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Ultrasound of tropical (parasitic) diseases

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Introduction

This chapter addresses the clinical and ultrasound findings for the major parasitic diseases, including amoebiasis, ascariasis, toxocariasis (visceral larva migrans), fascioliasis, small Asian liver flukes (*Clonorchis sinensis, Opisthorchis spp*), cystic and alveolar echinococcosis, schistosomiasis, and melioidosis.

Amoebiasis

Introduction

Amoebiasis is a parasitic infection caused by the protozoon *Entamoeba histolytica*. It is the third most frequent parasitic cause of death after malaria and schistosomiasis in developing countries, with an estimated 40,000 to 100,000 fatalities every year. Amoebic infection has been reported to affect approximately 12% of the world's population; in tropical and subtropical regions up to 50% of the population are affected although the majority of these infections are caused by the non-pathogenic *E. dispar*, which is morphologically indistinguishable from *E. histolytica*.

Infection is acquired by the faecal-oral route through ingestion of mature cysts passed in the faeces of infected individuals, this result from the poor sanitation, often found in resource-limited settings. After ingestion of mature cysts, excystation occurs in the small bowel. The trophozoites colonize the large intestine where they remain confined (non-invasive infection), multiplying and producing cysts that are passed in the faeces. In some patients, the trophozoites invade the intestinal mucosa (intestinal invasive disease), which causes characteristic flask-shaped ulcers, and may disseminate through the bloodstream to other sites such as the liver, lungs and brain (extra-intestinal disease) to cause amoebic abscesses.

These are usually located in the right lobe of the liver and are known as amoebic liver abscesses (ALA).

ALAs develop in less than 1% of *E. hiystolytica* infected patients. Adult males are affected 10 times more often than women (1). Abscesses form by coalescence of small foci of hepatic necrosis, and are made up of a central area of colliquation ("amoebic pus") surrounded by a rim of liver tissue and inflammatory cells in which the trophozoites feed and multiply. No capsule is present.

Clinical presentation

In non-endemic areas, symptoms of ALA typically begin a few months after the patient has travelled to an endemic region and include weight loss, high fever, chills and right upper quadrant abdominal or pleuritic pain.

Hepatomegaly and jaundice may be present, as well as atelectasis, pleural effusion and an elevated hemidiaphragm. Rupture into the pleural cavity presents with cough, pleuritic pain and dyspnoea. Occasionally, expectoration of brown amoebic material can occur if there is erosion of a bronchus. Abscesses located in the left hepatic lobe may rupture into the pericardium causing pericardial effusion and tamponade. In the abdominal cavity, rupture into the peritoneum occurs in 2–7% of cases, more often with abscesses located in the left lobe, but many other structures can be involved including bowel, large vessels, bile ducts and retroperitoneum. Finally, infection may spread to the skin and the central nervous system.

Diagnosis

The diagnosis of ALA is based on clinical findings, laboratory tests including antigenic and/or serologic testing and the identification of the parasite in fresh stool and abscess material and imaging techniques. Absent history of diarrhoea does not rule out ALA. The examination of the stool for ova and parasites is often negative in extra-intestinal amoebiasis. Leucocytosis without eosinophilia, hypoalbuminaemia and elevated alkaline phosphatase are common laboratory findings. Trophozoites are occasionally observed in abscess material. Serological tests are highly useful for the diagnosis of invasive amoebiasis. Antibodies are detectable 7–10 days after the onset of symptoms and gradually decrease in the 2 months following treatment; however, they may persist for years, which limits their diagnostic value in patients

from endemic areas. Other tests like RT-PCR and antigen detection on pus are available but their role is not yet established.

Ultrasound

Liver

Ultrasound is reported to be as sensitive as CT and MRI, but very early pre-colliquative stages cannot be detected. On ultrasound, ALA lesions are typically single (in over 60% of cases), located in the right hepatic lobe near the surface of the organ, round or oval in shape. They appear hypoechogenic, with initially irregular and ill-defined margins (first 4–5 days); occasionally they are hyperechoic. Later, with the progressive colliquation of necrotic material, the lesion assumes a homogeneous hypoechoic pattern, with regular, well-defined margins [Figure 1] (2, 3). This appearance typically occurs within 2 weeks. In immunocompromised patients, the amoebic abscess can assume a tumour-like or honeycomb appearance. In the healing phase, a slow progressive evolution can be observed with the lesion increasing in echogenicity and showing an irregular and ill-defined margin. Sometimes a sterile cystic cavity can persist for months or years (4-6).

Figure 1 Different sonographic appearance of ALA. Well-defined margins with almost echo-free content in a quasi-cystic ALA (a). Hypoechoic with centrally located necrotic areas (b). Large hypoechogenic lesion with almost solid content (c).

