

Multimodality imaging in diagnosis and management of alveolar echinococcosis: an update

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ABSTRACT

Alveolar echinococcosis is a parasitic disease limited to the northern hemisphere. The disease occurs primarily in the liver and shows a profile mimicking slow-growing malignant tumors. *Echinococcus multilocularis* infection is fatal if left untreated. It can cause several complications by infiltrating the vascular structures, biliary tracts, and the hilum of the liver. As it can invade the adjacent organs or can spread to distant organs, alveolar echinococcosis can easily be confused with malignancies. We provide a brief review of epidemiologic and pathophysiologic profile of alveolar echinococcosis and clinical features of the disease. This article focuses primarily on the imaging features of alveolar echinococcosis on ultrasonography, computed tomography, magnetic resonance imaging, diffusion-weighted imaging and positron emission tomography-computed tomography. We also reviewed the role of radiology in diagnosis, management, and follow-up of the disease.

Echinococcosis is the general name given to zoonotic infections caused by tapeworms (cestodes) in the genus *Echinococcus*. The life cycle of this parasite occurs in two different mammalian organisms (definitive host and natural intermediate host). Humans are accidental or aberrant intermediate hosts and are not a part of the natural life cycle of the parasite (1). The invasion of different organs by metacestodes, primarily the liver and lungs, causes severe problems in the intermediate or accidentally intermediate hosts (1, 2). The metacestodes *Echinococcus multilocularis* invade different organs in humans and shows growth and infiltration patterns mimicking neoplastic processes. In addition, diagnostic difficulties are encountered since it is not a common disease, particularly in nonendemic regions (3). Early diagnosis of the disease, as well as appropriate treatment and follow-up is very important in improving the patient's quality of life. Imaging is essential in the diagnosis, follow-up, and management of the disease.

Epidemiology and pathophysiology

In humans, the *E. granulosus* cestodes causes cystic echinococcosis (CE), *E. multilocularis* cestodes causes alveolar echinococcosis (AE), and *E. vogeli* and *E. oligarthrus* cause polycystic echinococcosis (also termed as neotropical echinococcosis). Although CE is common worldwide, AE is a manifestation seen only in the northern hemisphere. AE is more common in Russia, Central Asia, China, Northern Japan, Central Western Europe, Eastern Europe, Turkey, and Alaska. The exposure to *Echinococcus* eggs is affected by occupational and behavioral factors. The incidence of CE is highest in regions where sheep breeding is common. The risk of encountering AE is increased in human groups who spend more time in the wilderness. Polycystic echinococcosis, which has less medical and economic importance, is limited to Central and South America and few cases are reported in humans (1, 2).

AE infestation is almost equal in men and women. The peak age is reported between 50 and 70 years (2). The natural course of the disease consists of approximately 5–15 years of asymptomatic incubation period followed by a chronic period (1, 2). The disease is incidentally detected in more than one-third of the patients (3).

The definite hosts are foxes, whereas rodents are intermediate hosts in the life cycle of *E. multilocularis*. The eggs produced by the adult parasite are released into the environment by the fox and the cycle continues with digestion of contaminated food by the intermediate host. The eggs penetrate the bowel wall and invade the lymphatic and portal systems, and from there

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Received 7 October 2015; revision requested 14 October 2015; last revision received 9 December 2015; accepted 29 December 2015.

Published online 12 April 2016.
DOI 10.5152/dir.2015.15456

they spread to multiple organs. The parasite goes into a metacestode stage in natural intermediate hosts and in humans who are accidental hosts (1–3). The metacestode stage almost always occurs in the liver. It causes infiltrative mass lesions within the liver with multiple vesicles with a diameter varying from submillimeter to 3 cm. The border between the normal parenchyma and the diseased tissue is not clearly defined. In addition, these masses are characterized with diffuse fibrosis, calcific foci, and necrotic areas, which are prominent in the central zones (3). Extrahepatic primary involvement is very rare (1% of cases). Other intra-abdominal organs are invaded directly or organs, including brain, lungs, and bones, are secondarily affected with distant organ spread (hematogenous or lymphatic pathways). Multiorgan invasion is seen in 13% of the cases (1–3).

AE is a tumor-like chronic disease, which can be fatal if untreated or undertreated. Death can occur due to hepatobiliary complications and superimposed infections, secondary biliary cirrhosis and its complications, problems secondary to involvement of vascular structures, and invasion of distant organs (3).

Diagnostic criteria

The diagnosis of AE depends on the medical history, clinical findings, radiologic im-

aging modalities, laboratory evaluations, and histopathologic verification (3). At least two of the four following criteria have to be present for diagnosis of the disease: (I) characteristic lesions shown by imaging; (II) specific serum antibodies to *Echinococcus* antigens detected on laboratory tests; (III) pathologic verification of *E. multilocularis* metacestodes; (IV) identification of parasite nucleic acids in clinical specimens (4).

Clinical and laboratory findings

The clinical symptoms vary with the type of organ involved and the degree of the invasion. Jaundice and epigastric pain are the primary symptoms in hepatic invasion, but weight loss and malaise can also develop (5). With invasion of vascular structures and bile ducts, development of cholangitis, liver abscesses, secondary biliary cirrhosis, portal hypertension, and Budd-Chiari syndrome have been reported (6).

The involvement of lungs is usually detected incidentally. Chest pain, cough, dyspnea, and hemoptysis are the main symptoms. Lung involvement can develop through hematogenous dissemination of the primary lesion or direct invasion through transdiaphragmatic route (3, 7). With central nervous system involvement, neurologic symptoms and findings can occur similar to any other space-occupying lesion. Increased intracranial pressure, chronic headache, dizziness, vomiting, seizures, dysarthria, hemiparesis, aphasia, ataxia, and symptoms related to cranial nerve involvement can develop (7–10).

