arrow, central high T2 signal) and more solid coagulative (white triangle, central intermediate T2 signal) internal necrosis. The image also demonstrates caval compromise with direct trans-diaphragmatic extension towards the right lung base and a small volume right pleural effusion. (d) Fat-supressed T2-weighted imaging demonstrates some peripheral high hepatic parenchymal T2 signal along the anterior (white arrow) and medial margin (white triangle) of the left hepatic lesion, thought to represent high perilesional oedema. Note the presence of low T2 signal at the lesion margin thought to represent fibrotic tissue in (c) and (d).

together in early disease, give rise to a “bunch of grapes” or “honeycomb” appearance. Hyperintense T2 signal within larger lesions can distinguish liquefactive from coagulative necrosis (Fig 4c).[26,30] Perilesional acute inflammation can also cause higher parenchymal T2 intensity relative to adjacent parenchyma. Chronic fibro-inflammatory or fibrotic tissue both peripherally and centrally can be associated with heterogeneous iso-to hypointense T2 signal (Fig 4d).[31]

Low to isointense T1 signal is seen with avascular or necrotic tissue in larger cystic lesions (Fig 5a). Post-contrast enhancement is usually minimal, perilesional and appreciated best on later post-contrast phases, where it is thought to be related to the presence of fibro-inflammatory tissue

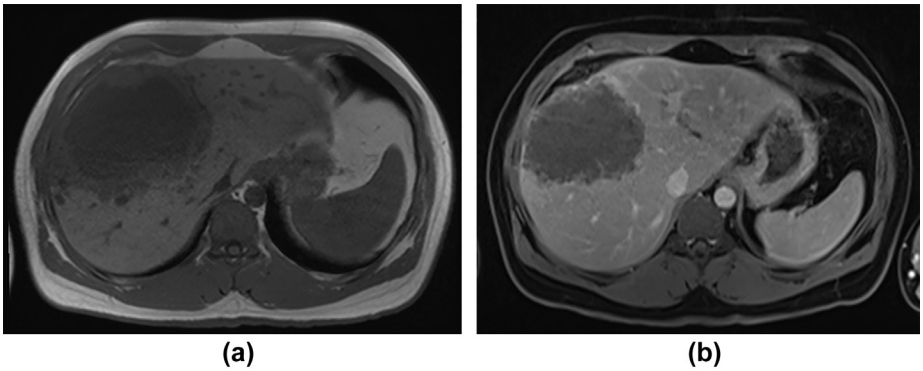

Figure 5 (a) T1-weighted MRI image demonstrating central low T1 signal within the cystic component and intermediate T1 signal at the lesion margin. (b) After intravenous contrast medium administration, fat-saturated imaging demonstrates minimal peripheral enhancement (thought to be related to the presence of fibro-inflammatory tissue).

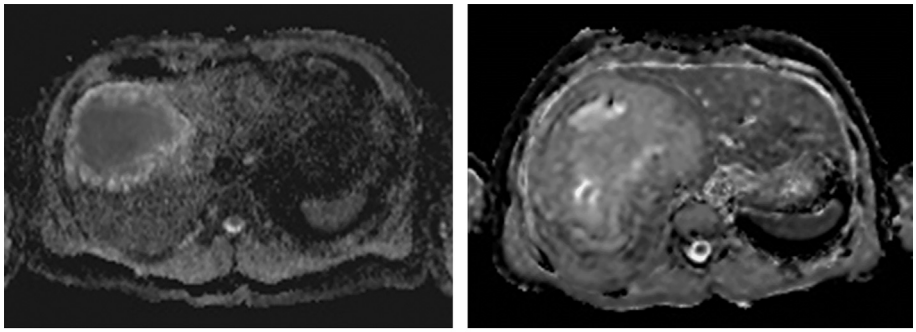

Figure 6 ADC maps derived from three b-values (0, 50, and 800 s/mm^2) demonstrate (a) central restriction within the cystic component suggestive of internal (infective) debris and (b) higher ADC within solid components of the lesion margin relative to unaffected parenchyma (appreciable at the margin of the lesion shown in (a) as well).