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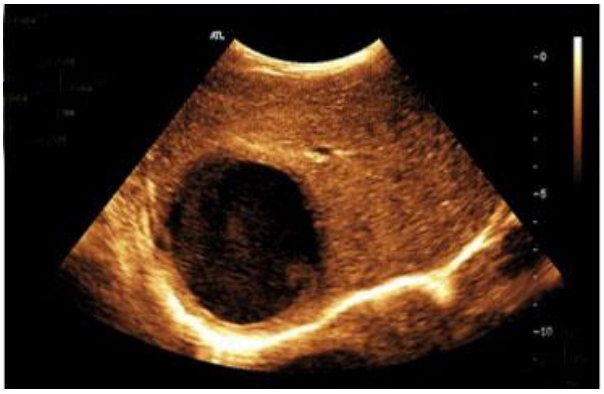

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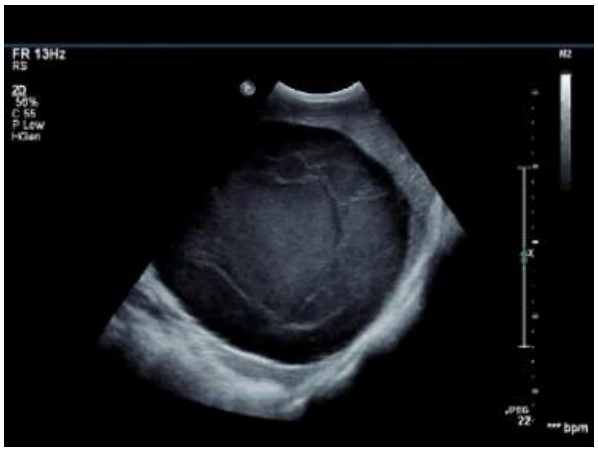

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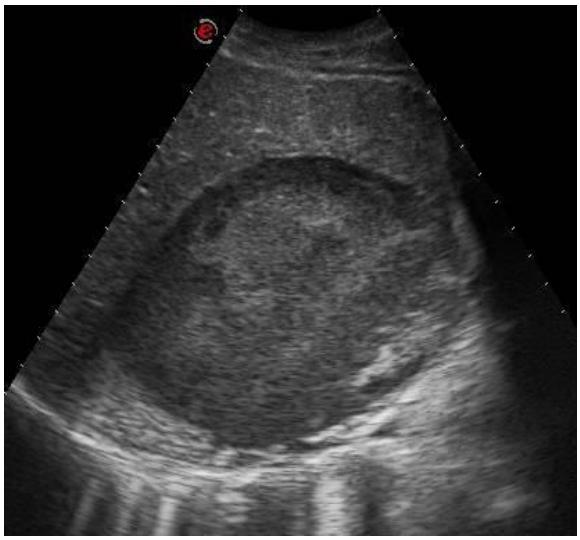

Gastrointestinal tract

Besides ALA, amoebic colitis is also often found on ultrasound where the colon wall is typically thickened and hypoechoic. Ultrasound may show the signs of severe ulcerative colitis including loss of layer structure, transmural inflammation and surrounding peri-intestinal inflammatory reaction, which are shown in Figure 2 (7).

Figure 2 **Amoebic colitis. Endoscopy reveals typical ulcerations (a). Ultrasound shows the signs of severe ulcerative colitis including loss of layer structure, transmural inflammation and surrounding peri-intestinal inflammatory reaction (b).**

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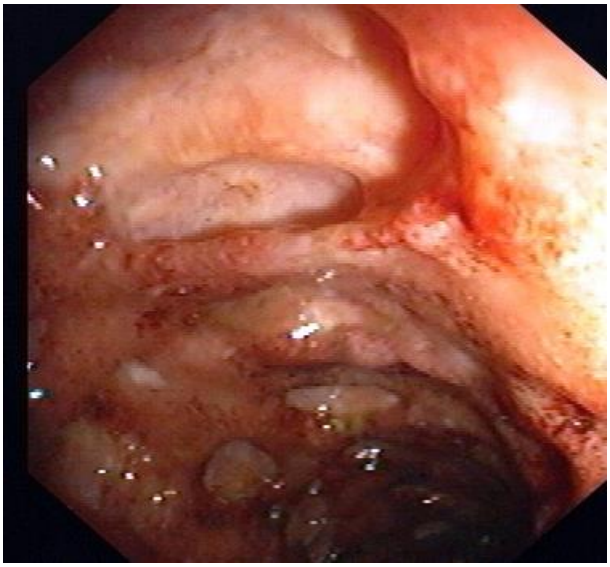

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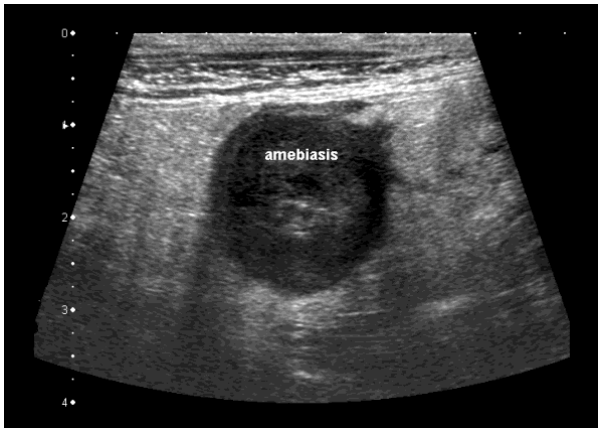