Routine laboratory tests do not reveal any specific results. Erythrocyte sedimentation rate is increased in most cases. Eosinophilia is usually not detected. Hypergammaglobulinemia is present in most cases. The presence of specific IgE antigens can be shown in blood specimen (5). Immunodiagnostic tests are more reliable in diagnosis of AE compared with CE due to presence of more specific antigens. Enzyme-linked immunosorbent assay (ELISA) shows high sensitivity but lower specificity with crude *E. multilocularis* antigens. In addition, cross-reactions of varying degrees exist between *E. multilocularis* and *E. granulosus* and some other helminth antigens. The best option for determination of serum antibodies in AE cases is to use purified antigens such as Em2, Em18, Em-alkaline phosphatase (pAP), and C-antigen or recombinant antigens such as Em11/3–10, Em10, and Em13. Sensitivity

rates of 90%–100% and specificity rates of 95%–100% have been reported with these antigens. Particularly, Em2 and Em2^{plus} ELISA (a combination of Em2 and recombinant Em11/3–10) are regarded as the most valuable tools for its diagnosis (2, 3, 5).

Other diagnostic measures have a complementary role in the early diagnosis of the disease (1, 2, 5). The histopathologic presence of the parasite and the detection of AE DNA with polymerase chain reaction (PCR), direct immunofluorescence, or immunohistochemistry tests on specimens obtained with surgical or percutaneous biopsy are important diagnostic criteria (3, 5).

Classification and staging

The European Network for Concerted Surveillance of Alveolar Echinococcosis and the WHO Informal Working Group on Echinococcosis (WHO-IWGE) developed a clinical classification termed as the PNM system, which is mainly based on imaging findings (Table 1). The PNM classification is a system similar to the Tumor-Node-Metastasis (TNM) classification, which is widely used in classification of malignant processes. This classification system determines how many parasites are present in the body, which organs are involved, and shows the extent and degree of the disease. Thus, the clinical condition of the patient is briefly standardized aiming to provide the best treatment options and guide the clinicians about the course of the disease (11). Category P shows the dissemination of the parasite in the liver, category N the involvement of the adjacent organs, and category M the distant metastases (11, 12). Following the determination of the P, N, and M categories, the patient is staged as I, II, IIIA, IIIB, or IV (Table 2). Consensus view of a number of experts on the stage-specific approach was summarized in a comprehensive review (12).

Imaging of alveolar echinococcosis

While radiologic imaging modalities play a major role, histopathologic examinations and PCR analysis are used for making the definite diagnosis. Conventional imaging methods, including x-ray, ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), have been used in the diagnosis, follow-up, and management of AE for several years (13). Recently, there have been new studies on the diagnosis and follow-up of the disease

Main points

- Alveolar echinococcosis (AE) is a rare parasitic disease that resembles a slowly growing metastatic malignancy and can be fatal when untreated or undertreated.
- In the diagnosis of AE, serology and imaging methods are often utilized; nevertheless, the diagnosis needs to be confirmed through additional support of histopathologic verification or detection of the parasite nucleic acid in the clinical sample.
- Imaging characteristics of the AE lesions are presence of typical calcifications and tiny cystic structures inside the lesions, absence of distinct vasculature inside the mass, and lack of obvious enhancement within the lesion except weak perilesional enhancement.
- CT is the most valuable modality for showing the typical calcifications that are observed in the AE lesions; whereas, MRI can best demonstrate the parasitic structures inside the mass.
- PET-CT is widely accepted as the most valuable imaging method in determining the effectiveness of medical treatment.

Table 1. PNM system for classification of human alveolar echinococcosis

P	Hepatic localization of the primary lesion
PX	Primary lesion cannot be assessed
P0	No detectable liver lesion
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 and biliary involvement of both lobes and/or with involvement of two hepatic veins
P4	Any lesion with extension along the portal vein, inferior vena cava, or hepatic arteries and the biliary tree
N	Extra hepatic involvement of neighboring organs or tissues ^b
NX	Cannot be evaluated
N0	No regional involvement
N1	Regional involvement of contiguous organs or tissues
M	Absence or presence of distant metastases ^c
MX	Not completely evaluated
M0	No metastasis
M1	Metastasis present

^aFor PNM classification, the plane projecting between the bed of the gallbladder and the inferior vena cava divides the liver in two lobes.

^bNeighboring organs and tissues include the diaphragm, lungs, pleura, pericardium, heart, gastric and duodenal wall, adrenal glands, peritoneum, retroperitoneum, parietal wall (muscles, skin, bone), pancreas, regional lymph nodes, hepatic ligaments, and kidney.

^cDistant metastasis locations include the lungs, distant lymph nodes, spleen, kidney, central nervous system, orbits, bone, skin, muscle, distant peritoneum, and retroperitoneum.

Table 2. Staging of alveolar echinococcosis on the basis of PNM classification

Stage of AE	P	N	M
Stage I	P1	N0	M0
Stage II	P2	N0	M0
Stage IIIa	P3	N0	M0
Stage IIIb	P1–3	N1	M0
	P4	N0	M0
Stage IV	P4	N1	M0
	Any P	Any N	M1

P, dissemination of the parasite in the liver; N, involvement of the adjacent organs; M, distant metastasis.

using contrast-enhanced ultrasonography (CEUS), diffusion-weighted imaging (DWI), magnetic resonance spectroscopy (MRS), positron emission tomography-computed tomography (PET-CT).

Ultrasonography

US is accepted as the first choice imaging modality in the diagnosis and follow-up. It is an adequate and efficient imaging modality in screening AE lesions. Since it is cheap, readily available, and does not contain radiation, US can be used in endemic regions as a fast diagnostic tool in large populations (13, 14). Involvement of the

liver is seen as mass lesions, which show a mixed heterogeneous echogenic pattern with irregular contours, including cystic necrotic areas and multiple distributed calcific foci. Less typical sonographic appearance is the hailstorm pattern with multiple hyperechogenic solid lesions (13, 15). This appearance is suggested to represent early AE lesions. It is important for radiologists in the endemic regions to correctly diagnose this less frequently presenting form, which can be confused with venous malformations and similar lesions (16). In addition to the gray scale US findings, absence of vascularity within the lesion on color Doppler imag-

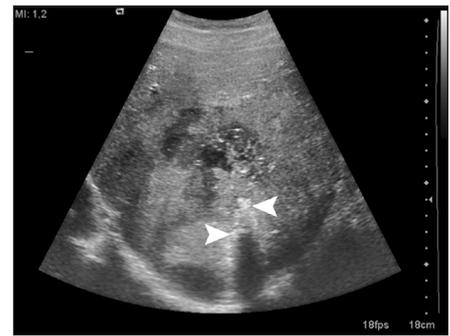


Figure 1. A 40-year-old man with hepatic alveolar echinococcosis. An oblique sonogram obtained through the right liver lobe shows a heterogeneous mass lesion with indistinct borders. The mass contains hyperechoic foci of calcification with posterior acoustic shadowing (arrowheads).

ing is helpful for confirming the diagnosis (17). Involvement of the hepatic veins, vena cava inferior, and portal vein and its branches can be evaluated with Doppler imaging. In addition, involvement and dilatation of the intrahepatic biliary ducts secondary to mass effect or invasion can be shown sonographically (13, 17) (Fig. 1).

