Echinococcoses – A Primer for Radiologists

Die Echinokokkosen aus Sicht der Radiologie

Authors

Tim Frederik Weber[1], Theresa Mokry[1, 2], Marija Stojkovic[3]

Affiliations

1 Diagnostic and Interventional Radiology, University Hospital Heidelberg, Germany
2 Radiology, German Cancer Research Center, Heidelberg, Germany
3 Tropical Medicine, Department of Infectiology, University Hospital Heidelberg, Germany

Key words

infection, tropical diseases, diagnostic radiology, CT, MR-imaging, abdomen

received 25.02.2023
accepted 10.05.2023
published online 19.07.2023

Bibliography

Fortschr Röntgenstr 2023; 195: 1106–1121
DOI 10.1055/a-2114-1980
ISSN 1438-9029

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence

Prof. Dr. Tim Frederik Weber
Diagnostic and Interventional Radiology, University Hospital Heidelberg, INF 410, 69120 Heidelberg, Germany
Tel.: +49/62 21/5 63 84 38
tim.weber@med.uni-heidelberg.de

ABSTRACT

Background Cystic (CE) and alveolar (AE) echinococcoses are zoonotic parasitoses that may pose diagnostic problems due to their relative rarity in Middle Europe.

Methods Based on a recent literature search and the observation of casuistics from a national echinococcosis treatment center, epidemiological, radiological, and therapeutic fundamentals are presented and important differences between AE and CE are discussed.

Results and Conclusion AE and CE must be regarded as completely different diseases, which differ from each other in every significant aspect. This applies not only to the epidemiological background of the patients but also to the biology of the diseases and their respective imaging features.

Key Points:

- AE and CE are very distinct from one another and must be considered separately.
- AE is endemic in Middle Europe and is known as malignant parasitosis due to its destructive growth form.
- CE is primarily seen in Middle Europe in individuals with migration background and has a rather benign character.

Citation Format

- Weber TF, Mokry T, Stojkovic M. Die Echinokokkosen – Einblicke aus Sicht der Radiologie. Fortschr Röntgenstr 2023; 195: 1106–1121

ZUSAMMENFASSUNG

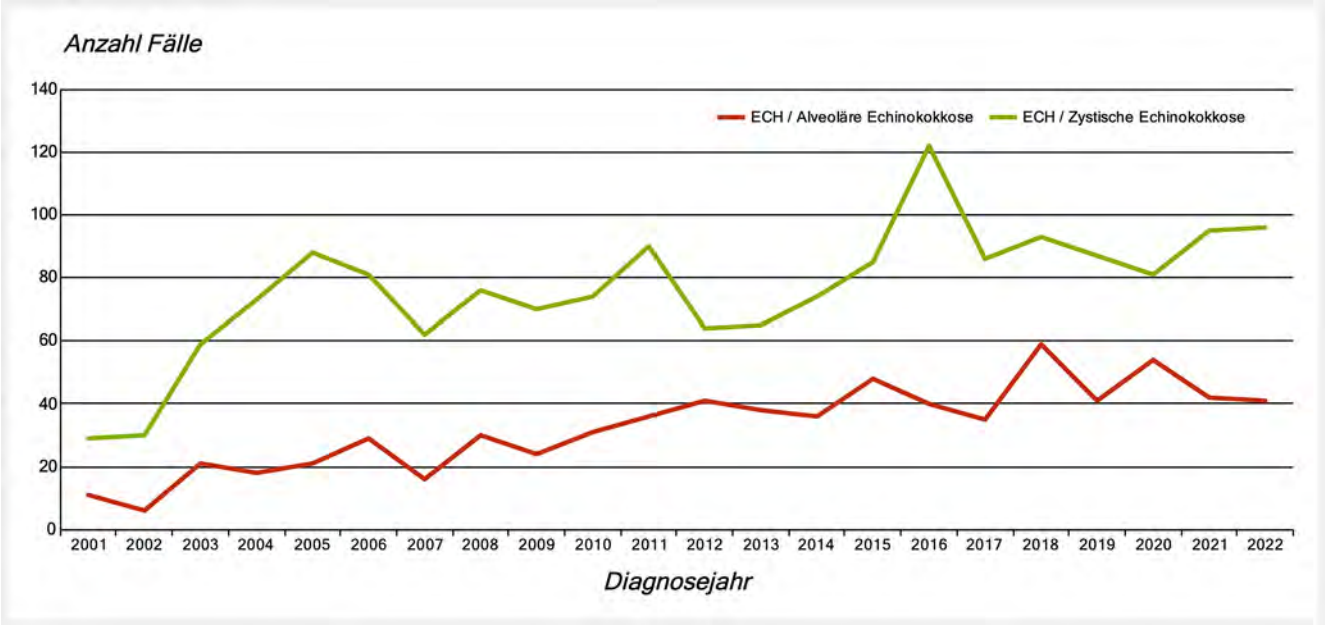
Hintergrund Die zystische (CE) und die alveoläre (AE) Echinokokkose sind zoonotische Parasitosen, die aufgrund der relativen Seltenheit in Mitteleuropa diagnostische Schwierigkeiten bereiten können.

Methode Auf Basis einer aktuellen Literaturrecherche und der Beobachtung von Kasuistiken eines nationalen Echinokokkose-Behandlungszentrums werden epidemiologische, radiologische und therapeutische Grundlagen zu den Echinokokkosen vermittelt und wichtige Unterschiede zwischen AE und CE herausgearbeitet.

Ergebnisse und Schlussfolgerung AE und CE sind als komplett unterschiedliche Erkrankungen anzusehen, welche in allen wesentlichen Dimensionen voneinander differieren. Dies betrifft nicht nur den epidemiologischen Hintergrund der betroffenen Personen, sondern auch die Biologie der Erkrankungen und deren bildgebenden Eigenschaften.

Introduction

The term “echinococcoses” includes two different parasitic zoonoses that differ significantly from one another with regard to important aspects [1]: Cystic echinococcosis (CE) and alveolar echinococcosis (AE). These two disease must be strictly differentiated from one another since misdiagnosis can have fatal consequences [2]. A third form of human echinococcosis (neotropic echinococcosis) is seen only regionally in Latin America and is not taken into closer consideration here. The commonly used term “hydatidosis” or “hydatid disease” should only, if at all, be used in reference to



▶ **Fig. 1** New diagnoses of cystic and alveolar echinococcosis reported between 2001 and 2022 for Germany (data from: Robert Koch Institute: SurvStat@RKI 2.0, https://survstat.rki.de, query date: 1/31/2023, ECH: echinococcosis).

CE but it is also regularly used incorrectly in the international literature to refer to AE. For this reason, we suggest not to use these expressions when talking about either one of the echinococcoses. Ambiguity in nomenclature and overlapping terminology contribute to misunderstandings regarding echinococcoses. This issue is addressed by a recommendation by the World Association of Echinococcosis (WAE) regarding the standardization of terminology. The recommended terms are used in this article [3].

Differences between CE and AE relate not only to epidemiology, diagnosis, and treatment but also to growth patterns and appearance on radiological imaging. The only thing the two parasitoses have in common is that they are infestations with the larval stage of a tapeworm of the genus *Echinococcus*. CE is caused by the dog tapeworm (*Echinococcus granulosus*) and AE by the fox tapeworm (*Echinococcus multilocularis*). Humans are infected by ingesting the eggs. The larvae primarily affect the liver or more rarely other organs. The clinical presentation is usually characterized by expansive growth in CE and by infiltrative growth of cysts in AE. Symptoms typically only occur years after infection. AE is endemic in Germany, while CE is mainly imported from other countries. An increase in case numbers has been observed in Germany for both types of echinococcoses over the last 20 years (▶ **Fig. 1**). Person-to-person transmission is not possible, not even during medical procedures.

Radiology plays an important role in detecting echinococcosis in the right situation and characterizing it as one of the two echinococcoses, thus allowing timely and optimal treatment. The goal of this article is not only to describe the radiological features of these diseases but also to provide a synopsis of other disease aspects, thus helping to improve general understanding. This review article is based on a selective literature search using key words associated with echinococcosis. Recommendations from professional societies and the World Health Organization were taken into particular consideration. Observations from case studies of a national echinococcosis treatment center were used in the case of aspects with insufficient evidence. ▶ **Table 1** provides a comparison of the differences in important disease dimensions.