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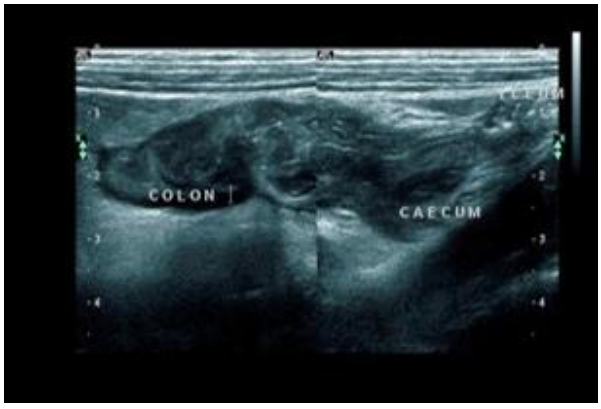

Amoebic colitis with its diverse clinical appearances and extraintestinal manifestations cannot be sonographically differentiated from colitis of other aetiology. Superinfection in ulcerative colitis is differential diagnosis. Attention should be paid to concomitant sonographic findings (ameboma, liver abscess) since they can be suggestive of amoebiasis despite the fact that multiple (pyogenic) liver abscesses can also occur in all acute and chronic inflammatory intestinal diseases (8, 9).

Differential diagnosis

The differential diagnosis includes pyogenic liver abscesses (PLA) (10-12), echinococcal cysts (13) and hepatic neoplasia (14, 15). Patients with pyogenic liver abscesses tend to have more severe forms of the disease; they have positive blood cultures, are often older with significant co-morbidities such as diabetes, and have a history of recent biliary disease or surgery. On ultrasound, PLA tend to be multiple with irregular and faded margins. Their echogenicity varies depending on the stage of the disease, from hypoechoic (pre-suppurative and resolution phase) to anechoic with floating or stratified echoes, or hyperechoic (suppurative phase). In the chronic phase, PLA walls may be hyperechoic with a thick fibrous capsule; they are sometimes surrounded by a thin hypoechoic halo. Echinococcal cysts are typically asymptomatic. The appearance is rarely misleading (13). However, infected or complicated echinococcal cysts may not be easily differentiated. Malignant cystic or metastatic hepatic tumours can present as cystic lesions and should be considered in the differential diagnosis of ALA (16).

Treatment

In ALA, medical treatment is the mainstay of therapy and puncture and drainage rarely required. Ultrasound-guided percutaneous drainage of abscesses followed by microscopic examination is diagnostic and therapeutic (5, 6). Amoebic “pus” has a typical “anchovy paste” appearance [Figure 3], the sonographic appearances of the punctured liver abscesses are shown in Figure 4.

Figure 3 **"Anchovy paste" appearance of amoebic material drained from a liver abscess.**

Figure 4 **Amoebic abscesses. Incidental finding of multiloculated liver abscesses with liver like parenchyma echogenicity using panoramic imaging (a). Detail of the left liver lobe (b). Two hypoechoic amoebic liver abscesses; after CEUS, there is no enhancement of the lesions (c).**

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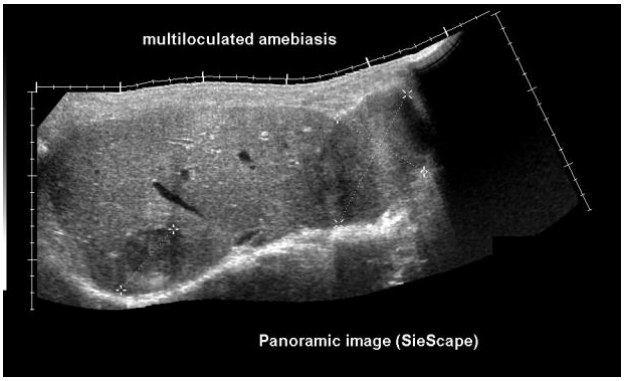

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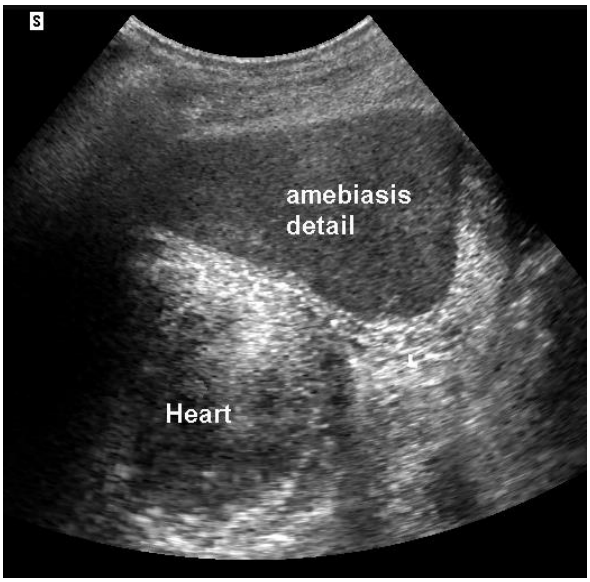