Computed tomography

CT is the primary imaging modality in detecting the anatomic location and dissemination of the lesions, characterization of the lesions, and detection of the typical calcifications (3, 13). It is useful in evaluating the relationship of the hepatic lesions with the vascular structures and bile ducts. Furthermore, extrahepatic organ involvement can be shown. This is important in determining the resectability of the lesions and their P, N, M stages (3, 13, 18). On unenhanced CT, AE lesions appear as tumor-like masses with irregular borders, heterogeneous internal structures, and multiple distributed calcific foci (Fig. 2). While no significant intralesional enhancement is seen on contrast-enhanced CT, mild enhancement can be seen in the peripheral fibro-inflammatory tissue on delayed phase. Hypodense necrotic areas can sometimes be seen as large cystic cavities within the center of the lesion (Figs. 3, 4). Atrophy and capsular retraction secondary to vascular and biliary involvement can be detected in the affected liver lobe (3, 13).

Extrahepatic primary organ involvement is very rare. The lungs are the most commonly involved organs with secondary AE (5). Direct radiography can be used as the initial imaging modality in lung involvement. The x-ray findings are nonspecific and are seen as multiple small opacities with

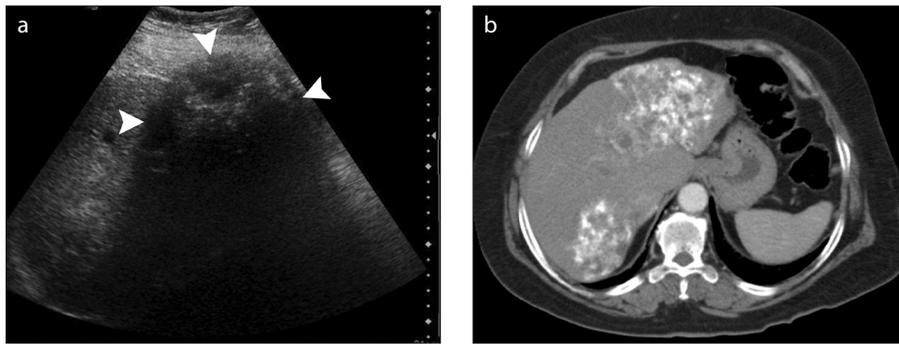


Figure 2. a, b. A 66-year-old male with *E. multilocularis* infection of the right and the left liver lobes. Gray-scale US image (a) from the left lobe of the liver shows a highly calcified heterogeneous lesion (arrowheads). Note that the posterior border of the parasitic mass is obscured due to strong posterior acoustic shadowing. Abdominal CT image (b) obtained after the administration of intravenous contrast depicts two hepatic masses with indistinct margins including diffuse hyperdense foci of coarse calcification.

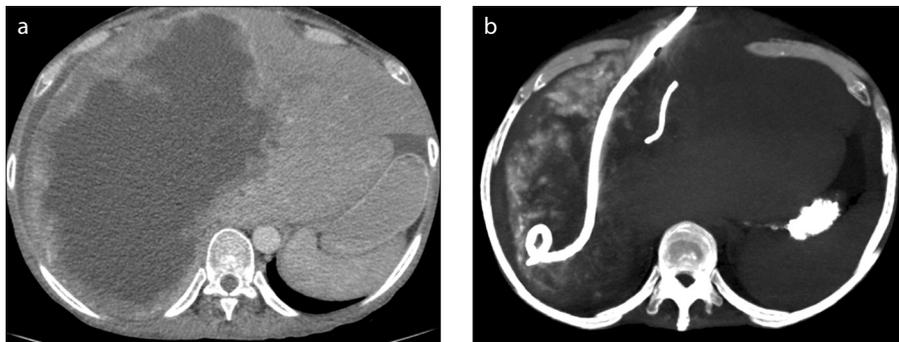


Figure 3. a, b. A 39-year-old man with complicated *E. multilocularis* infection of the liver. Contrast-enhanced axial CT image (a) shows a huge mass with a central fluid-filled area. Right portal vein and right and middle hepatic veins are invaded by the parasitic mass (not shown). The lesion also compresses the left portal vein branch (not shown). Axial maximum intensity projection (MIP) CT image (b) demonstrates a collapsed cavity in the right hepatic lobe with a pigtail drain inserted. This 10F percutaneous drainage catheter was easily placed into the cavity under sonographic guidance. After placement of the catheter, 3000 mL of infected fluid was drained.

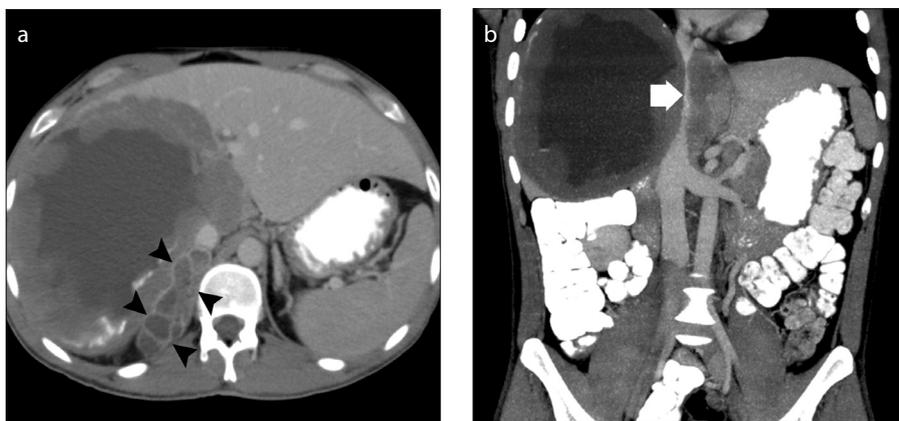


Figure 4. a, b. A 29-year-old man with alveolar echinococcosis involvement of the liver and the right adrenal gland. Axial contrast-enhanced CT image (a) demonstrates an infiltrating tumor-like hepatic mass including a few scattered hyperattenuating foci of calcification and large areas of hypoattenuation corresponding to necrosis. Diffuse enlargement of the right adrenal gland containing numerous cysts with thin walls is present on this CT image (arrowheads). Note that the walls of cysts within the gland show mild enhancement. The left adrenal gland is normal. A coronal contrast-enhanced MIP image (b) reveals severe narrowing of the intrahepatic inferior vena cava (arrow).