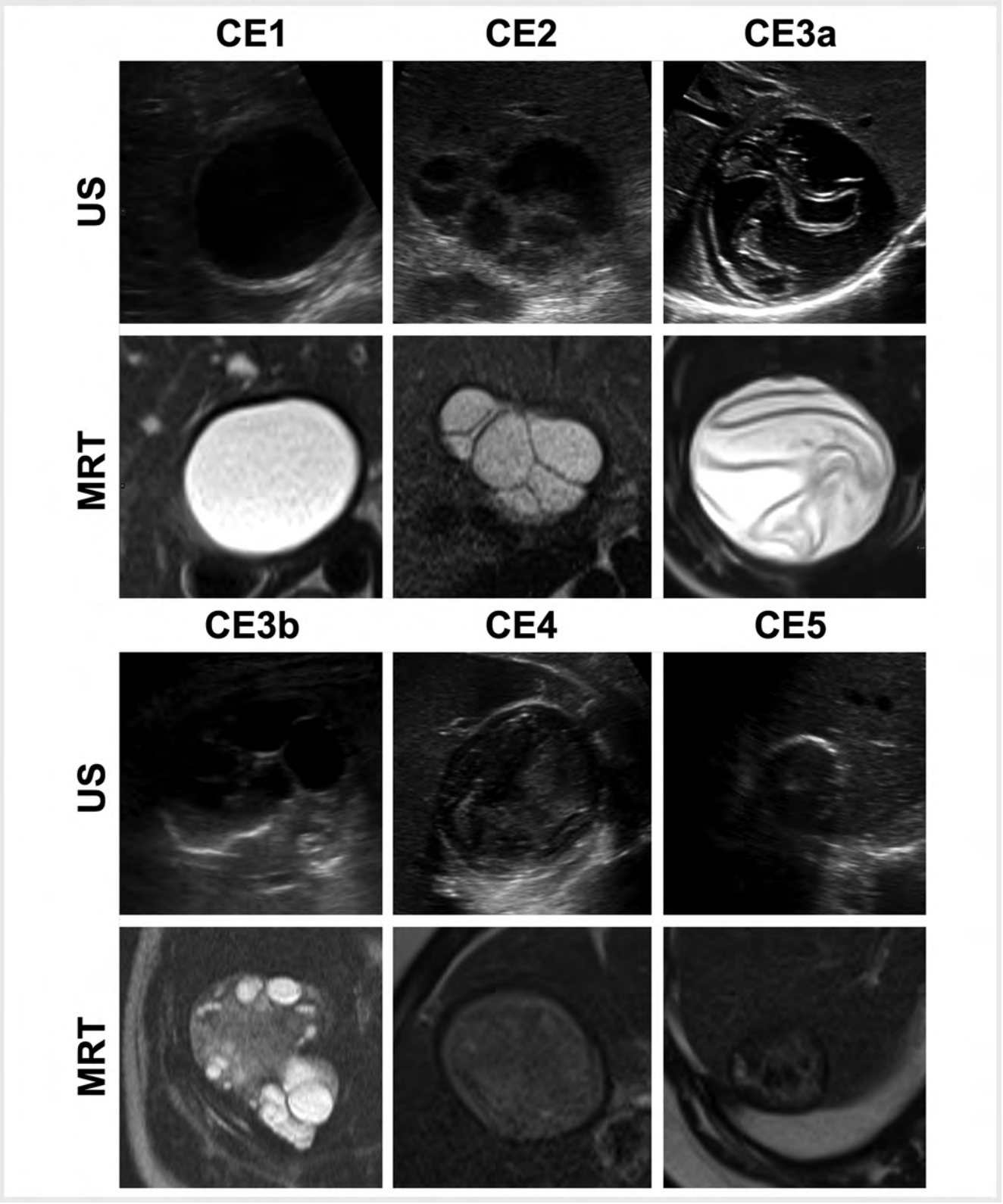
▶ **Table 1** Summary of differences between cystic echinococcosis (CE) and alveolar echinococcosis (AE) considering the diagnostic setting in Germany.

	CE	AE
Biology	Benign	Malignant
Growth pattern	Expansive	Infiltrative
Course	Progression in stages	Progressive
Pharmacotherapy	Parasitocidic	Parasitostatic
Epidemiology	Worldwide	Temperate zones northern hemisphere
Background of affected persons	Migration	Native population

Cystic echinococcosis

Epidemiology and parasitology

E. granulosus and thus CE are present globally. It is highly endemic in the (eastern) Mediterranean Area, in the Near East, in Central Asia, in North and East Africa, and in South America. CE is only sporadically seen in individual cases in the native population in German-speaking countries [4]. Almost all cases diagnosed in



▶ **Fig. 2** WHO stages of cystic echinococcosis on ultrasound (US) and MRI (source: Stojkovic M, Müller J, Junghanss T, Weber TF. Radiological Diagnoses in the Context of Emigration: Infectious diseases. Fortschr Röntgenstr. 2018; 190 (2): 121–133).

▶ **Table 2** WHO stages of cystic echinococcosis.

Stage	Description	Characteristic signs	Viability
WHO-CE1	Unilocular cyst	Double line sign	Active
WHO-CE2	Multilocular cyst without solid components	Rosette sign	Active
WHO-CE3a	Unilocular cyst with detached endocyst	Water lily sign	Transitional
WHO-CE3b	Multilocular cyst with solid components	Swiss cheese sign	Active
WHO-CE4	Solid finding without cysts	Ball of wool sign with canalicular matrix	Inactive
WHO-CE5	Solid finding without cysts	Acoustic shadows	Inactive
WHO-CL	Simple unilocular cyst	None	CE possible in suitable context

German-speaking countries are in people with a migration background. The epidemiological context is therefore an important factor for assessing the pretest probability for the presence of CE upon detection of an unclear cystic lesion.

The adult worm lives in the intestine of dogs (or other dog-like animals like dingos and hyenas) and is approx. 1 cm long. The eggs produced by the worm and excreted in the excrement of the final host are ingested by an intermediate host. In the intermediate host, the larvae migrate from the intestine to the target organs and form cysts (metacestodes), which represent the infectious parasite stage for the final host. After the death of the intermediate host, the cycle is completed when the final host consumes the infected organs. Typical intermediate hosts include sheep and other hooved animals. Humans are an aberrant intermediate host. The main risk factors for CE in humans are pastoral animal husbandry, uncontrolled slaughter, and poor hygienic conditions. The liver is the most common site of infection, followed by the lung. In general, CE can occur anywhere in the body. Rupture of the cysts can result in secondary CE in neighboring organs (e. g., peritoneal cavity, pleural space).

The wall of a CE cyst is comprised of three layers (from inside to outside): Germinal layer, laminated layer, adventitial layer. The germinal layer and laminated layer are of parasitic origin and are collectively referred to as the endocyst. The adventitial layer is formed by the host as part of a fibroinflammatory reaction and is also referred to as the pericyst.

Diagnosis and imaging

General information

In the case of corresponding epidemiology, CE is diagnosed based primarily on imaging and less on serology. Serological tests often yield false-negative results primarily in the case of new cysts that have not yet resulted in sufficient antigen contact. Percutaneously aspirated cyst contents should only be examined for diagnosis in exceptional cases using special safety precautions. In the case of puncture and aspiration of CE cyst contents, anaphylactic reactions and spreading of infectious material can occur.

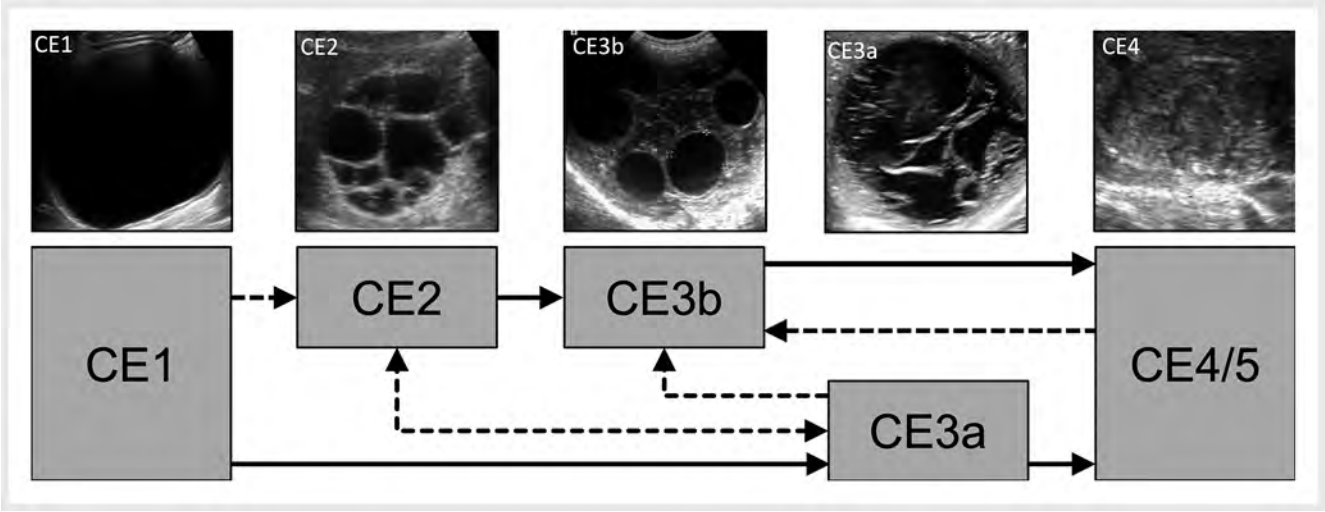
CE primarily causes a macrocystic lesion with clear margins and expansive growth. The growth rate is typically approx. 1 cm (0 to 3 cm) per year [5]. The asymptomatic incubation time is usually multiple years. CE cysts can achieve a considerable size. They undergo a natural development process of evolution and involution that can end in the spontaneous inactivation of cysts characterized by consolidation. During this development process, the CE cysts have different image properties that are summarized in the WHO classification of CE in 5 stages (▶ **Fig. 2**, ▶ **Table 2**) [6].