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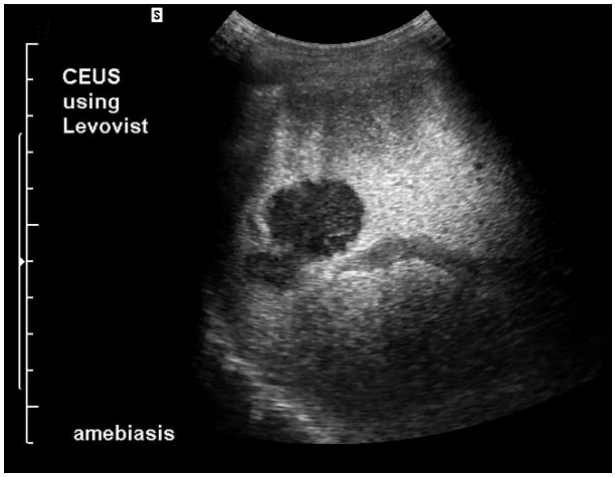

Primary treatment of uncomplicated amoebic liver abscess consists of a tissue agent and a luminal agent to eliminate intraluminal cysts.

Metronidazole

Patients with uncomplicated amoebic liver abscess are traditionally treated with metronidazole orally 3 x 500 mg for 7 to 10 days (17). The cure rate is >90%. Shorter duration of treatment is not recommended. Intravenous treatment generally offers no advantage since metronidazole is well absorbed from the gastrointestinal tract. In case of slow response to metronidazole or relapse following therapy, percutaneous catheter drainage, and/or a prolonged course of metronidazole may be warranted. In pregnancy, metronidazole

treatment should be considered in severe disease, but its use should be carefully evaluated since it crosses the placenta and enters the foetal circulation. Tinidazole, as compared to metronidazole in a randomized prospective study, has proven early clinical response, shorter treatment course, favourable rate of recovery, and high tolerability (18). Thus, tinidazole maybe preferred over metronidazole in ALA, at the dosage of 2 g once daily for 5 days.

Luminal agents

Following systemic treatment for invasive amoebiasis using tinidazole or metronidazole, treatment to eliminate intraluminal parasites is recommended, even if stool microscopy is negative. The most commonly used drug is paromomycin 3 x 750 mg (25 to 30 mg/kg) for 7 days if no severe colitis is present (also in pregnant women). Severe colitis is treated as mentioned above with metronidazole. As less effective alternatives, diloxanide furoate 3 x 500 mg p.o. for 10 days or chloroquine 600 mg base for two days, followed by 300 mg daily for three weeks can be used (19, 20), which are also active against the parasites in the gut lumen.

Abscess drainage

In uncomplicated amoebic liver abscess, there is no benefit for drainage in addition to medical therapy. Ultrasound-guided percutaneous drainage, and less frequently surgical drainage, is indicated in cases of imminent rupture or risk of rupture into the pericardium, treatment failure, large cysts (>10 cm) or in pregnant women. Although size is often cited as the main reason to drain ALA percutaneously, the evidence on which this decision is made is still weak and prospective studies are needed (5, 6, 21). Aspiration may be recommended for patients with lack of clinical response within 5 – 7 days, in patients with uncertainty about the diagnosis (22) and in large abscesses located in the left liver lobe (5, 6). In patients of recurrent or large abscesses drainage with pigtail catheter is preferred.

Follow up and prognosis

Ultrasound is useful for follow-up because the abscess resolution generally occurs between 10-300 days and correlates directly with the initial size of the abscess cavity (23). In approximately 5% of ALA patients' resolution is not complete and post-ALA residual lesions may be found. These are usually hypo- to isoechoic compared to liver tissue and show a

hyperechoic wall. The residual lesions have been found to persist for more than a decade and may pose differential diagnostic problems (24).

Ascariasis

Introduction

An estimated 1.2 billion people are infected by *Ascaris lumbricoides*, making ascariasis the most common human helminthic infection (25). Although most infections are asymptomatic, over 250 million people are estimated to suffer from associated morbidity, and more than 200,000 deaths are attributed to ascariasis every year. Ascariasis is a significant cause of biliary disease in areas where the rate of infection is high and *Ascaris*-infections account for up to 10-19% of all hospital admissions. Ascariasis is found throughout the world, but it is more common in warm climates and overcrowded rural communities with inadequate sewage systems (26). The infection is more common and severe among children, whereas biliary ascariasis is more common in adults (27, 28).

Adult worms live in the small intestine, usually the jejunum, in which the females produce eggs that are passed into the faeces. In the environment, the larva develops within eggs in approximately 3 weeks. Infection occurs through ingestion of material (soil, food or water) contaminated with larva containing (i.e. fertile) eggs. Once swallowed, the larvae hatch and invade the intestinal mucosa. They then migrate through the portal and then systemic circulation to the lungs. Here the larvae penetrate the alveolar walls, ascend the bronchial tree to the throat and are swallowed again. On reaching the small intestine, they develop into adult worms [Figure 5] within 2–4 weeks.

Figure 5 Adult *Ascaris lumbricoides* worm.