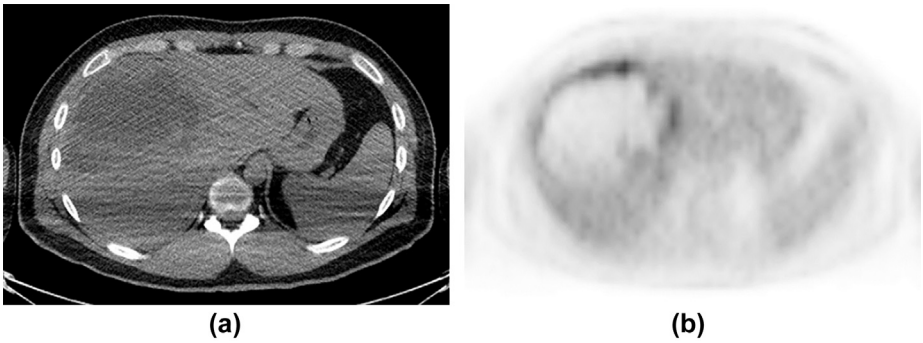

Figure 7 Unfused (a) unenhanced CT and (b) FDG-PET imaging from a combined PET/CT study demonstrate patchy peripheral uptake with absent uptake within the central cystic component.

(Fig 5b). Assessment of lesion calcification is difficult with MRI, but occasionally this is associated with foci of hyperintense or hypointense T1 signal.[6,26,30]

DWI may be useful diagnostically—unlike malignant liver tumours, AE is not associated with restricted diffusion. Lesion apparent diffusion coefficient (ADC) values are usually greater than those of adjacent unaffected hepatic parenchyma, but not as high as ADC values within cystic lesions or as low as ADC values in malignant lesions (Fig 6).[25,32,33]

FDG-PET

FDG-PET avidity is classically seen at the periphery of AE lesions, within involved perilesional soft tissue (Fig 7).[34] The source of avidity remains unclear, but is thought to arise from host cells responding to the parasite rather than from the AE larvae themselves.[35–37] Delayed imaging (3 hours following injection of FDG) is advisable due to lower reported rates of false-negative results,[38] particularly as negative studies do not exclude AE. FDG PET is also useful in assessing treatment response (discussed later).

Differential diagnoses and distinguishing features (Table 2)

On US, pseudocystic AE lesions can classically be mistaken for cystadenomas, cystadenocarcinomas, or even cystic echinococcosis lesions. The presence of irregular borders and paucity of peripheral vascularity on colour Doppler US would, however, favour AE over alternate diagnoses (Fig 1b).[6,26]

With CT, AE lesions mimicking cholangiocarcinoma, biliary cystadenomas/cystadenocarcinomas, metastases, and atypical HCC have all been reported (Fig 8), but the key distinctive CT features of AE lesions are the presence of the calcification, hypo-attenuating cystic components, and the absence of contrast enhancement, or only mild perilesional enhancement.[6,25,29,39–42]

Table 2
Differential diagnoses of AE lesions.

	Differential diagnoses/mimics
Solid/small cystic (<2cm)	Haemangioma Granuloma Inflammatory pseudotumour Hepatocellular carcinoma Cholangiocarcinoma Metastasis
Large pseudo-cystic (>10 cm)	Simple cyst Cystadenoma Cystic echinococcosis Cystadenocarcinoma Hepatocellular carcinoma Cholangiocarcinoma Metastasis