Imaging methods and classification

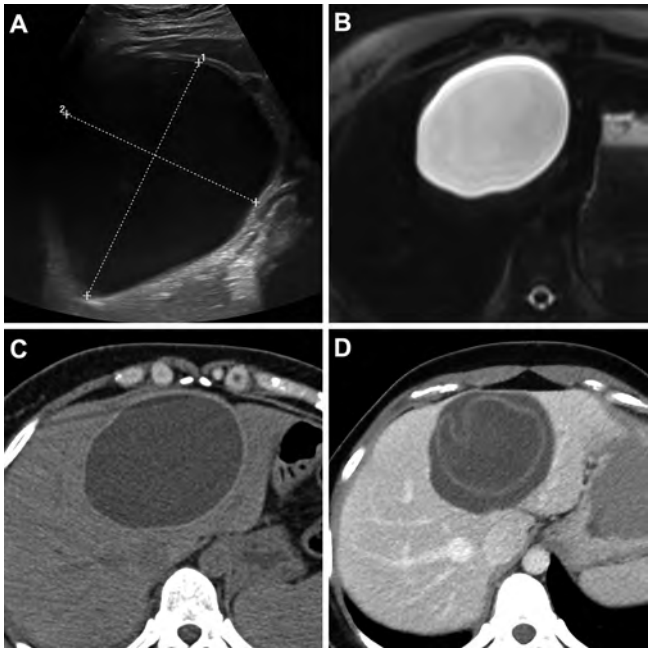
The WHO stages provide information about the viability of cysts and allow differentiation between active, transitional, and inactive cysts. The cyst stages occur in a certain order. However, they do not progress in a strictly unidirectional manner toward complete involution (▶ **Fig. 3**). Therefore, transformation from inactive stages into more active stages is possible. The descriptors of the WHO stages are primarily related to hepatic manifestations but can be largely applied to other organs.

Imaging, preferably ultrasound (US) or magnetic resonance imaging (MRI), is used to assign a CE cyst to a WHO stage. CT is only of limited use for diagnosis and classification [7]. The image properties of the individual stages can be pathognomonic for CE in the case of a suitable epidemiological context. When no pathognomonic signs of CE can be detected on imaging but there is sufficient pretest probability for CE, the cysts are referred to as WHO-CL (cystic lesion). In these cases, CE can be neither detected nor ruled out on imaging.

New CE cysts (WHO-CE1) are unilocular cysts. Only when the host forms a pericyst can this early CE stage, e. g., in the liver, be differentiated from dysontogenetic cysts. In this case, the double line sign, which means that the pericyst and endocyst can be identified as separate wall layers, can be seen on US. The double line sign is considered pathognomonic for CE in a corresponding epidemiological context but can only be visualized with US not with CT or MRI. The wall of a hepatic CE cyst is sometimes hyperdense compared to the liver parenchyma on non-contrast CT (▶ **Fig. 4**). The protoscolices produced by the germinal layer and found in the cyst fluid can sometimes be seen as the “snowstorm sign” on ultrasound in the case of active CE cysts. The protoscolices settle on the floor of the cyst as a function of gravity and are stirred up when the patient changes from a lying to a sitting position. Otherwise, the contents of WHO-CE1 cysts are anechoic on



▶ **Fig. 3** Sequence of WHO stages of cystic echinococcosis. The dotted arrows show a change of stage with increasing activity. Therefore, the stages do not necessarily move in one direction toward involution. It is possible for inactive stages to transform to more active stages (CE3a to CE2 or CE3b, depending on the degree of consolidation of the CE3a lesion; CE4 to CE3b).



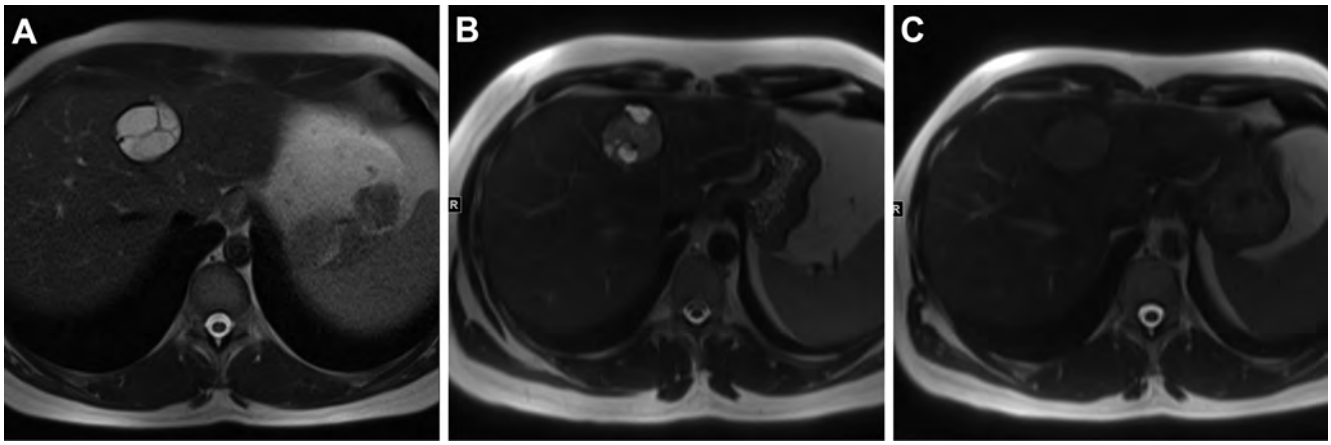
▶ **Fig. 4** WHO CE1 lesion with transformation to stage WHO-CE3a. On ultrasound the unilocular lesion shows a double line sign **A** in the periphery. On heavily T2-weighted MRI, the lesion is homogeneously CSF-isointense **B**. On non-contrast CT, the cyst wall is slightly hyperdense compared to the liver background **C**. Four months after time point C, a repeat CT examination shows transformation to stage WHO-CE3b with the water lily sign **D**.

US, fluid-equivalent with density values of < 20 HU on CT, and CSF-isointense on MRI.

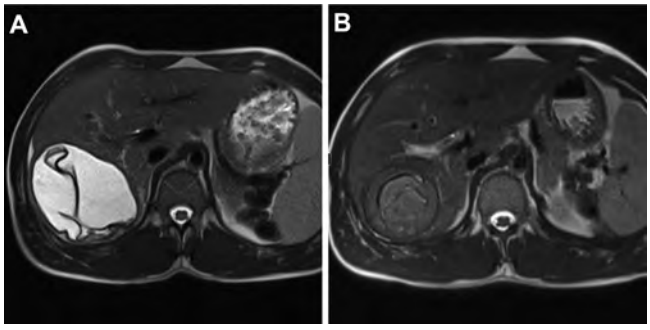
WHO-CE1 cysts can develop in two directions. Firstly, one or more secondary cysts (daughter cysts) can form within the primary cyst (mother cyst), resulting in a multilocular cyst (WHO-CE2) (▶ **Fig. 5**). Daughter cysts can occupy almost the entire volume of the mother cyst (▶ **Fig. 2**). This is referred to as the rosette sign. WHO-CE2 cysts are active cysts. The daughter cysts can be reliably visualized with US and MRI. This cannot be reliably achieved with CT. The rosette sign is characteristic for CE in an appropriate epidemiological context. However, it can be difficult to differentiate from complicated cystic lesions with a different etiology. Differential diagnoses include cystic neoplasm (mucinous cystic neoplasm of the bile ducts, intraductal papillary neoplasm of the bile ducts) or complicated non-neoplastic cysts. Daughter cysts are rounded and self-contained. Therefore, interrupted and irregular septations and complex cyst fluid are not indicative of CE. For example, hemorrhage is not seen in CE. The contents of a CE cyst never enhance after administration of a contrast agent.

Secondly, the endocyst can detach from the pericyst and float in the cyst fluid as a floating membrane (WHO-CE3a). This is known as the water lily sign. The water lily sign is pathognomonic for CE and be reliably visualized with US and MRI. On T2-weighted MRI, the endocyst is hypointense compared to the fluid in the cyst (▶ **Fig. 6**). The detachment of the endocyst initiates involution of the cyst. Stage WHO-CE3a is currently viewed as the only transitional stage. However, in approximately half of cases, WHO-CE3a lesions contain viable pathogenic material so that progression to an active multilocular cyst with daughter cysts is possible [8].