Clinical presentation

Although infection is commonly asymptomatic or causes only few symptoms, actively motile adult worms can migrate to different segments of the gastrointestinal tract, into the oropharynx and the nose. The most common complication of ascariasis is mechanical bowel obstruction caused by a large number of worms, which may also cause volvulus, intussusception or intestinal perforation. They can enter the appendix and cause appendicular colic and gangrenous appendicitis (27). Severe pathology is associated with the migration of the worms through the duodenal papilla into the biliary system or the pancreatic duct, resulting in obstruction, perforation or pancreatitis. In addition, the intestinal bacteria carried by the worm can induce pyogenic cholangitis and empyema of the gallbladder (28). The adult worms usually migrate out of the biliary tract shortly after inducing symptoms; however, dead worms or their fragments in the bile duct can serve as a nidus for stone formation causing obstruction, and on-going inflammation can result in the development of strictures.

Diagnosis

Diagnosis of intestinal ascariasis is usually achieved by parasitological stool examinations with visualization of the eggs. In patients with high worm burden the worms can be also excreted as a whole.

Ultrasound

Ascaris lumbricoides worms in the intestinal tract may be missed by ultrasound because of bowel gas. Ultrasound is a highly sensitive and specific non-invasive method for the detection of worms in the biliary tract [Figure 6], although the diagnosis of biliary ascariasis requires a high index of suspicion because the worms move in and out of the biliary tract and can be missed on biliary imaging (27, 28).

Figure 6 Ultrasound images of *Ascaris lumbricoides* in the gallbladder (a) in the common bile duct (b) and in the intrahepatic bile ducts (c) as well in the appendix (d) and the gut (e, f).

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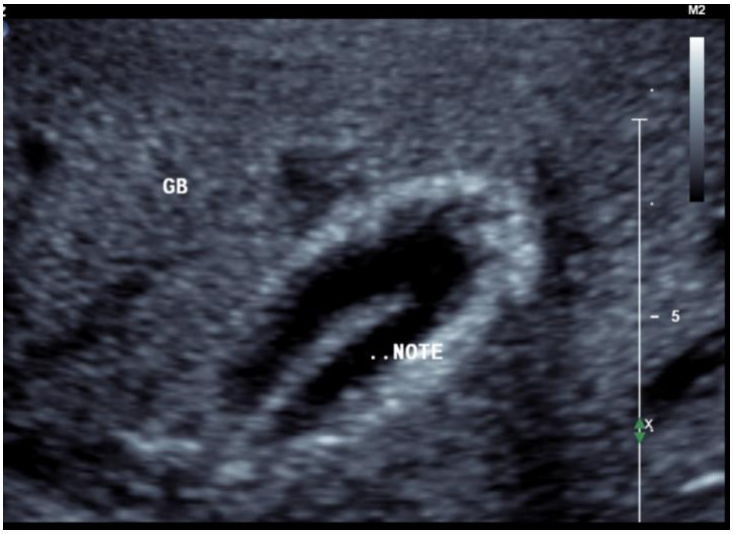

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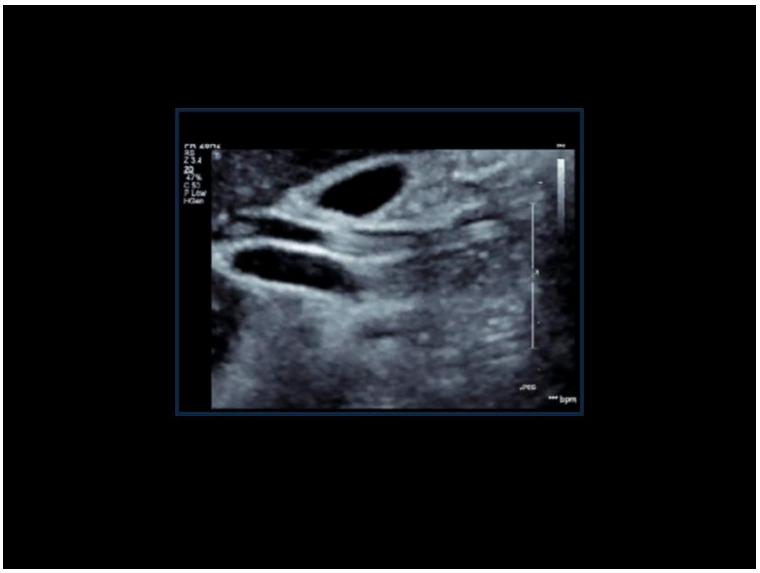

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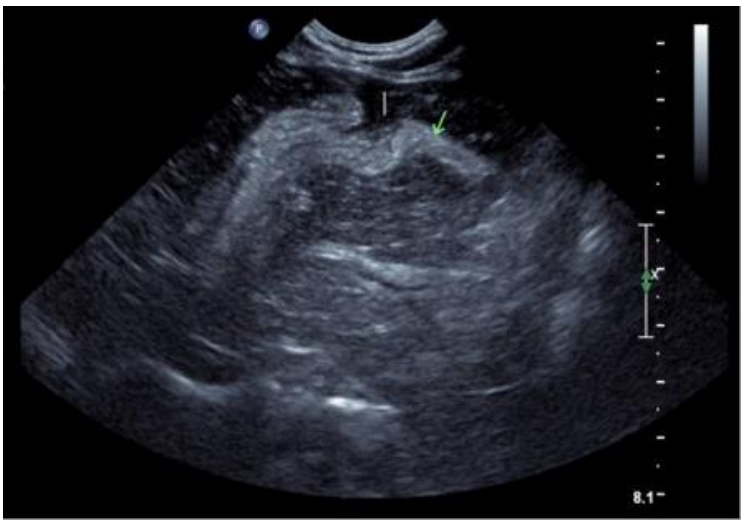