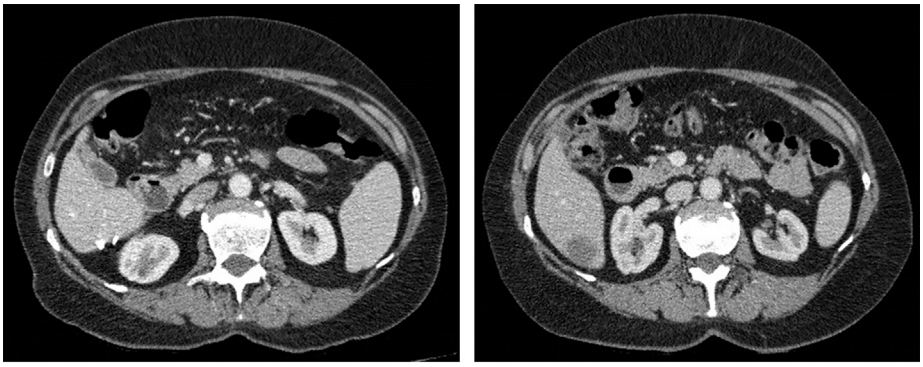

Figure 8 AE mimicking hepatic metastatic disease. A patient with colorectal cancer was found (a) on post-surgical follow-up scans to have a small cluster of right posterior hepatic peripheral high density lesions thought initially to be post-surgical, (b) later seen to evolve into an ill-defined low density focus (presumed to represent a metastatic deposit). Biopsy proved the lesion was in fact AE.

Using MRI, similarities between Kodama type 2 and 3 lesions and cystadenoma, cystadenocarcinoma, cholangiocarcinoma, and intrahepatic metastases are a common source of misdiagnosis. The absence of significant post-contrast enhancement and calcification can help distinguish AE lesions. Distinction of AE lesions for other Kodama lesion types using imaging alone can be more problematic: type 1 AE lesions can mimic cystadenoma; type 4 lesions can resemble large granulomas, inflammatory pseudotumours, hepatocellular carcinoma (HCC), and other solid tumours; while type 5 lesions can also be mistaken for simple cysts. The clinical history, serology, and histology obtained from biopsy can help guide radiological diagnosis in these instances.[5,9,30,39,40,43]

The absence of central uptake on FDG-PET within necrotic tissue can also be used as an additional distinguishing feature from other centrally metabolically active differential diagnoses (e.g., HCC, solid metastases, or cholangiocarcinoma).

Radiological reporting and disease classification/staging

Radiological reporting of intrahepatic disease should describe the key imaging features of liver lesions, as well as any complicating features, such as central abscess formation, biliary/vascular obstruction/invasion, and secondary atrophy (and contralateral hypertrophy), as these are important prognostic factors and may identify targets for more immediate management (e.g., biliary drainage). Reports should also specify the distribution of lesions (where there are multiple) with focus on the relationships with key vascular (hepatic arterial branches, portal vein/central portal venous branches, and hepatic veins) and biliary structures. This information, along with the distribution of hepatic disease will be critical to assessing the feasibility of surgical management.

Finally, reporting of local extrahepatic extension (and complications thereof) and metastatic lesions (where appropriate) are essential to assessing the overall burden of disease. Staging as proposed by the World Health Organisation (WHO) PNM system ("P", parasitic mass; "N", neighbouring organ involvement; "M", metastatic disease)[3] can be valuable in aiding multidisciplinary team management decisions (Table 3).

Management and image-guided intervention

Left untreated, AE has a very high mortality. Prompt recognition of the possible diagnosis and early referral to a specialist centre for confirmation of the diagnosis and management are therefore essential.

Management is ideally surgical, with radical resection advocated for all disease where possible, with curative

Table 3
PNM classification of alveolar echinococcosis.[3]

P — Primary hepatic parasitic lesion	
PX	Primary tumour cannot be assessed
P0	No detectable tumour in the liver
P1	Peripheral lesions without proximal vascular and/or biliary involvement
P2	Central lesions with proximal vascular and/or biliary involvement of one lobe[a]
P3	Central lesions with hilar vascular or biliary involvement of both lobes and/or with involvement of two hepatic veins
P4	Any liver lesion with extension along the vessels[b] and the biliary tree
N — Neighbouring (extra-hepatic) organ involvement (e.g. diaphragm, lung, pleura, pericardium, heart, gastric and duodenal wall, adrenal glands, peritoneum, retroperitoneum, abdominal wall, pancreas, regional lymph nodes, liver ligaments, kidney)	
NX	Cannot be evaluated
N0	No regional involvement
N1	Regional involvement of contiguous organs or tissues
M — Absence/presence of distant metastasis (e.g. lung, distant lymph nodes, spleen, CNS, orbital, bone, skin, muscle, kidney, distant peritoneum and retroperitoneum)	
MX	Not completely evaluated
M0	No metastases[c]
M1	Metastasis

[a] For the purposes of PNM classification, the liver is separated into two lobes separated by a plane projecting between the gallbladder fossa and inferior vena cava.
[b] Vessels including inferior vena cava, portal vein and arteries.
[c] Based on exclusion of metastatic disease using head CT and chest radiography.