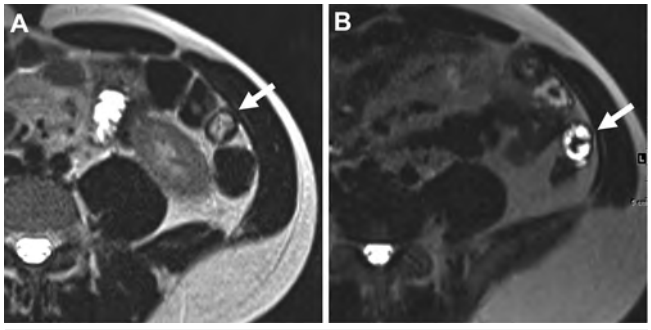
The consolidation of the cyst contents of WHO-CE3a and WHO-CE3b lesions results in increasing inactivation of CE cysts. However, a lesion continues to be classified as WHO-CE3a as long as fluid is still present. If both daughter cysts and consolidated components can be seen in a multilocular CE cyst, it is classified as WHO-CE3b (▶ **Fig. 5**). The transition from stage WHO-CE2 to WHO-CE3b is therefore gradual. WHO-CE3b has long been referred to as a transitional stage. However, today, it tends to be considered an active cyst stage since complete spontaneous consolidation is rare and these cysts tend to progress [8, 9]. Progressive daughter cysts can penetrate the wall of the mother cyst and spread exophytically into the surrounding area. WHO-CE3b cysts



▶ **Fig. 5** WHO-CE2 lesion with transformation to stage WHO-CE4. T2-weighted MRI initially **A** shows a multilocular cyst without solid components (WHO-CE2). 4 years later **B**, partial consolidation is present (WHO-CE3b). Another 2 years later **C**, the lesion is completely consolidated (WHO-CE4).



▶ **Fig. 6** WHO-CE3a lesion with transformation to stage WHO-CE4. T2-weighted MRI **A** shows a unilocular cyst with detached endocyst (water lily sign) (WHO-CE3a). On follow-up MRI 1.5 years after percutaneous treatment **B**, the lesion is consolidated and has transformed to an inactive stage (WHO-CE4). The endocyst is still visible within the consolidated matrix as a canalicular structure.

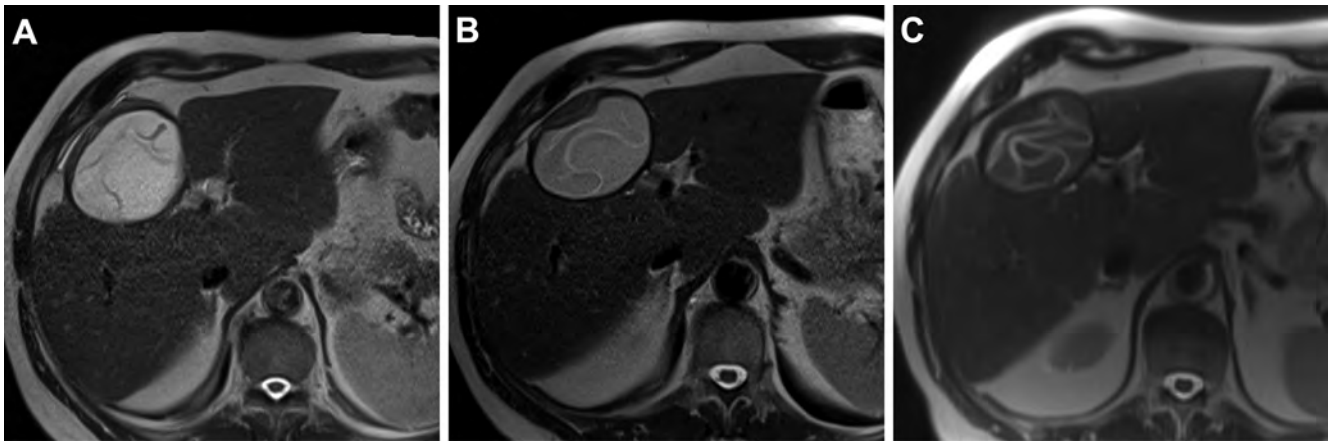


▶ **Fig. 7** Reactivation of a WHO-CE4 lesion. T2-weighted MRI initially **A** shows a peritoneal WHO-CE4 lesion (left paracolic). 3 years later **B** new intralesional daughter cysts formed, indicating reactivation (WHO-CE3b).

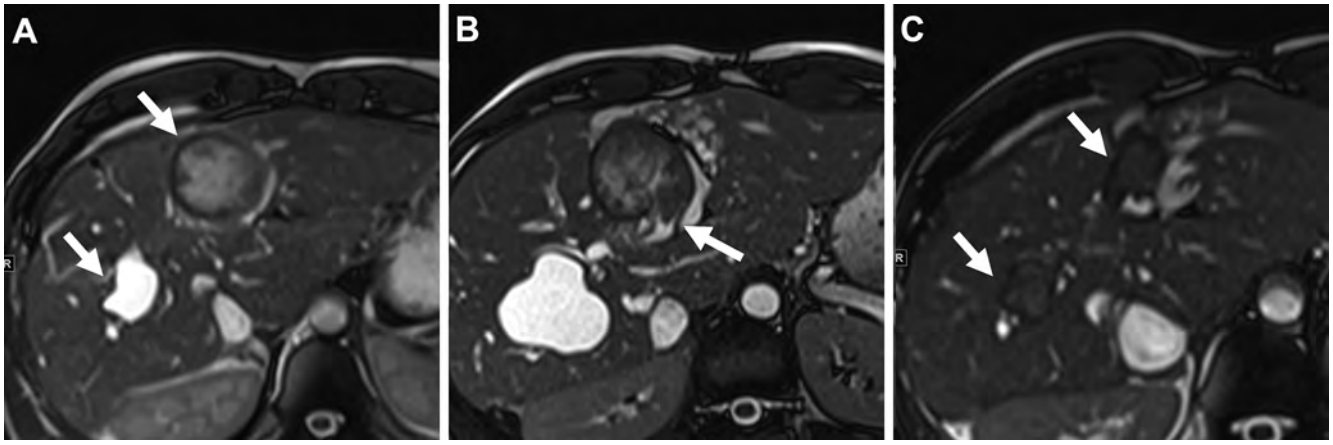
must be differentiated from cystic metastases. Contrast-enhanced imaging is needed here since CE cysts do not enhance with contrast agent due to the lack of vascularization even of the solid components. Therefore, WHO-CE3b lesions do not arise directly from WHO-CE3a lesions. Daughter cysts can in turn form in WHO-CE3a lesions so that they can transform into WHO-CE2 or CE3b lesions depending on the presence of solid components.

Cysts with complete consolidation of the cyst matrix are classified as stage WHO-CE4. This is initially an inactive cyst stage. However, reactivation of WHO-CE4 findings occurs, is seen more commonly in the case of consolidation triggered by pharmacotherapy, and is expressed in the (renewed) detection of daughter cysts (▶ **Fig. 7**) [10, 11]. The probability of reactivation of spontaneously inactivated CE manifestations is very low. WHO-CE4 findings are seen on imaging as masses with a canalicular matrix structure, which is also referred to as the ball of wool sign and is caused by the endocysts enclosed in the consolidated cyst fluid or by the walls of the daughter cysts. The fluid contained in the cyst and thus the signal intensity on T2-weighted MRI decrease over time. Newly consolidated WHO-CE4 findings are still clearly hyperintense on T2-weighted imaging compared to the liver background. Old consolidated findings can have a fibrotic signal intensity and can be iso- to hypointense with respect to the liver background (▶ **Fig. 8**). Therefore, the transition from non-consolidated to consolidated cyst matrix is continuous. The diagnosis of a completely consolidated cyst matrix and thus an inactive WHO-CE4 stage requires the absence of CSF-isointense components on heavily T2-weighted MRI. Anechoic segments should no longer be visible on US. WHO-CE4 lesions can be differentiated from other solid masses based on the lack of contrast uptake.

Inactive CE findings with wall calcifications that are so significant that only the calcium and its acoustic shadows are visible on US are classified as stage WHO-CE5. However, calcifications are seen in all CE stages [12]. Therefore, WHO-CE4/5 lesions is used as a generalized term. Since the cyst matrix cannot be properly evaluated on ultrasound in the case of severe wall calcifications, we recommend MRI upon initial detection of such a lesion to rule out daughter cysts masked by acoustic shadows.



▶ **Fig. 8** Long-term course of a WHO-CE4 lesion. T2-weighted MRI initially **A** shows a WHO-CE3a lesion with water lily sign due to detached endocyst. 2 years later **B**, the cyst contents still have relatively high signal intensity but are no longer CSF-isointense and are thus consolidated. The endocyst is hyperintense with respect to the remaining cyst contents so that the cyst stage is WHO-CE4. 7 years later **C**, the signal intensity of the cyst contents of the WHO-CE4 lesion has further decreased.



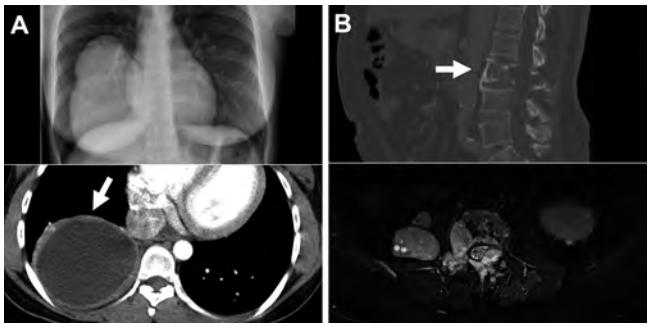
▶ **Fig. 9** Cystic echinococcosis with cystobiliary fistula. MRI (balanced steady state free precession technique) initially **A** shows a consolidated anterior WHO-CE4 lesion and a posterior WHO-CE1 lesion (double line sign on ultrasound). 6 months later **B**, the patient presents with obstructive jaundice and evidence of infection. Fistula formation into the adjacent bile duct with presence of cyst contents within the bile duct can be seen. The WHO-CE1 lesion shows a progressive increase in size. The fistula and cyst infection are treated with endoscopic and percutaneous drainage. Albendazole treatment is also initiated. Follow-up imaging 2.5 years later **C** shows a decrease in the size of the anterior WHO-CE4 lesion without persistence of the fistula and transformation of the posterior lesion to WHO-CE4.