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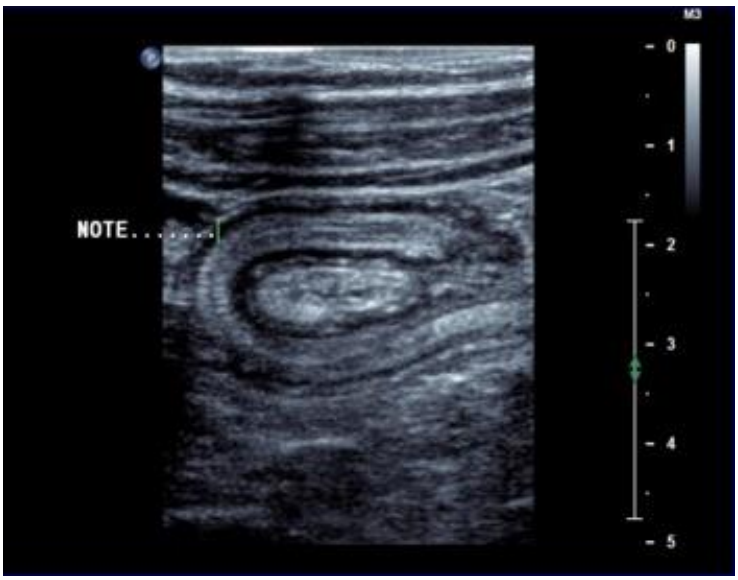

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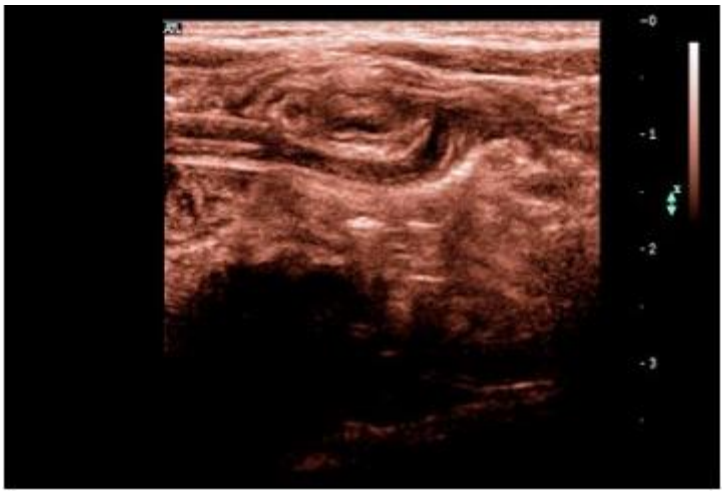

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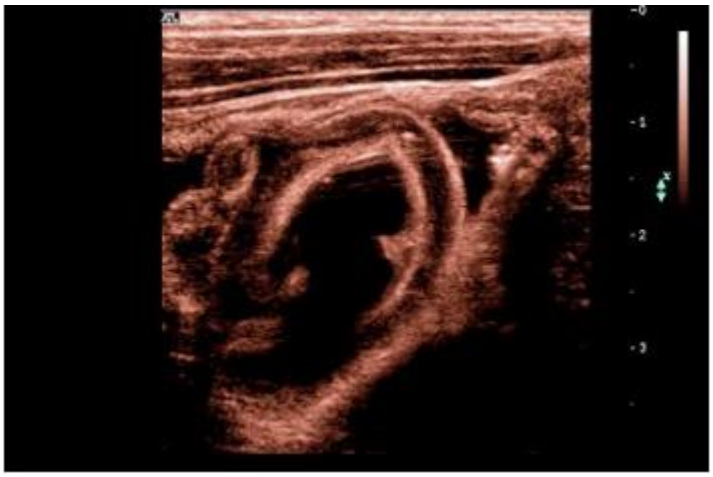

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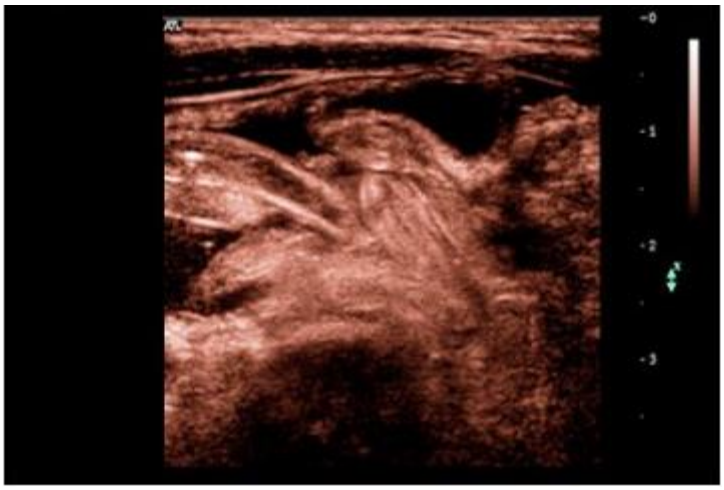


Adult *A. lumbricoides* are 15–35 cm long and 2–6 mm in diameter, with a peculiar sonographic appearance (29). In longitudinal sections, they have an echogenic non-shadowing tubular

structure with a hypo- or anechoic centre, and can be seen moving with a slow-waving pattern. Multiple worms in the bile duct produce a spaghetti-like image, with alternating echogenic and anechoic strips or, if densely packed in the bile duct, can appear as an hyperechoic pseudotumour. On transverse sections, a “bull’s eye” echo can be seen owing to the presence of a worm in the dilated bile duct.