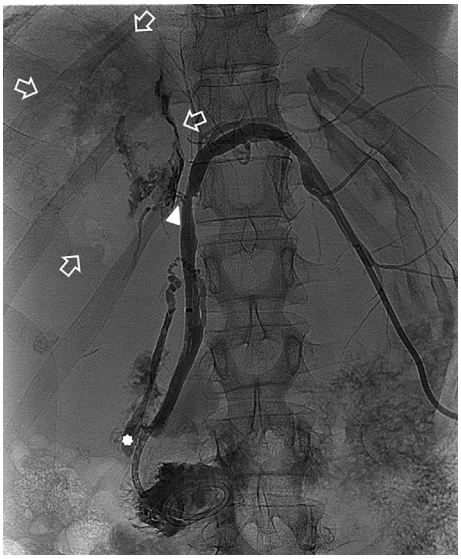

Figure 9 Percutaneous biliary intervention in the management of AE. A tubogram via a left-sided internal–external drain demonstrates appropriate siting for a large cavitating right-sided AE lesion (white arrows) that communicates with the central biliary tree (white triangle). Opacification of the gallbladder (asterisk) and cystic duct are also noted.

intent in some cases.[19] Adjuvant benzimadazole treatment is recommended, but chemotherapy is parasitostatic and not parasitocidal. Drug treatment regimens are costly and where curative resection is not possible, lifelong.[22,23,44] Radiological interventions may be useful for inoperable disease (i.e., WHO PNM staging P3 disease and above). Alongside simultaneous benzimadazole therapy, radiological interventions can have a significant impact on morbidity and mortality.[3]

Superinfection of central necrotic components of AE lesions occurs commonly and can drive bacterial sepsis (Fig 2b). Image-guided drainage of these abscesses whilst on systemic antibiotic treatment has been shown to significantly improve outcomes.[26]

The incidence of biliary invasion has been reported as approximately 11% in AE.[45] Obstruction and invasion can cause upstream biliary stasis resulting in cholangitis and eventual biliary sepsis. In this setting, there is a role for endoscopic retrograde cholangiopancreatography (ERCP; and stenting) or percutaneous transhepatic biliary drainage, which have been shown to improve clinical outcomes (Fig 9).[18,26,45]

Finally, although uncommon, there are reports of endovascular intervention in the setting of secondary