Complications of a hepatic CE manifestation

CE manifestations have an expansive growth pattern in general and first become symptomatic due to a displacement effect or complications. Hepatic CE manifestations are common incidental findings or are discovered as part of the workup of nonspecific abdominal symptoms. The displacement effect can result in compression of bile ducts and thus manifest as obstructive cholestasis. In the case of the formation of cystobiliary fistulas, the CE manifestation connects to the bile duct system so that solid cyst contents enter the bile ducts and can also cause obstructive cholestasis (▶ **Fig. 9**). Anaphylactoid reactions and cholangitis can occur in this case. Cystobiliary fistulas can be visualized best with heavily T2-weighted MRI sequences (also MRCP) and with dynamic contrast-enhanced imaging [13].

Cyst infection results in abscess formation in CE manifestations and occurs primarily in cystobiliary fistulas or in older cyst stages also without cystobiliary fistulas. Increased contrast uptake of the cyst wall (pericyst) and the area surrounding the cyst or a new diffusion restriction in diffusion weighting can be indicative.

Rupture of hepatic CE cysts results in dissemination into the abdominal cavity. Acute cyst rupture can also result in anaphylactoid reaction and can be life-threatening. The spread of cyst contents into the abdominal cavity results in secondary peritoneal CE manifestations that develop in stages comparable to liver cysts. Due to the exophytic spread of daughter cysts out of the mother cyst, intravasal distribution of CE manifestations, e. g., into the hepatic veins and the inferior vena cava, can occur. This can result in cyst embolisms in the pulmonary vessels.



▶ **Fig. 10** Extrahepatic manifestations of cystic echinococcosis. **A** shows the radiograph (top) and CT scan (bottom) of uncomplicated pulmonary CE (WHO-CE1). **B** shows CE of the bone with manifestation in L3 on CT (top) and T2-weighted MRI (bottom). Note the diffuse infiltrating osteodestructive character of the CE of the bone, which also includes paraosseous portions in the lumbar soft tissues in this case.

Extrahepatic CE manifestations and special features

CE can manifest in all regions of the body including visceral organs, the central nervous system (CNS), and the musculoskeletal system. The resulting symptoms depend on the site of manifestation. The radiological properties typically correspond to those that have already been described. There are special features with respect to lung, bone, and the CNS that warrant more detailed discussion.

Lung

After the liver, the lung is the second most commonly affected organ (▶ **Fig. 10**). Pulmonary CE manifestations tend to form early cystobronchial fistulas since the adventitial layer is thinner than in other organs. The leakage of cyst contents into the respiratory tract results in the risk of anaphylaxis and asphyxia. Perifocal pulmonary infiltrates due to the spread of cyst contents or superinfection are common. Complete filling of CE manifestations with air or the collapse of cysts make the diagnosis of CE difficult since pathognomonic signs are absent. The limitations of CT in the evaluation of cyst contents for diagnosing CE are particularly noticeable in the lung. However, the detection of an endocyst floating in a cyst that is partially filled with air and fluid is a classic finding on CT and radiography. This impression originally coined the term “water lily sign”.

Bone

CE of the bone is diagnosed more frequently in older people beginning in the fifth decade of life [14]. Since an adventitial layer is absent, there is an aggressive, diffusely infiltrating distribution pattern with preferred formation of microvesicular multilocular lesions compared to other locations [15]. CE of the bone is therefore a destructive process with a poor prognosis that can spread from bone to paraosseous soft tissues and vice versa [14]. CE of the bone is most commonly seen in the spinal column and is often complicated there by compression of the spinal cord (▶ **Fig. 10**) [14, 16]. However, penetration through the dura into the dural sac is considered rare [15]. The diffuse growth pattern usually makes complete resection of vertebral CE manifestations impossible. Therefore, surgical procedures involving the spinal column must usually be limited to decompression and stabilization [17].

CNS

Cerebral CE is rare and is primarily seen in children and adolescents [18]. In the brain, a unifocal finding in a supratentorial position is most common. The active cyst stages WHO-CE1 and WHO-CE2 are almost always present at the time of diagnosis [19]. Infratentorial CE manifestations or manifestations located primarily in the spinal cord are rare. The rupture of cerebral cysts can result in secondary dissemination into the spinal column. This typically results in multifocality. Intramedullary or extramedullary intradural spinal manifestations must be differentiated from extradural spinal manifestations in primary vertebral CE.

Treatment of CE

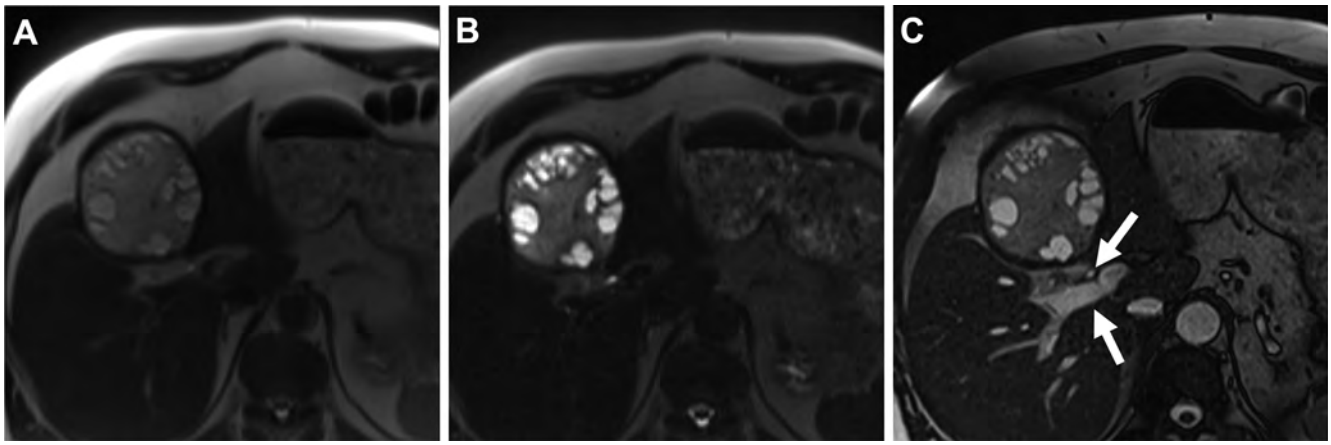
In principle, there are 4 options for treating CE. Treatment is selected based on the stage, location, and size of cysts as well as the presence of complications. CE patients should be treated at a designated center.

Treatment with medication

Albendazole (ABZ) is used for treatment. The goal of treatment is lasting inactivation, i. e., transition of the cyst to stage WHO-CE4/5. The best response to primary ABZ therapy is achieved in the case of unilocular cyst stages WHO-CE1 and WHO-CE3a ≤ 6 cm with an inactivation rate of approx. 40–60 %. Treatment lasts 3–6 months. The consolidation of cyst contents is a gradual process that often takes 12 months or longer. The decision regarding the use of medication to treat lung cysts is complex due to the possibility of treatment-induced rupture with development of cystic bronchial fistulas and the occurrence of associated complications. In the case of disseminated echinococcosis, organ manifestations, e. g., in the CNS, or bone involvement, ongoing or periodic treatment with ABZ can be necessary [20].

Surgical treatment

Primary surgical therapy is typically performed for multilocular cysts > 6 cm (WHO-CE2 and WHO-CE3b), cysts > 10 cm regardless of the cyst stage, and cysts with complications. There are two different types of surgical method: the cyst is punctured in a controlled manner and the contents are aspirated (conservative surgery, endocystectomy) or the cyst is completely removed without being punctured using a liver resection method (radical surgery). In the case of conservative surgery, a protoscolicidal substance (20 % NaCl) is instilled after aspiration of the cyst contents when possible. The presence of cystobiliary fistulas must first be definitively ruled out since 20 % NaCl is cholangiotoxic and can cause sclerosing cholangitis and liver failure. Prophylaxis with ABZ is performed perioperatively 1–2 days prior to surgery and is continued for 1–3 months [21].



▶ **Fig. 11** Effects of T2-weighting on the visual representation of cystic echinococcosis. T2-weighted MRI shows a WHO-CE3b lesion in the liver. The increase in echo time from 66 ms **A** to 402 ms **B** results in improved differentiability of the cyst contents and allows better detection of CSF-isointense components. Using the balanced steady state free precession technique, the fluid in the cyst as well as blood vessels and bile ducts appear hyperintense **C**.