Treatment

The management strategy for patients with biliary ascariasis depends on the clinical situation; it can include conservative management, endoscopic extraction or surgical intervention. In most cases, pathology resolves with pharmacological treatment and response to treatment can be monitored by ultrasound (30). Conservative treatment includes the use of analgesics, antibiotics for pyogenic cholangitis and oral administration of albendazole, which paralyses the worms so that they can be expelled. Symptoms resolve within 3 days in 60–80% of patients, accompanied by the disappearance of worms on ultrasound. Endoscopic intervention is indicated in cases of acute severe pyogenic cholangitis, recurrent biliary colic non-responsive to analgesics, high amylasaemia, and when the worms persist in the bile duct for longer than 3 weeks (probably because they are dead). Endoscopic extraction of worms across the papilla leads to rapid resolution of symptoms and can be performed using grasping forceps or a Dormia basket (31). Surgical intervention is required when endoscopic treatment fails, or if the worms are located in the intrahepatic bile ducts or in the gallbladder.

Toxocariasis (visceral larva migrans)

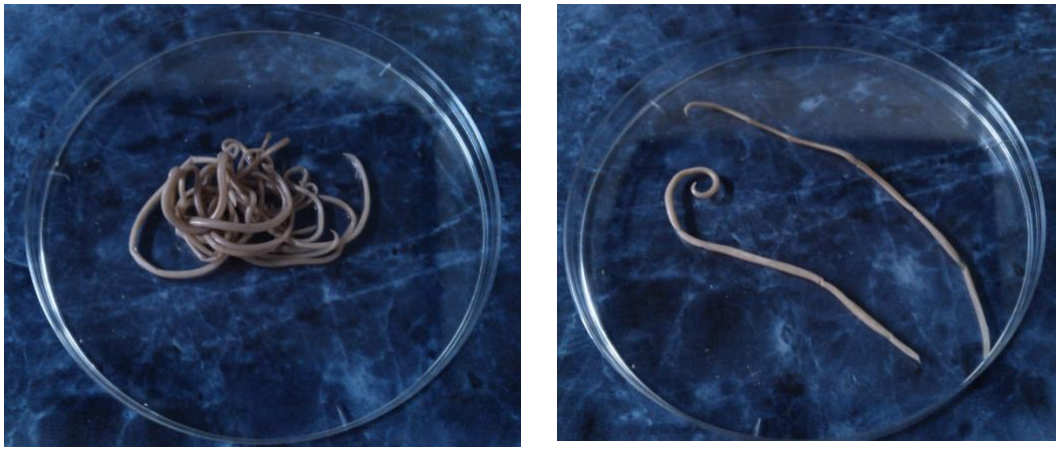
Introduction

Toxocara spp. are nematodes that affect dogs and cats worldwide. In these definitive hosts, the adult worms reside in the small intestine where the females produce eggs that are released with the faeces. After approximately one month an infective larva develops in the egg, which can then be ingested by a definitive host (dog or cat) or by paratenic hosts (including humans). In all cases, the eggs hatch in the intestine and the larvae penetrate the bowel wall and migrate through the liver to the lungs and other tissues. In young, pregnant and lactating dogs and cats, the worms complete the cycle and develop into adults. In older

dogs and cats (generally), and in the paratenic hosts, the larvae encyst in various organs and do not reach maturity. Dogs, cats and humans can also acquire the infection by ingestion of raw or undercooked meat of paratenic hosts, which contain the encysted larvae.

Human toxocariasis is caused by the larvae of the dog parasite, *T. canis* [Figure 7], or less commonly caused by the cat parasite, *T. cati*. Their migration through, and encystation in host's tissues can cause a severe local reaction, with eosinophilic infiltration and formation of granulomas or eosinophilic abscesses. The associated disease is referred to as visceral *larva migrans* (VLM) or ocular *larva migrans* in cases of eye involvement.

Figure 7 Adult *Toxocara canis* worms.



Clinical presentation

Clinically, most patients are asymptomatic and the infection is diagnosed during the investigation for peripheral eosinophilia. When symptoms are present, they are characteristically a self-limiting febrile eosinophilic syndrome with fever, peripheral eosinophilia, hepatomegaly, abdominal pain or discomfort and possibly cough and dyspnoea.

Diagnosis

The diagnosis of VLM is made by serology, which detects antibodies specific for *Toxocara* excretory-secretory antigens. Serology can also help differentiate VLM from eosinophilic

syndromes caused by other tissue migrating larvae, such as *Fasciola spp.*, *Paragonimus spp.*, *Schistosoma* spp, *Ascaris spp.*, *Trichinella spp*, filariae, *Ancylostoma spp.*, *Strongyloides stercoralis*, *Gnathostoma spp, Balysascaris procionis* and *Capillaria hepatica*, which may have similar clinical and imaging features (32, 33), although serologic cross-reactions are also possible.