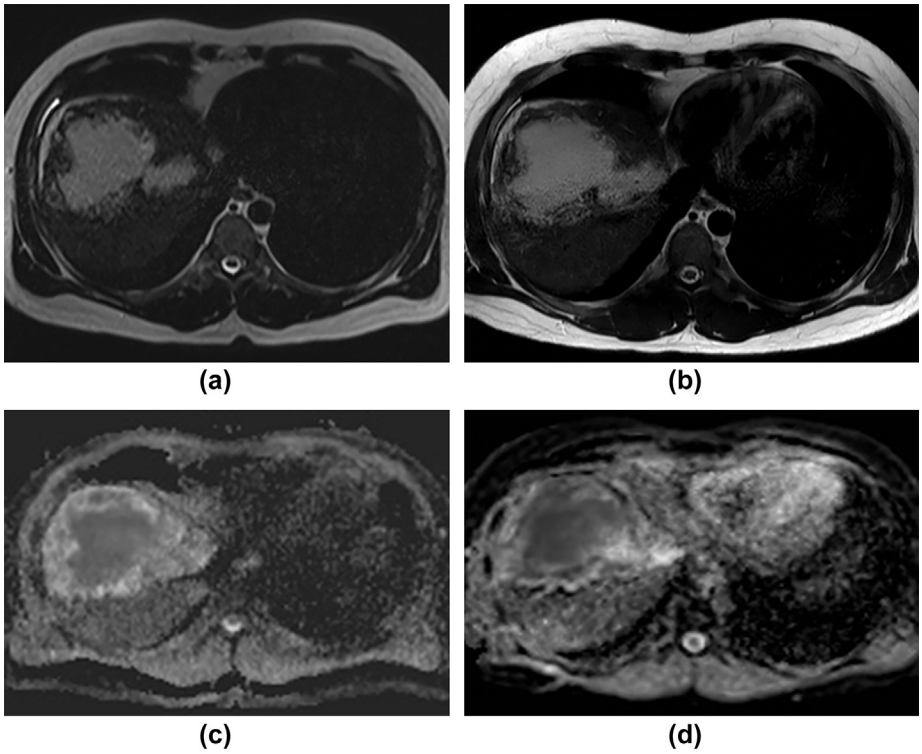

Figure 10 One-year interval MRI follow-up of a large, right-sided type 3 AE lesion, from a patient receiving albendazole therapy. Axial T2-weighted features on the (a) initial and (b) 1-year follow-up scan, allowing for technical and positional differences demonstrate stable appearances both in terms of size and morphology. Contemporaneous ADC maps derived from three b-values (0, 50, and 800 s/mm^2) obtained (c) initially and (b) after 1-year, however, demonstrate ADC reductions at the lesion margin, which could yet yield an alternative biomarker for the assessment of treatment response.

Budd–Chiari syndrome, with palliative stent decompression of obstructed hepatic venous outflow.[46]

Radiological assessment of treatment response

Although serology can become negative following R0 resection, assessment of serological response following treatment in the setting of partially resected or inoperable disease is difficult.[3] Imaging surveillance is advised in all cases, with current guidelines advising morphological/size assessment using short-interval US and 2–3 yearly CT/MRI.[3,5] Arguably, in non-endemic areas with greater access to cross-sectional imaging, MRI follow-up would be more appropriate with increasing intervals between scans where there is stable disease. The relationship between lesion size and disease burden is however poor: this is because increases/reductions in the size of large volume central cystic components may match infection/resolution of superadded infective abscess components rather than the AE itself. Furthermore where lesions are unresectable, these can remain stable in size despite treatment, a likely reflection of parasitostatic (rather than parasitocidal) medical treatments and lesion rigidity arising from the fibrous reaction they induce.[25]

PET/CT has been proposed as a tool for follow-up, with reduced/negative perilesional avidity following treatment.[37] *In vitro* studies have demonstrated that perilesional PET avidity is related to host immune cell uptake rather than metacestodal uptake.[36] which together with observed disease recurrence in the presence of PET negativity favours PET avidity as a marker of host response (rather than active infection). Initial PET can therefore be useful and reductions in PET avidity can be indicative of treatment response, but the absence of PET avidity should not be taken as a marker of disease resolution—lifelong chemotherapy is advised even where stable lesions have become PET negative.[25,44]

DWI is not routinely used, but may yet be a promising tool for the follow-up of AE lesions (Fig 10).[32] Uninvolved perilesional areas on T1/T2-weighted imaging can demonstrate restricted diffusion and the potential to quantify this and potential post-treatment reduction in ADC values over time could yet yield a new and better biomarker for the assessment of treatment response.[32,33]

Summary and conclusions

AE is a rare parasitic infection mainly affecting the liver with imaging features most commonly of a solid/cystic infiltrating mass, very different from the more common CE, which typically has a cystic morphology. Diagnosing AE is difficult as it can mimic various liver malignancies: although there are some distinguishing imaging features, clinical features, serology, and biopsy can in combination with imaging help to establish the diagnosis. Treatment is ideally radical surgery, but in resource-poor settings, difficulties with access to treatment can account for poor outcomes. In better-resourced but non-endemic areas, unusual imaging features can lead to delayed/misdiagnosed disease, resulting in inappropriate management and avoidable patient morbidity/mortality. Suspected diagnoses should therefore be escalated to tertiary centres at the earliest possible stage, where timely confirmation of diagnosis with a view to radical resection of early operable disease gives patients the best possible chance of disease-free survival.