Percutaneous methods

Unilocular cysts in stage WHO-CE1 and WHO-CE3a < 10 cm can be treated with PAIR *(puncture, aspiration, instillation, reaspiration)* [22]. After aspiration of the cyst contents, 95 % alcohol is instilled to sterilize the cyst contents and is then reaspirated after approx. 15 minutes. Prior to instillation of the protoscolicidal substance, the presence of cystobiliary fistulas must be definitively ruled out due to the risk of toxic cholangitis. Treatment with ABZ is performed periinterventionally 1–2 days prior to puncture and is then continued for 3–6 months.

Watch and wait

A watch and wait approach can be adopted in the case of cysts already in inactive stage CE4 or CE5 at the time of diagnosis and that are in an uncomplicated location [20].

Follow-up

Cysts that were treated with medication or PAIR should be followed up for at least 5 years after an inactive cyst stage is reached. Primarily inactive cysts should also be followed up for 5 years. After surgical therapy, follow-up imaging should be performed 3 months postoperatively to document seromas or biliomas since this can be difficult to subsequently differentiate from cyst recurrence. The follow-up period after surgery is 10 years.

Information regarding the MRI technique

T2 weighting is the basis for the diagnosis and staging of CE because the internal structure of the lesions is best visualized with this contrast-enhanced technique [7]. Since consolidated components can have a relevant water content depending on age, a heavily T2-weighted sequence protocol should be used to allow identification of CSF-isointense fluid components. MRCP helps to identify biliary complications [13]. We additionally acquired a *balanced steady-state free precession* sequence protocol (BSSFP), with which not only the lesion contents but also the blood vessels and bile ducts can be simultaneously visualized (▶ **Fig. 11**). As a result, intravenous contrast administration is not needed for MRI follow-up imaging. However, in the case of suspicion of complications like superinfection, contrast enhancement should be used. The available data on the value of diffusion weighting is heterogeneous. The ADC value of inactive cysts is smaller than that of active cysts [23]. A differentiation between WHO-CE1 cysts and simple dysontogenetic liver cysts is not possible with DWI [24].

Alveolar echinococcosis

Epidemiology and parasitology

E. multilocularis and thus AE are seen in most parts of the northern hemisphere, particularly in temperate regions, but not in the southern hemisphere. The endemic region ranges from North America to Central and Eastern Europe and Central and Northern Asia. It is most prevalent in China. Bavaria and Baden-Württemberg are the most affected regions in Germany. Foxes in the Central Uplands and in the Alpine foothills are more frequently infected with *E. multilocularis* than in the lowlands. In Bavaria, the fox tapeworm is detected on average in every third to fourth fox [25]. Nonetheless, the prevalence of human AE is low. Between 20 and 60 cases are reported annually in Germany (▶ **Fig. 1**). Since only a small number of people are infected in spite of the prevalence in animals, humans as aberrant intermediate hosts are not particularly prone to the development of AE [26]. In Germany, people with AE are usually primarily from the native population.

In addition to foxes, dogs and cats can also act as final hosts for *E. multilocularis*. Natural intermediate hosts are rodents and other small mammals. By coming in direct contact with eggs clinging to the fur of an infected final host or by touching contaminated soil, humans can get the eggs on their hands and then subsequently ingest them. Transmission by means of contaminated food or water is suspected [27, 28]. The main risk factors are farming, forest-

ry, and hunting [27, 29]. AE is a recognized occupational disease among farmers in Germany.

Diagnosis and imaging

General information

AE is often diagnosed with a delay. In a case series, management decisions were initially made based on a misdiagnosis in one-third of 88 AE patients [2]. Typical misdiagnoses include CE, cholangiocarcinoma, and hemangioma. However, the combination of imaging and serology is often sufficient for the diagnosis of AE. Serological tests are usually positive in AE although false-positive results are possible. In cases of doubt, a biopsy, which can be performed without special safety precautions, should be performed. Anaphylactic reactions and spreading of infectious material are not to be expected.

AE typically causes a microcystic lesion that has an irregular margin, diffuse infiltration, and destructive growth and is multilocular to varying degrees. The liver is usually affected. Due to its aggressive behavior, AE is also referred to as a malignant parasitosis. The primary parasitic cyst is usually approx. 1 cm large. The small cysts are accompanied by a strong diffuse fibroinflammatory peripheral reaction, which can be the dominant finding. The infiltrative growth results in liquefactive necrosis, which can cause the formation of large intralesional pseudocysts. These pseudocysts are filled with debris and bile. Calcifications are the rule.

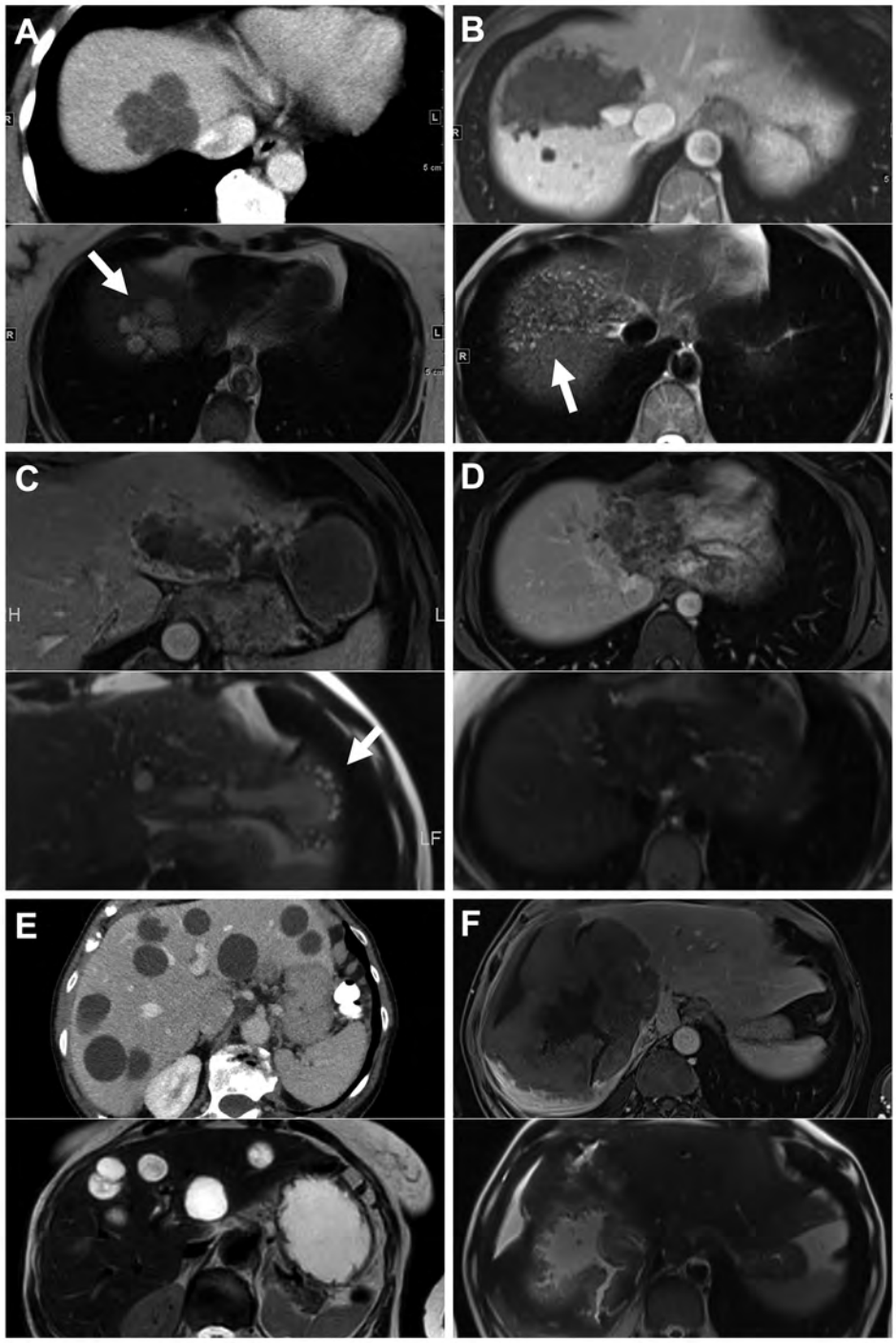
AE does not develop in stages directly comparable to CE. However, a connection between the image properties and temporal evolution of AE manifestations is postulated (see below) [30]. Abortive AE with spontaneous inactivation is possible [31]. No or only small focal liver lesions are then typically present. However, the US, MRI, or CT image properties in individual cases do not allow definitive conclusion about pathogen activity. It is assumed that pathogen activity can be better evaluated with FDG-PET/CT.