irregular borders or as irregularities on the diaphragm surface. The lesions are prone to disseminate in the peripheral zones (19). They are seen as low-density masses with

lobular contours on CT. Calcifications can be detected inside the lesions (3). In addition, it should be noted that cavitation may also occur in lung lesions (20). Differentiation of

AE from metastatic malignancies may be difficult in the presence of bilateral multiple lesions (3, 21).

CT is the best imaging modality for showing the characteristic morphologic features of the AE lesions in intra-abdominal organs. Other abdominal organs are affected by direct invasion or metastatic dissemination of the primary lesions. Invasions of the diaphragm, perirenal region, abdominal lymph nodes, peritoneum, mesenteric tissues, spleen, pancreas, adrenal glands, kidneys, gallbladder, retroperitoneum, abdominal wall, and the stomach have been reported (3, 15, 22–24). The spleen is the most commonly invaded intra-abdominal organ by metastasis. Rarely, it can be directly invaded by liver lesions (22). Lesion characteristics similar to the liver are seen on splenic invasion imaging (15, 25). Involvement of the primary adrenal glands is extremely rare (26). Usually invasion occurs by extension of the parasitic mass located within the right liver lobe or by metastatic dissemination (23, 24). A heterogeneous low-density diffuse expansion is visualized on adrenal gland involvement. There may be cystic areas or necrotic cavities inside the lesion and they can include calcifications (23, 24, 26) (Fig. 4). The peritoneal and mesenteric tissues can be involved by direct invasion or peritoneal seeding. Multiple millimetric sized nodular-cystic implants can be seen on the peritoneal surfaces and in the omentum. Millimetric focal calcific foci can be seen within the lesions. This appearance can mimic pseudomyxoma peritonei (3, 15).

Primary involvement of the bone and soft tissues is very rare. CT or MRI is used for imaging. Muscle invasion can present as masses with cystic cavities mimicking bacterial abscesses (27). The involvement is usually by invasion from the primary lesion or metastatic dissemination. The most commonly involved bone is the vertebral column and the sternum (3, 15, 28). Involvement of the ribs, pelvic bones, and lower extremity bones has also been reported (28). The destructive parasitic lesions within the bone can mimic malignant metastases (3) (Fig. 5).

There is a paucity of information about the use of CT perfusion imaging in AE. This examination was used for detecting microcirculation in hepatic AE lesions. A good correlation between blood flow, blood volume, and microvessel density was shown in the marginal zones of AE lesions. However, it was stated that the main problem of this examination in clinical practice is the exposure to high dose

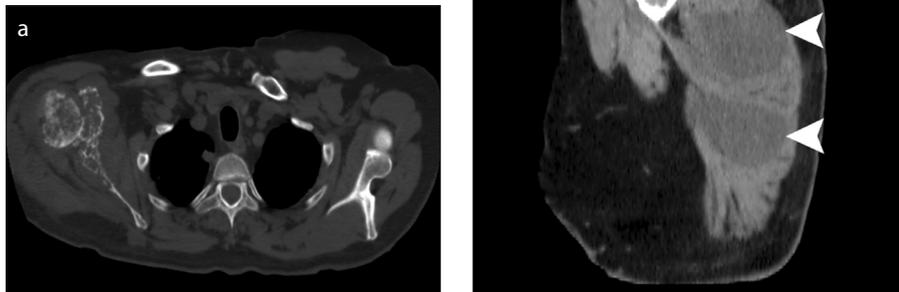


Figure 5. a, b. A 47-year-old man with recurrent hepatic alveolar echinococcosis disseminated in the scapula, humeral head, and soft tissues. Axial unenhanced follow-up CT image demonstrated a cystic mass with thick walls adjacent to the area of surgery compatible with disease recurrence (not shown). An axial image with bone window from unenhanced chest CT (a) shows diffuse expansile lytic lesions of the scapula and the head of the humerus. Unenhanced sagittal multiplanar reformatted (MPR) CT image (b) shows multiple large well-marginated cystic parasitic lesions (arrowheads) within subcutaneous tissue and muscle planes of the right shoulder.

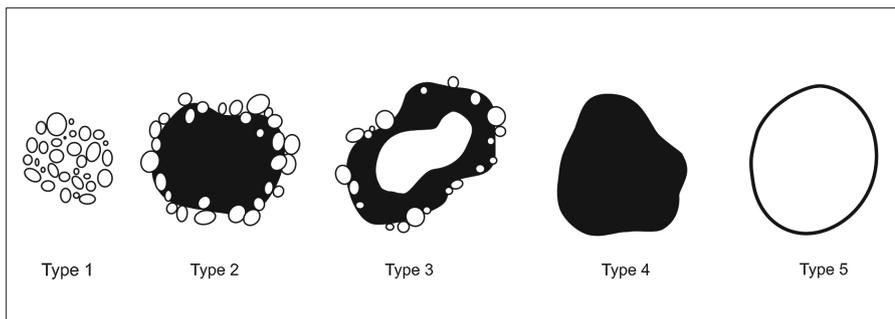


Figure 6. Illustrative scheme of Kodama's MRI classification system for hepatic alveolar echinococcosis lesions. Adapted from Kodama et al. (30).

radiation. On the other hand, iodine concentration measurements in dual-energy CT can be used more safely to achieve a similar goal. Furthermore, well-perfused areas in the marginal zones of the lesions can be clearly demonstrated by using fused iodine map in spectral CT examination (13). After all, these findings are all considered to be a reflection of the presence of periparasitic granulomatous tissue, which is detected as increased metabolic activity on PET-CT. Perfusion CT imaging may be useful in distinguishing AE from malignancies in difficult-to-diagnose hepatic AE cases. Furthermore, this modality can also be used for monitoring treatment response (29).