Looking ahead, developments in imaging have the potential to advance the care of AE patients significantly: the application of quantitative imaging methods that probe both compositional elements of disease (e.g., MR spectroscopy, T1 mapping, T2* mapping), functional (e.g., novel radionuclide tracers, contrast-enhanced US, perfusion CT/MRI, DWI and intra-voxel incoherent motion MRI) and biomechanical/structural components of disease (e.g., MR elastography and textural analysis) have the potential to yield better tools for AE diagnosis, delivery of treatment, and assessment of treatment response.

Conflict of interest

The authors declare no conflict of interest.

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References

1. Tennert U, Schubert S, Tröltzsch M, *et al*. Pitfall alveolar echinococcosis in non-endemic areas alveolar echinococcosis migrating northward. *Ann Hepatol* 2010;**9**(1):99–103.
2. Deplazes P, Rinaldi L, Alvarez Rojas CA, *et al*. Global distribution of alveolar and cystic echinococcosis. *Adv Parasitol* 2017;**95**:315–493.
3. Brunetti E, Kern P, Vuitton DA. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. *Acta Trop* 2010;**114**(1):1–16 https://doi.org/10.1016/j.actatropica.2009.11.001.
4. Eckert J, Conraths FJ, Tackmann K. Echinococcosis: an emerging or re-emerging zoonosis? *Int J Parasitol* 2000;**30**(12–13):1283–94 https://doi.org/10.1016/S0020-7519(00)00130-2.
5. Bulakci M, Kartal MG, Yilmaz S, *et al*. Multimodality imaging in diagnosis and management of alveolar echinococcosis: an update. *Diagn Interv Radiol* 2016;**22**(3):247–56 https://doi.org/10.5152/dir.2015.15456.
6. Kantarci M, Bayraktutan U, Karabulut N, *et al*. Alveolar echinococcosis: spectrum of findings at cross-sectional imaging. *RadioGraphics* 2012;**32**(7):2053–70 https://doi.org/10.1148/rg.327125708.
7. Mueller J, Stojkovic M, Berger AK, *et al*. How to not miss alveolar echinococcosis in hepatic lesions suspicious for cholangiocellular carcinoma. *Abdom Radiol* 2016;**41**(2):221–30 https://doi.org/10.1007/s00261-015-0561-2.
8. Ozkok A, Gul E, Okumus G, *et al*. Disseminated alveolar echinococcosis mimicking a metastatic malignancy. *Intern Med* 2008;**47**:1495–7 https://doi.org/10.2169/internalmedicine.47.1228.
9. Stojkovic M, Mickan C, Weber T, *et al*. Pitfalls in diagnosis and treatment of alveolar echinococcosis: a sentinel case series. *BMJ Open Gastroenterol* 2015;**2**(1):e000036 https://doi.org/10.1136/bmjgast-2015-000036.
10. Eckert J, Deplazes P. Alveolar echinococcosis in humans: the current situation in Central Europe and the need for countermeasures. *Parasitol Today* 1999;**15**(8):315–9.