Imaging methods and classification

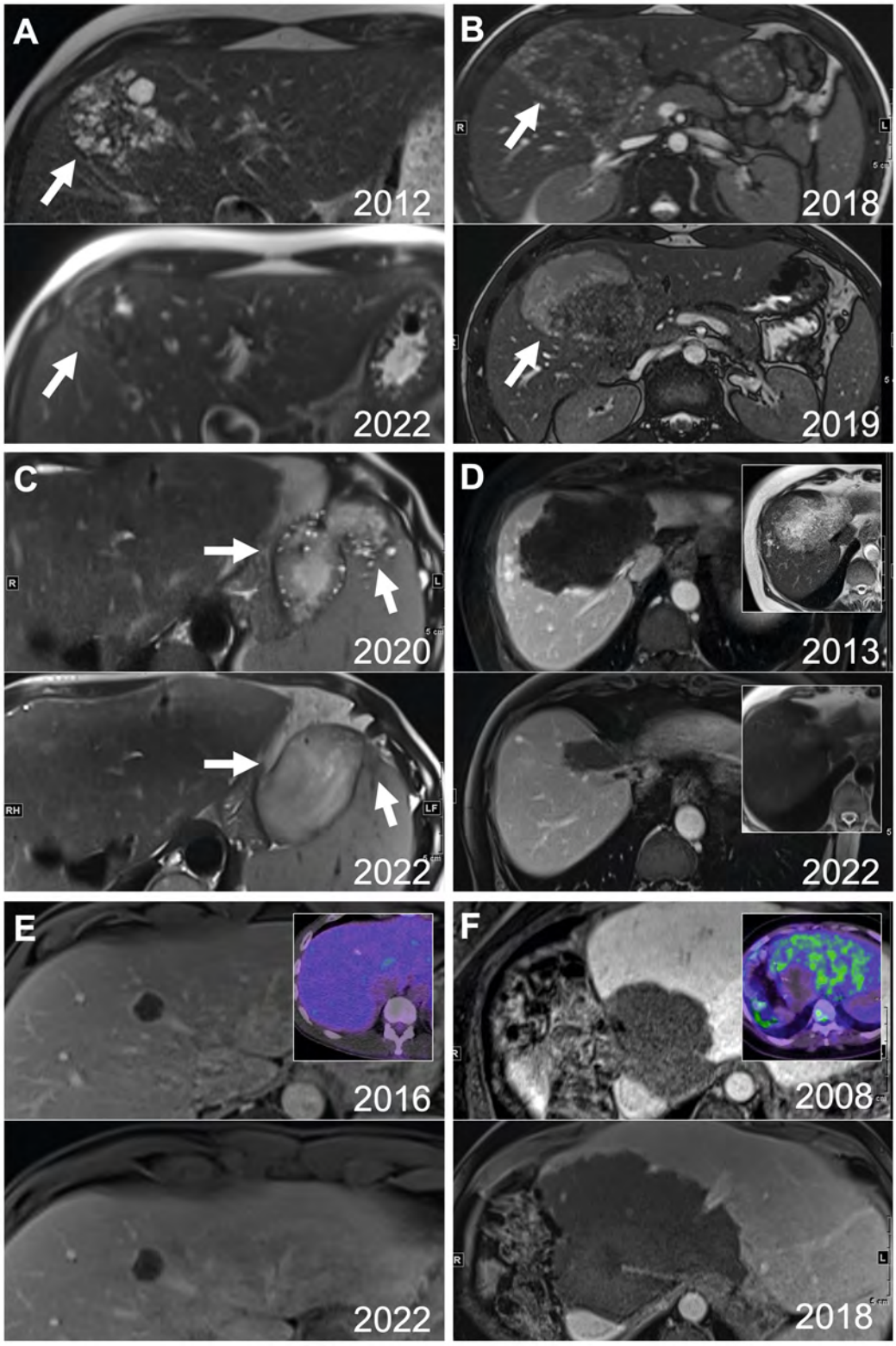
The morphological diversity of AE manifestations is large (▶ **Fig. 12**). Therefore, AE should always be included in the differential diagnosis of unclear liver lesions. The spectrum ranges from purely cystic to purely solid findings. However, the main radiological finding is the combination of cystic components, solid components, hypovascularity, and calcification. These image properties should be considered diagnostic for AE particularly in connection with positive serology. Hypovascularity of solid components with almost no contrast uptake and the detection of calcification are good discriminators compared to the primary differential diagnosis of intrahepatic cholangiocellular carcinoma [32]. AE tends to grow along vascular structures like hepatic veins or branches of the portal vein. This often results in territorial expansion under consideration of the hepatic segment anatomy. Narrow perivascular branches can also form and compromise critical structures at a distance from the main finding, e. g. as a result of infiltration of the hilum [33].

MRI is particularly suitable for visualizing typical image properties. The microcystic character is most visible on heavily T2-weighted sequence protocols. The solid fibrotic component is hypointense on T2-weighted imaging. After contrast administration, only septal enhancement in the walls of the microcystic changes or primarily late venous diffuse enhancement in the periphery of the fibrosis is seen. CT has advantages with respect to the detection of calcification, which at MRI can only be satisfactorily achieved with special techniques [34].

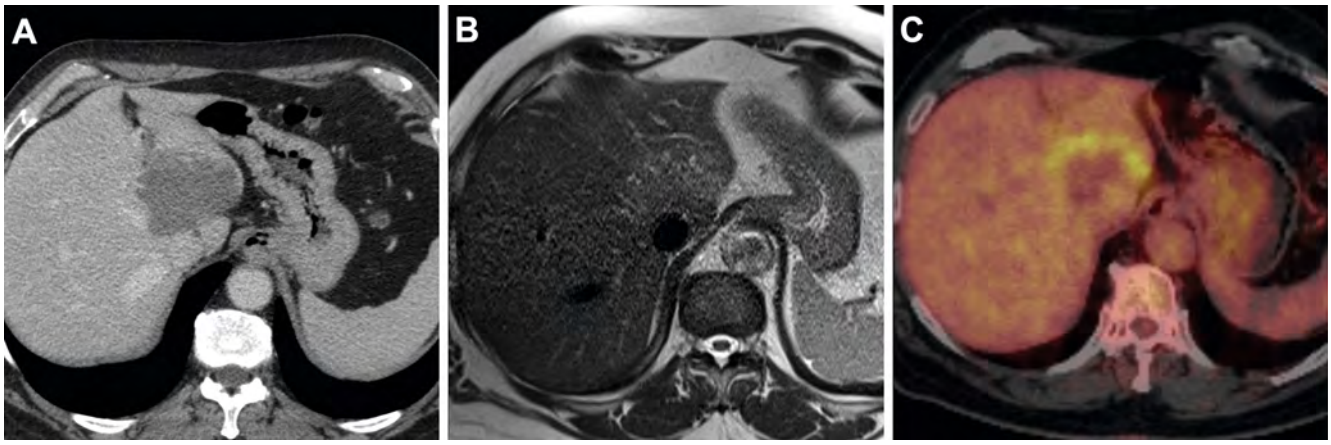
The diversity of the imaging findings is reflected in the various AE classification systems that have been published. The Kodama classification, which classifies lesions as 5 types based on the presence of cystic components and solid components, is commonly used for MRI [35] (▶ **Fig. 12**). The characteristic morphology described above falls under types 2 (without pseudocyst) and 3 (with pseudocyst). The Kodama classification does not have an effect on immediate management. The Ulmer working group presented the EMUC-US and EMUC-CT classification (Echinococcus Multilocularis Ulm Classification) for US and CT. In CT classification, various calcification patterns are defined in addition to the primary morphology with consideration of the presence of cystic and solid components [36]. The US classification includes 5 patterns, with the hailstorm pattern (inhomogeneous mass with irregular margin and hyperechogenic portions) and the pseudocystic pattern being most common [37]. It is important that AE lesions can be hyperechogenic (without acoustic shadows due to calcifications) on US and are thus a differential diagnosis to liver hemangiomas (hemangioma-like pattern according to EMUC-US). The EMUC-CT classification was transitioned into the AEUC classification (Alveolar Echinococcosis UIm Classification) under consideration of new information regarding, for example, temporal changes in AE manifestations [30]. The suggestion published in this journal presents a possible evolution model of AE manifestations with correlating image properties. It is postulated that hepatic AE starts as a small cystoid or metastasis-like lesion (AEUC-1) and progresses either to a diffuse infiltrating or circumscribed tumor-like lesion (AEUC-2 and 3) or to a regressive residual finding consisting of solid tissue and calcium (AEUC-5). In the case of further progression of AEUC-2 or 3 lesions, large intralesional (pseudo-) cystic components develop (AEUC-4). It has been observed that advanced forms can transition to regressive stage AEUC-5 [30]. However, the risk of AE is continuous progression resulting in increasing organ destruction. Untreated advanced AE therefore has a chronic progressive and potentially fatal course. Medication can change the image properties of AE manifestations. Therefore, multilocular microcystic components can regress or fibrotic portions or pseudocystic necrosis can increase. A noticeable decrease in the total lesion size is not typical (▶ **Fig. 13**).



▶ **Fig. 12** Spectrum of image properties of alveolar echinococcosis. **A** (top, CT after contrast agent, bottom, T2-weighted MRI) shows an unusual AE finding with a multilocular cystic liver lesion with smooth margins and without solid components (Kodama type 1). **B** (top, T1-weighted MRI after contrast administration, bottom, T2-weighted MRI) shows a typical AE finding with diffuse infiltrating liver lesion with segmental spread, pronounced hypovascularity, and coexistence of small cysts and fibrotic solid components (Kodama type 2). **C** (top, T1-weighted MRI after contrast administration, bottom, T2-weighted MRI) shows a typical AE finding with a diffuse infiltrating liver lesion with spread beyond the liver to the left and hypovascularized fibrotic components, pseudocystic liquefactive necrosis, and small cysts (Kodama type 3). **D** (top, T1-weighted MRI after contrast administration, bottom, T2-weighted MRI) shows a typical AE finding with a diffuse infiltrating, completely solid, hypovascularized liver lesion (Kodama type 4). **E** (top, CT after contrast administration, bottom, T2-weighted MRI) shows an unusual AE finding with unilocular cysts without solid components (Kodama type 5). **F** (top, T1-weighted MRI after contrast administration, bottom, T2-weighted MRI) shows a typical AE lesion with a liver mass that is solid and hypovascular in the periphery and pseudocystic necrotized in the center including connection to the bile duct.