Magnetic resonance imaging

MRI is complimentary to CT in the abdominal and musculoskeletal system invasion by AE and has a major role in the central nervous system invasion (3). It can help in diagnosis of noncalcified suspicious lesions. MRI is not as successful as CT in show-

ing calcifications pathognomonic for AE. Observed as hyperdense lesions on CT, calcifications may have different signal properties on T1-weighted and T2-weighted images (17). MRI is the best imaging modality characterizing the different components in a parasitic lesion, as well as showing the invasion of the vascular and biliary structures. Since MRI is very useful in showing extension to neighboring organs, it should be included in the preoperative imaging (13, 16, 30). The typical MRI finding of AE in the liver is a mass lesion with infiltrative characteristics having irregular borders and internal heterogeneity with necrotic areas in the center. These show hypo- or isointensity on T1-weighted images and hypo-, iso-, or hyperintense signal features on T2-weighted images (3, 13, 16, 30). Hemorrhage and fat tissue within the lesion is not an expected finding. AE lesions are hypovascular masses that develop diffuse areas of necrosis as a result of inadequate vascular supply as they grow in size. The absence of contrast

uptake in a large proportion of the mass following intravenous contrast administration is an important diagnostic feature of these lesions. Mild peripheral contrast enhancement is seen on gadolinium-enhanced T1-weighted images (3). Perilesional fibroinflammatory tissue is considered to be responsible for such contrast enhancement. However, perilesional areas with intense and delayed contrast enhancement can be seen in some patients (16). Vascular structures can be visualized by dynamic contrast MRI. Invasion and thrombosis of the portal vein can lead to lobar atrophy (31).

AE lesions consist of cystic and solid components. Small smooth cysts reflect metacystic vesicles whereas large irregular cystic areas reflect liquefaction necrosis. The cystic areas within the masses are best shown by T2-weighted images and are hyperintense. T2-weighted imaging is extremely valuable for the identification of AE lesions, which best characterizes parasitic cystic structures sometimes defined as "honeycomb" or "bunch of grapes" (13). Such cysts are less than 1 cm in size, round or ovoid in shape, and they tend to be aligned at the periphery of a lesion (16). The solid component is formed by coagulation necrosis, granuloma, and/or calcification. These areas are iso- or hypointense on T2-weighted images (16, 30). Low signal on T2-weighted images can be interpreted as the result of very small vesicles embedded in fibrous tissue (16, 30). Kodama et al. (30), proposed an MRI classification for liver AE lesions, with five types: type 1 (4%), multiple small round cysts without a solid component; type 2 (40%), multiple small round cysts with a solid component; type 3 (46%), a solid component surrounding a large and/or irregular pseudocyst with multiple small round cysts; type 4 (4%), a solid component without cysts; type 5 (6%), a large cyst without a solid component. In their series, small parasitic cysts were detected in 96% of lesions (Fig. 6). The authors stated that type 1 lesions represent the earliest stage of the disease, type 2 lesions the second stage, and type 3 lesions the advanced stage. In addition, it was advocated that type 4 lesions show similarities with type 2, and type 5 lesions with type 3. However, there is not enough literature data on the correlation between the Kodama classification and prognosis.

Magnetic resonance cholangiopancreatography (MRCP) has replaced percutaneous cholangiography, a more invasive imaging modality that can be complicated with

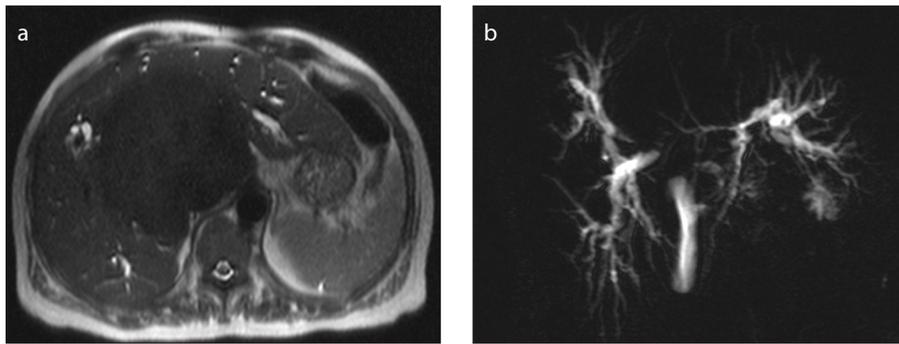


Figure 7. a, b. A 53-year-old woman with alveolar echinococcosis of the liver involving the biliary tree. Axial T2-weighted image (a) reveals a big homogeneously hypointense mass and marked dilatation of biliary ducts. A coronal thin-section image from magnetic resonance cholangiopancreatography (b) shows the hepatic mass compressing the hilar biliary ducts. Note the apparent intrahepatic biliary dilatation.

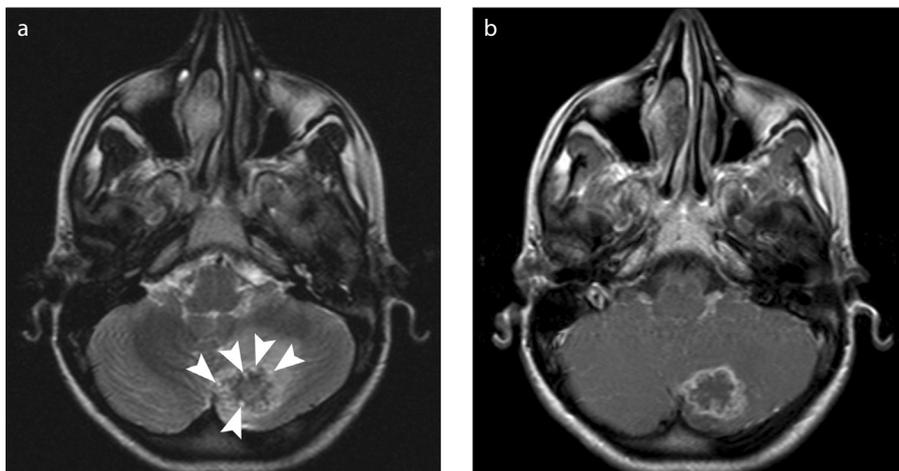


Figure 8. a, b. A 21-year-old female with disseminated *E. multilocularis* infection. Axial MRI scans show a tumor-like mass with irregular margin in the left cerebellar hemisphere. The lesion is seen inhomogeneously hypointense on T2-weighted image (a). An area of edema surrounding the parasitic lesion is seen. Note multiple tiny cysts in the lesion (arrowheads). Axial T1-weighted postcontrast image (b) demonstrates irregular rim-like peripheral enhancement on the border of the mass.