11. Thompson RC. Biology and systematics of echinococcus. *Adv Parasitol* 2017;**95**:65–109.
12. Brehm K, Koziol U. *Echinococcus*–host interactions at cellular and molecular levels. *Adv Parasitol* 2017;**95**:147–212.
13. Monteiro KM, Lorenzatto KR, de Lima JC, *et al*. Comparative proteomics of hydatid fluids from two *Echinococcus multilocularis* isolates. *J Proteomics* 2017;**162**:40–51 https://doi.org/10.1016/J.JPROT.2017.04.009.
14. Gottstein B, Beldi G. Infectious Diseases (Fourth Edition). In: Cohen J, Powderly WG, Opal SM, editors. *Infectious Diseases (Fourth Edition)*. 4th ed. Elsevier; 2017.
15. Yang YR, Vuitton DA, Jones MK, *et al*. Brain metastasis of alveolar echinococcosis in a hyperendemic focus of Echinococcus multilocularis infection. *Trans R Soc Trop Med Hyg* 2005;**99**(12):937–41 https://doi.org/10.1016/j.trstmh.2005.04.020.
16. Demir MK, Kilicoğlu G, Akinci O. Alveolar hydatid disease of the liver: brief review and spectrum of adjacent organ invasion. *Australas Radiol* 2007;**51**(4):346–50 https://doi.org/10.1111/j.1440-1673.2007.01748.x.
17. Stojkovic M, Junghanss T. Cystic and alveolar echinococcosis. *Handb Clin Neurol* 2013;**114**:327–34 https://doi.org/10.1016/B978-0-444-53490-3.00026-1.
18. Graeter T, Ehing F, Oeztuerk S, *et al*. Hepatobiliary complications of alveolar echinococcosis: a long-term follow-up study. *World J Gastroenterol* 2015;**21**(16):4925–32 https://doi.org/10.3748/wjg.v21.i16.4925.
19. Mihmanli M, Idiz UO, Kaya C, *et al*. Current status of diagnosis and treatment of hepatic echinococcosis. *World J Hepatol* 2016;**8**(28):1169–81 https://doi.org/10.4254/wjh.v8.i28.1169.
20. Ohsaki Y, Sasaki T, Shibukawa K, *et al*. Radiological findings of alveolar hydatid disease of the lung caused by *Echinococcus multilocularis*. *Respirology* 2007;**12**(3):458–61 https://doi.org/10.1111/j.1440-1843.2007.01055.x.
21. Kern P. Clinical features and treatment of alveolar echinococcosis. *Curr Opin Infect Dis* 2010;**23**(5):505–12 https://doi.org/10.1097/QCO.0b013e32833d7516.
22. Eckert J. *WHO/OIE manual on echinococcosis in humans and animals: a public health problem of global concern*. Paris: World Organisation for Animal Health; 2001.
23. McManus DP, Zhang W, Li J, *et al*. Echinococcosis. *Lancet (London, England)* 2003;**362**(9392):1295–304 https://doi.org/10.1016/S0140-6736(03)14573-4.
24. Bulakci M, Ilhan M, Bademler S, *et al*. Efficacy of ultrasound-guided core-needle biopsy in the diagnosis of hepatic alveolar echinococcosis: a retrospective analysis. *Parasite* 2016;**23**:19 https://doi.org/10.1051/parasite/2016019.
25. Liu W, Delabrousse É, Blagosklonov O, *et al*. Innovation in hepatic alveolar echinococcosis imaging: best use of old tools, and necessary evaluation of new ones. *Parasite* 2014;**21**:74 https://doi.org/10.1051/parasite/2014072.
26. Bresson-Hadni S, Delabrousse E, Blagosklonov O, *et al*. Imaging aspects and non-surgical interventional treatment in human alveolar echinococcosis. *Parasitol Int* 2006;**55**(Suppl):267–72 https://doi.org/10.1016/j.parint.2005.11.053.
27. Kratzer W, Gruener B, Kaltenbach TEM, *et al*. Proposal of an ultrasonographic classification for hepatic alveolar echinococcosis: *Echinococcus multilocularis* Ulm classification—ultrasound. *World J Gastroenterol* 2015;**21**(43):12392–402 https://doi.org/10.3748/wjg.v21.i43.12392.
28. Cai DM, Wang HY, Wang XL, *et al*. Ultrasonographic findings of small lesion of hepatic alveolar echinococcosis. *Acta Trop* 2017;**174**(37):165–70 https://doi.org/10.1016/j.actatropica.2016.01.030.
29. Graeter T, Kratzer W, Oeztuerk S, *et al*. Proposal of a computed tomography classification for hepatic alveolar echinococcosis retrospective study. *World J Gastroenterol* 2016;**22**(13):3621–31 https://doi.org/10.3748/wjg.v22.i13.3621.