▶ **Fig. 13** Various courses of alveolar echinococcosis. **A** shows a decrease in microcystic components as treatment response. **B** shows an increase in pseudocystic liquefactive necrosis during treatment. AE manifestation in the spleen in **C** shows a reduction of small cysts during treatment, an increase in perisplenic necrosis, and a decrease in the intrasplenic size. **D** shows the decrease in size and the transformation of the small cysts to fibrotic tissue. The PET-negative AE manifestation in **E** does not show any changes in the spontaneous course. The PET-negative AE manifestation in **F** shows a progressive increase in size in spite of pharmacotherapy.



▶ **Fig. 14** FDG-PET/CT in alveolar echinococcosis. **A** (CT) and **B** (T2-weighted MRI) show a typical AE finding with diffuse infiltrating, hypovascular liver lesion comprised of small cysts and fibrotic tissue. FDG-PET/CT shows enhancement in the periphery.

▶ **Table 3** WHO PNM classification for AE.

Category	Definition
P0	No liver manifestation
P1	Peripheral lesion(s) without proximal vascular or biliary involvement*
P2	Central lesion(s) with proximal vascular or biliary involvement of one half of the liver*,#
P3	Central lesion(s) with proximal vascular or biliary involvement of both halves of the liver and/or involvement of 2 hepatic veins*,#
P4	Lesion(s) extending along the large vessels§
N0	No extrahepatic spread into neighboring organs per continuitatem or into regional lymph nodes
N1	Extrahepatic spread into neighboring organs per continuitatem or into regional lymph nodes
M0	No distant metastases
M1	Distant metastases

* The phrase "proximal vascular or biliary involvement" is not explicitly defined in the PNM classification. We use it when the right anterior or posterior portal vein branch is involved on the right and the left portal vein branch is involved on the left.

Right and left halves of the liver are separated by the plane of the middle hepatic vein.

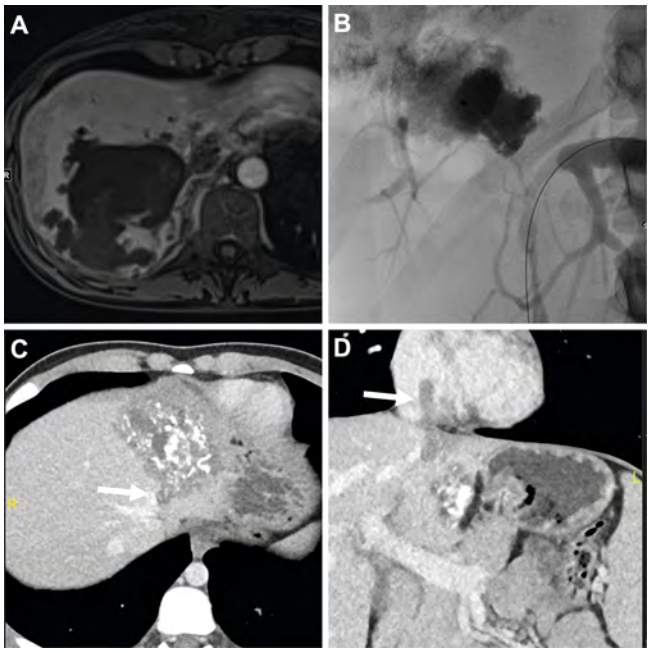
§ Involvement of the large vessels refers to the main portal vein, hilar hepatic artery, and inferior vena cava.

PNM classification

The malignant character of AE is reflected in the PNM classification introduced by the WHO for the categorization of the extent of hepatic AE based on the TNM classification [38]. The intrahepatic parasite infestation (P), the involvement of neighboring organs (N), and metastasis to other organs (M) are summarized in the PNM classification (▶ **Table 3**). The categorization of intrahepatic disease extent is based on the involvement of the large liver vessels. The N-category includes both regional lymph node metastases as well as extrahepatic infiltration per continuitatem. Metastases are most common in the lung [39] sometimes with embolic character in the case of macroscopic liver vein invasion. The brain can also be affected by metastases.

FDG-PET

There are indications that FDG-PET can be used to evaluate the activity of AE. It must be taken into consideration that the extent of the host's fibroinflammatory reaction and not the metabolic activity of the pathogen is measured with FDG-PET [40]. Therefore, tracer uptake can only be viewed as an indirect surrogate parameter for parasitic activity (▶ **Fig. 13, 14**). An additional PET scan should be acquired 3 hours after tracer application since this facilitates differentiation between PET-positive and PET-negative findings [41]. It has been observed that treatment with medication sometimes results in PET-negative results for AE manifestations. Whether FDG-PET can be used for the stratification of medication-based treatment is the subject of scientific debate and is a controversial topic of discussion. Only retrospective studies on this topic are available. The hypothesis is that treatment with ABZ can be discontinued in the case of a lack of tracer uptake in AE manifestations. However, in this situation, recurrence and progression rates of approx. 50 % have been observed (see ▶ **Fig. 13**) [40]. In combination with negative serology, recurrence seems less common [42]. Under consideration of the heterogeneous data, we feel that discontinuation of pharmacotherapy in a controlled manner and with ongoing imaging follow-up can be considered in individual cases depending on the risk profile for AE progression provided that serology and FDG-PET are negative. FDG-PET/CT is not one of the services covered by statutory health insurance for AE. There is currently no general recommendation by the professional societies to use FDG-PET for treatment monitoring.



▶ **Fig. 15** Complications of alveolar echinococcosis. **A** (MRI after contrast administration) shows typical AE liver lesion in which the protuberances in the periphery represent connections to the bile ducts. The endoscopic retrograde cholangiography image in **B** shows a broad connection to the intralesional necrotic cavity on the right bile duct. **C** and **D** (CT after contrast administration) show a typical AE liver lesion that extends via macrovessel invasion into the left hepatic vein and the right atrium.

Complications of hepatic manifestations

AE is often first diagnosed after local complications have developed. Hepatic AE manifestations centrally located in the liver typically result in biliary complications due to stenosis of the bile duct [43]. Liquefactive necrosis can connect to the bile ducts so that pseudocysts can be filled with debris as well as bile making them susceptible to superinfection (▶ **Fig. 15**). Vascular complications are the result of stenosis and occlusion of the portal vein, hepatic veins, or inferior vena cava. This can result in portal hypertension or Budd-Chiari syndrome. A macrovessel invasion can occur and extend for example via the inferior vena cava into the right atrium (▶ **Fig. 15**). Infiltration per continuitatem from the liver can cross the diaphragm and enter the lung with corresponding pulmonary (pneumonia) and pleural (effusion, empyema) complications.

Treatment of AE

AE has all of the characteristics of a malignant disease and should therefore be treated in the same way in an interdisciplinary manner including psychological care. A majority of patients are already at an advanced disease stage at the time of diagnosis so that curative treatment is not possible. In principle, there are 2 options for treating AE.

Surgical treatment

Radical surgical resection of AE manifestations is the only curative treatment option and is performed according to the rules of tumor surgery. After R0 resection, the patient receives adjuvant treatment with ABZ for 2 years. Patients undergo 10 years of postoperative imaging and serological follow-up.

Treatment with medication

Patients who are not eligible for curative resection typically receive palliative ABZ treatment for their entire lives. Palliative surgical interventions are rarely necessary in the case of complications that cannot be otherwise controlled. ABZ has a primary parasitostatic effect so that new growth of AE lesions can be expected after the discontinuation of treatment. In rare cases (usually mild infections) in which a parasiticidic effect of the ABZ, die off of the AE manifestations, or an abortive course is suspected, a controlled discontinuation of ABZ can be considered. As explained above, such an approach could be a possibility particularly in the case of negative serology and FDG/PET. Liver transplantation is the last resort, last but not least due to the high reinfestation rates.

Follow-up

Follow-up should be performed for the patient's entire life in the case of treatment with medication, non-curative resection, and presumably inactive AE lesions [1].

Conclusion

CE and AE are rare in Germany and should be viewed as two completely different diseases. CE tends to be benign and can either be treated surgically in a minimally invasive manner or be transitioned to an inactive stage with a non-surgical method. CE develops in stages with characteristic image properties. AE is considered a malignant parasitosis with a chronic progressive course and progressive organ destruction. AE treatment is based accordingly on oncological treatment principles including radical resection or palliative pharmacotherapy. AE has a very variable image morphology that hardly allows conclusions about pathogen activity. Both diseases usually affect the liver, but CE in particular can have a primary extrahepatic manifestation. Imaging is an essential part of diagnosis and treatment monitoring for both AE and CE.

Conflict of Interest

The authors declare that they have no conflict of interest.

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