cholangitis and septic shock. MRCP has an important impact on planning of surgery or interventional palliative procedures by showing biliary tract compression, distortion, and biliary tract invasion by the parasitic mass (Fig. 7). In addition, it can show the presence of a connection between the biliary tracts and necrotic pseudocystic cavities (3, 13, 16).

Recently, diffusion-weighted imaging (DWI) has emerged as a promising imaging modality in characterizing the liver lesions (32, 33). The diffusion of water molecules in malignant lesions is limited due to increased cellularity and decreased intercellular space. However, this is not an expected finding in AE lesions. Apparent diffusion coefficient (ADC) is a valuable tool in the diagnosis of focal liver lesions. Higher ADC values than the liver parenchyma are seen

on DWI images obtained at a b value of 800 s/mm^2 (3, 13). The restriction of diffusion can be secondary to abscess formation of the infected lesion. Therefore, the lack of general restriction of diffusion in AE lesions is a valuable finding in distinguishing them from malignancies (3). Nevertheless, there are not enough publications on this topic. In 2014, Becce et al. (34) were the first to report a study involving the DWI findings and ADC values in 22 patients with 63 AE lesions. In this study, the total ADC values of the AE lesions were found to be clearly higher than the cutoff values on prior studies with malignant lesions. In contrast, the ADC values of AE lesions were significantly lower than the values of simple liver cysts. Thus, ADC values could potentially be used in differentiating AE lesions from simple cysts and malignant lesions.

Another important area for MRI use is the brain involvement by AE. There are few articles reporting the imaging findings of AE in the brain. Lobulated multilocular cystic masses with irregular rim enhancement are seen on contrast-enhanced MRI (Fig. 8). Calcifications within the lesion and perilesional edema can be detected (3, 10). On T2-weighted and fluid attenuation inversion recovery images, a heterogeneous low-signal mass with high-signal circumferential areas secondary to adjacent edema is seen (3). We have very limited information regarding the use of DWI, MRS, and perfusion MRI in detection of AE lesions in the brain. However, the normal N-acetylaspartate/creatinine and choline/creatinine rates obtained from the lesion on MRS suggest a non-neoplastic origin of the lesion (10). On DWI, the lesions show mild decrease in signal features without diffusion restriction (3, 35).

PET-CT

Conventional radiologic imaging modalities do not give information regarding the metabolic activity of parasitic lesions. In contrast, 18F-fluorodeoxyglucose (FDG)-PET is suggested to show the viability and metabolic activity in AE lesions (16, 36, 37). An increased FDG uptake is observed in neoplastic and inflammatory-infectious lesions. In this context, a decrease in FDG uptake in these lesions following the medical treatment indicates a good response to the treatment. Therefore, PET/CT has been used for a long time for follow-up in these patients (38). While FDG uptake is positive in the peripheral zones of the parasitic lesions, no uptake is present in the central necrotic tissue (38). There is a strong inflammatory response around the parasitic lesions within the liver. The increased inflammatory response and metabolic activity of the inflammatory cells may explain the increased uptake. However, the target of FDG is not clear in AE lesions (38, 39). In an *in vitro* study (39), it was shown that the FDG is taken up by the immune cells rather than the *E. multilocularis* metacystodes. PET/CT cannot explain the viability of the parasite directly and a negative study does not mean the death of the parasites completely. However, it can reliably evaluate the inflammatory response and can show the parasitic activity indirectly (40). Therefore, it is the most accepted imaging modality in adjusting the primary therapy, the long-term benzimidazole therapy in inoperable patients, and in follow-up of the patients (12, 13, 40). Imaging with delayed PET/CT