30. Kodama Y, Fujita N, Shimizu T, *et al*. Alveolar echinococcosis: MR findings in the liver. *Radiology* 2003;**228**:172–7 https://doi.org/10.1148/radiol.2281020323.
31. Claudon M, Bessieres M, Regent D, *et al*. Alveolar echinococcosis of the liver: MR findings. *J Comput Assist Tomogr* 1990;**14**(4):608–14.
32. Becce F, Pomoni A, Uldry E, *et al*. Alveolar echinococcosis of the liver: diffusion-weighted MRI findings and potential role in lesion characterisation. *Eur J Radiol* 2014;**83**(4):625–31 https://doi.org/10.1016/j.ejrad.2013.12.025.
33. Kantarci M, Pirimoglu B. Diffusion-weighted MR imaging findings in a growing problem: hepatic alveolar echinococcosis. *Eur J Radiol* 2014;**83**(10):1991–2 https://doi.org/10.1016/j.ejrad.2014.07.013.
34. Reuter S, Schirrmeister H, Kratzer W, *et al*. Pericystic metabolic activity in alveolar echinococcosis: assessment and follow-up by positron emission tomography. *Clin Infect Dis* 1999;**29**(5):1157–63 https://doi.org/10.1086/313438.
35. Azizi A, Blagosklonov O, Lounis A, *et al*. Alveolar echinococcosis: correlation between hepatic MRI findings and FDG-PET/CT metabolic activity. *Abdom Imag* 2015;**40**(1):56–63 https://doi.org/10.1007/s00261-014-0183-0.
36. Porot C, Knapp J, Wang Junhua, *et al*. Development of a specific tracer for metabolic imaging of alveolar echinococcosis: a preclinical study. In: *36th Ann. Int. Conf. IEEE Eng. Med. Biol. Soc.* Piscataway, NJ: IEEE; 2014. p. 5587–90 https://doi.org/10.1109/EMBC.2014.6944893.
37. Stumpe KDM, Renner-Schneiter EC, Kuenzle AK, *et al*. F-18-fluorodeoxyglucose (FDG) positron-emission tomography of *Echinococcus multilocularis* liver lesions: prospective evaluation of its value for diagnosis and follow-up during benzimidazole therapy. *Infection* 2007;**35**(1):11–8 https://doi.org/10.1007/s15010-007-6133-9.
38. Caoduro C, Porot C, Vuitton DA, *et al*. The role of delayed ^{18}F-FDG PET imaging in the follow-up of patients with alveolar echinococcosis. *J Nucl Med* 2013;**54**(3):358–63 https://doi.org/10.2967/jnumed.112.109942.
39. Bulakci M, Yilmaz E, Cengel F, *et al*. Disseminated alveolar hydatid disease resembling a metastatic malignancy: a diagnostic challenge—a report of two cases. *Case Rep Radiol* 2014;**2014**(Figure 2):638375 https://doi.org/10.1155/2014/638375.
40. Kohlenberg A, Wüsten O, Dierkes C, *et al*. Hepatobiliary and pancreatic: alveolar echinococcosis mimicking hepatocellular carcinoma. *J Gastroenterol Hepatol* 2010;**25**(10):1712 https://doi.org/10.1111/j.1440-1746.2010.06499.x.
41. Polat KY, Ozturk G, Aydinli B, *et al*. Hepatobiliary and pancreatic: alveolar hydatid disease. *J Gastroenterol Hepatol* 2004;**19**(11):1319 https://doi.org/10.1111/j.1440-1746.2004.03629.x.
42. Tüzün M, Hekimoflu B. Various locations of cystic and alveolar hydatid disease: CT appearances. *J Comput Assist Tomogr* 2001;**25**(1):81–7 https://doi.org/10.1097/00004728-200101000-00014.
43. Aoki T, Hagiwara M, Yabuki H, *et al*. Unique MRI findings for differentiation of an early stage of hepatic alveolar echinococcosis. *BMJ Case Rep* 2015;**2015**:2–6 https://doi.org/10.1136/bcr-2014-208123.
44. Reuter S, Buck A, Manfras B, *et al*. Structured treatment interruption in patients with alveolar echinococcosis. *Hepatology* 2004;**39**(2):509–17 https://doi.org/10.1002/hep.20078.
45. Ozturk G, Polat KY, Yildirgan MI, *et al*. Endoscopic retrograde cholangiopancreatography in hepatic alveolar echinococcosis. *J Gastroenterol Hepatol* 2009;**24**(8):1365–9 https://doi.org/10.1111/j.1440-1746.2009.05877.x.
46. Vogel J, Görich J, Kramme E, *et al*. Alveolar echinococcosis of the liver: percutaneous stent therapy in Budd–Chiari syndrome. *Gut* 1996;**39**(5):762–4.