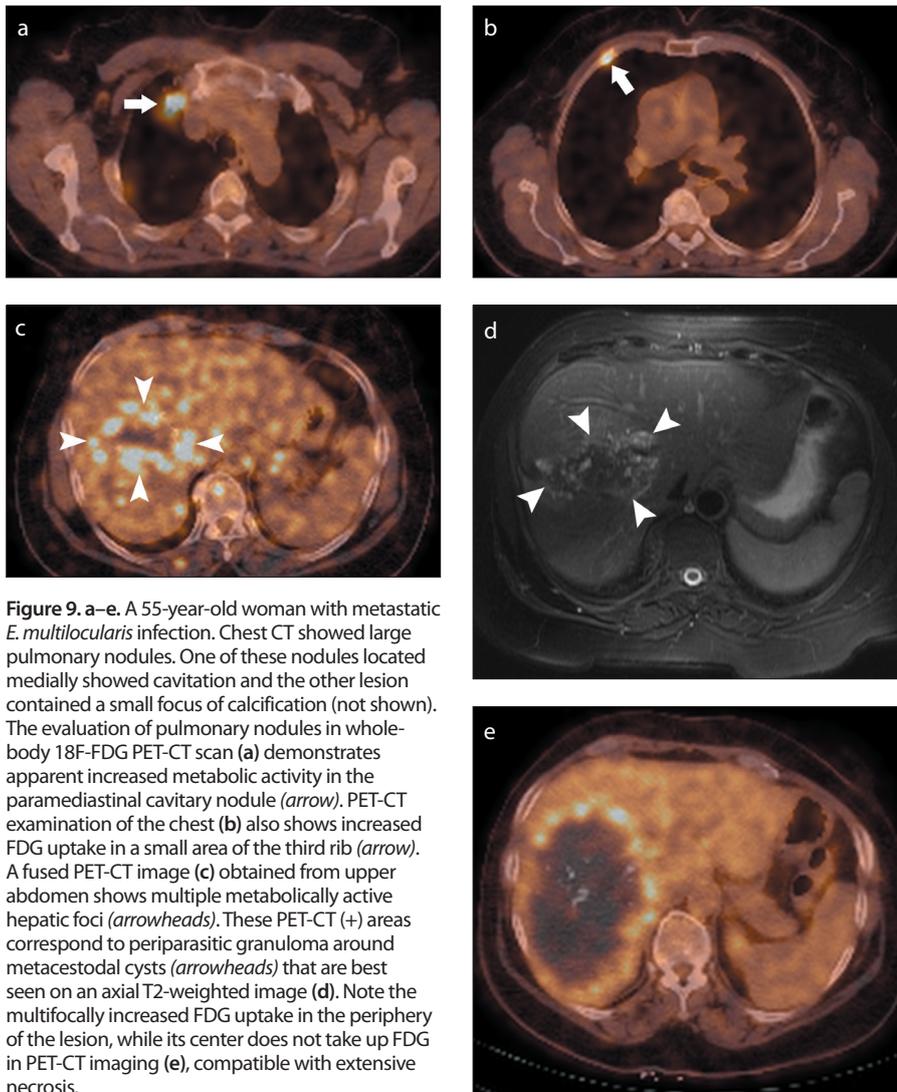


Figure 9. a–e. A 55-year-old woman with metastatic *E. multilocularis* infection. Chest CT showed large pulmonary nodules. One of these nodules located medially showed cavitation and the other lesion contained a small focus of calcification (not shown). The evaluation of pulmonary nodules in whole-body 18F-FDG PET-CT scan (a) demonstrates apparent increased metabolic activity in the paramediastinal cavitary nodule (arrow). PET-CT examination of the chest (b) also shows increased FDG uptake in a small area of the third rib (arrow). A fused PET-CT image (c) obtained from upper abdomen shows multiple metabolically active hepatic foci (arrowheads). These PET-CT (+) areas correspond to periparasitic granuloma around metacestodal cysts (arrowheads) that are best seen on an axial T2-weighted image (d). Note the multifocally increased FDG uptake in the periphery of the lesion, while its center does not take up FDG in PET-CT imaging (e), compatible with extensive necrosis.

(3 h after the injection) is recommended to avoid false negative results in cases remaining negative after standard imaging. A study stressing the increased sensitivity of delayed FDG PET showed that the use of delayed PET/CT together with cytology is a reliable method in patient follow-up (41). In a recent study, MRI findings were compared with PET/CT, and the presence of parasitic microcysts (type 1, 2, and 3 lesions in Kodama's classification) was suggested to correlate with a metabolically active disease (42) (Fig. 9).

Contrast-enhanced US

Contrast-enhanced ultrasonography (CEUS) is one of the imaging modalities suggested in the diagnosis and follow-up of hepatic AE (13). Using CEUS with Levovist®, Suzuki et al. (43) observed irregular bordered defective areas described as “worm-eaten” and reported that CEUS is beneficial in the early diagnosis of the disease. However, con-

trast enhancement of AE lesions on US is still a controversial topic. This can be attributed to the use of first generation contrast material in initial studies and its limitations (13, 44). Ehrhardt et al. (44), by referring to their study results, suggested that SonoVue® - CEUS is an alternative to PET/CT in showing the metabolic activity of the disease and in adjusting the chemotherapy. However, the limited number of studies as well as the limited number of study objects do not provide satisfactory data (13).

Treatment and the role of interventional radiology

Radical surgery is the first line of treatment in diseases where the lesion can be completely excised and has been a turning point in the treatment of AE (2, 12). Early diagnosis is very important in lowering the rate of inoperable patients and the need

for radical surgery (2). Liver transplantation is the last resort and should be reserved only for incurable symptomatic biliary AE cases. Cure is achieved in only half of the transplant recipients (45, 46). Furthermore, immunosuppression following the transplantation can increase duplication of the parasite and lead to metastatic dissemination (12, 18, 47). Currently, there is no parasiticidal drug that can be used in the treatment of AE. Benzimidazoles (mebendazole and albendazole) are parasitostatic drugs that can be used against parasitic metacestodes (2, 12, 16). Although benzimidazoles are widely regarded as parasitostatic, it has been reported that they may, in some cases, exert parasiticidal effect and thus the treatment may be safely terminated after some time (37, 40). On the other hand, these drugs have some side effects and are potentially teratogenic. Moreover, prolonged treatment has a high cost. It is also debated how long the treatment should be continued, and a reliable parameter showing the effectiveness of chemotherapy is lacking. The basic reason for this is the difficulty in detecting the viability of the parasites *in vivo* (37). In a recent study, the combined use of FDG-PET and antibody levels against the recombinant Em11/3-10 antigen was reported as a promising method for assessing disease activity (48). High cost and high levels of radiation exposure are the main limitations of PET-CT. In contrast, PET-MRI, a novel hybrid imaging technique, causes a lesser amount of radiation exposure (49). Despite the absence of any conclusive data, it may presumably replace PET-CT in the follow-up of AE cases. The consensus view of a number of experts on a stage-specific approach for the treatment was summarized in a review (12).

Collection of specimens from the parasitic masses with fine needle aspiration or core needle biopsy under imaging guidance is important in histopathologic diagnosis, particularly in controversial cases (21). Furthermore, evaluation of the parasitic antigens and DNA from the biopsy specimens is helpful in diagnosis (5). Interventional radiology procedures are used when there is abscess formation in the cavities in the center of the mass, development of jaundice secondary to biliary duct obstruction with or without cholangitis, hepatic or portal vein thrombosis and variceal bleeding secondary to portal hypertension (4). Percutaneous stent placement has been reported to be successful in cases with Budd-Chiari

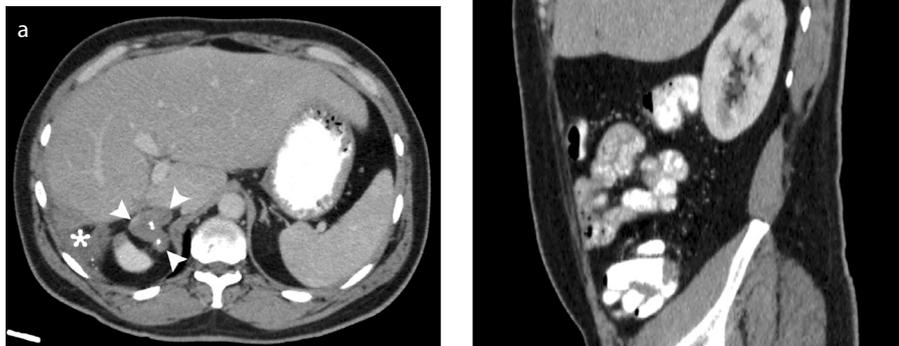


Figure 10. a, b. A 34-year-old man with recurrent disseminated *E. multilocularis* infection after right hepatectomy. An axial contrast-enhanced follow-up abdominal CT (a) reveals masses that emerged close to the operation site (*asterisk*) and the right adrenal gland (*arrowheads*). Note that the adrenal mass contains two small foci of calcification. Sagittal MPR CT image (b) demonstrates multiple pulmonary lesions that developed due to spread of the parasitic mass via the transdiaphragmatic pathway (*arrow*).

syndrome secondary to obstruction of the hepatic veins and vena cava inferior (50). Percutaneous drainage of abscesses within the center of the masses during antibiotic therapy significantly improves the patients' clinical outcome (6, 16) (Fig. 3). Percutaneous transhepatic biliary drainage has an important role in treatment of cholangitis, which can develop secondary to biliary ductal obstructions. External or internal biliary drains can get clogged since they can stay for several years in patients and therefore should be replaced regularly (16). In summary, interventional radiology has an important role in confirming the diagnosis of AE and in palliative treatment of a number of complications.

Follow-up of patients with alveolar echinococcosis

Radical resection is crucial and may cure the patient. The resectability rates reported in the literature show a wide spectrum (4%–87%) and generally reflect stage of the disease at presentation. On the other hand, in most cases, palliative surgery has provided limited benefit. Considering the resemblance of parasitic lesions with a malignant tumor, it is recommended to perform surgical procedures with a 2 cm safety margin as in oncologic surgery (12, 51). On the other hand, Kawamura et al. (52) reported that long-term survival rates approached 100% in cases that underwent complete resection with a surgical margin below 1 cm (R0) and received chemotherapy after surgery. Nev-

ertheless, it is also reported that in some patients treated by "curative" resections, recurrence may occur after several years (18, 53). Thus, it is concluded that long-term, possibly life-long, follow-up is required (53). In this regard, sectional imaging techniques (US, CT, and MRI) play an important role in monitoring the patients. (Figs. 5, 10). In particular, treated patients should be followed up by US at short intervals and by CT and/or MRI at longer intervals of 2–3 years (12). Recurrences may occur in AE cases undergoing transplantation. Therefore, it is recommended to follow these cases closely (54).

Differential diagnosis

Primary or metastatic malignant liver neoplasms can be considered in the differential diagnosis of AE. In sonographic examination, the observation of "hailstorm pattern," characterized by multiple hyperechoic solid lesions, can be confused with hepatic hemangiomas (16). Kodama's classification guides the differential diagnosis list of AE lesions. Type 1 lesions may be confused with cystadenomas or localized Caroli disease. Type 2 and 3 lesions, on the other hand, may be confused with cystadenoma, cystadenocarcinoma, or peripheral cholangiocarcinoma. However, these lesions generally take up contrast medium and do not show calcification. Type 4 lesions appear solid, and their differential diagnosis may include many hepatic neoplasms. The cystic-necrotic component of the lesions can sometimes be dominating. Type 5 lesions may be confused

with simple cysts, hydatid cysts, and hepatic abscesses (3, 16, 30, 55). On CT examination, when cystic component and calcifications are not dominating, the disease is most frequently confused with cholangiocarcinoma. Lesions with a predominant cystic component may be confused with cystadenoma-adenocarcinoma, hydatid cyst, or abscess (3). In cases with suspected AE lesions, combined use of CT and MRI increases the odds of making a correct diagnosis. In cases with other affected organs, the list of differential diagnosis differs according to primary versus secondary involvement. In case of secondary and remote organ involvement, AE lesions are mainly confused with metastatic malignant neoplasms (21).

In lung involvement, infection of *E. granulosus*, Wegener granulomatosis and other granulomatous diseases can be considered (3). In brain involvement, AE lesions can be confused with various infectious, parasitic, and neoplastic diseases (3, 8, 10). In osseous and soft-tissue involvement, tuberculosis, primary and metastatic neoplasms should be considered in the differential diagnosis (3).

The most significant radiologic characteristics of the AE lesions can be stated as the presence of typical calcifications and tiny cystic structures inside the lesions, the absence of distinct vasculature inside the mass, and the absence of clear contrast enhancement except for weak perilesional enhancement. An increased 18F-FDG uptake in PET-CT scan is generally observed in a ring shape at the periphery of the lesion.

Conclusion

AE may be easily misdiagnosed as a metastatic malignant tumor by inexperienced physicians, especially in nonendemic regions. It is important for the radiologist to be familiar with multimodality imaging findings of this disease. US can be utilized as the initial imaging method and for scanning purpose. Furthermore, US can guide the interventional procedures. CT and MRI play an important role in ensuring the diagnosis, planning of surgical operation, and following up the patients with AE. PET-CT is a supporting tool in determining the effectiveness of treatment. Interventional procedures are very important both in diagnosis and treatment of complicated patients. Radiology has a key role in guiding the clinician in terms of early diagnosis and appropriate treatment. In return, this will improve the quality of life and prolong the survival of the patient.

Acknowledgements

We would like to thank Prof. Dr. İlgin Özden from the Department of Hepatobiliary and Pancreatic Surgery at Istanbul University, Istanbul Faculty of Medicine for his valuable support and cooperation. Also, we would like to thank medical illustrator Özge Papakçı Aydın for drawing Fig. 6.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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