Ultrasound

Sonographic abnormalities include non-specific hepatomegaly, lymphadenopathy and pleuro-pericardial effusions. Hepatic granulomas appear as multiple small hypoechoic lesions with ill-defined margins, usually oval, angulated or trapezoid in shape and occasionally with a central spot or line ("bean sign") [Figure 8] (34, 35). Sometimes lesions conglomerate to form a large area of mixed echogenicity. The lesions are similar to those observed in acute fascioliasis as both parasitic diseases are characterized by ill-defined hypoechoic, rather small cystic lesions, eosinophilic liver infiltrations and periportal lymphadenopathy (34-36).

Figure 8 Sonographic appearance of liver lesions caused by migration of *Toxocara* larvae. A small, hypoechogenic lesion is seen in the seventh segment of the liver in an oblique subcostal (a) and longitudinal scan (b).

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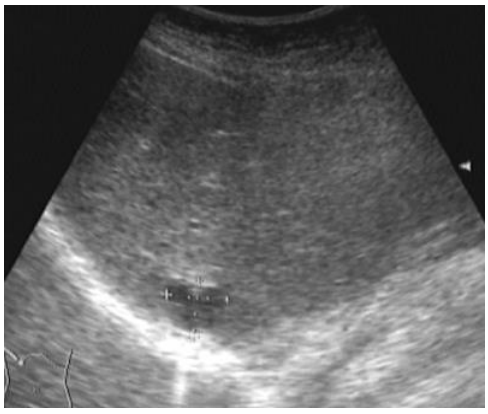

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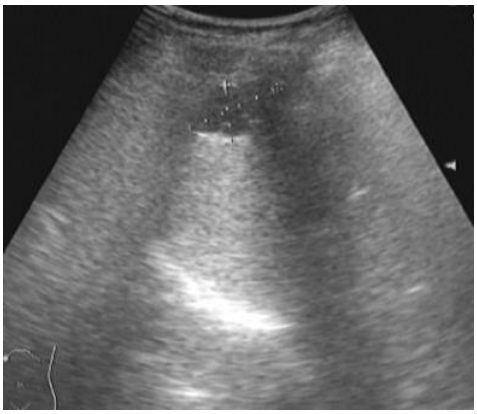
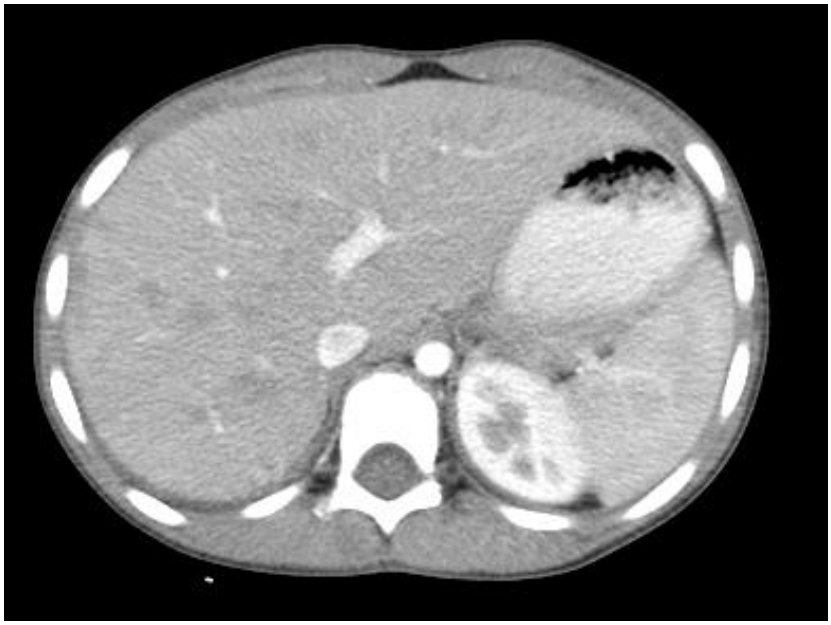


The main differential diagnoses of VLM hepatic lesions are hepatic metastases and lesions caused by the migration of other parasites (37-39). Diagnostic clues include that hepatic nodules in toxocariasis have ill-defined margins, are uniform in size and are usually not spherical in shape (36). Contrast CT and MRI can help in the differential diagnosis because *Toxocara* lesions are best seen or only seen in the portal venous phase [Figure 9]. A rim of enhancement is frequently observed in liver metastasis, but seldom seen in toxocariasis (40-42).

Figure 9 CT appearance of liver lesions caused by migration of *Toxocara* larvae. Small hypodense nodules are seen across the liver parenchyma.



Toxocariasis is mostly a self-limiting disease. On follow-up images, lesions usually improve and resolve spontaneously unless the patient is re-infected. The position and number of the lesions can change over time due to the migration of the larvae, which supports the diagnosis of VLM. Treatment includes the use of albendazole and steroids for severe symptoms (43).

Fascioliasis

Introduction

Fascioliasis is a zoonotic infection of the liver and the bile ducts caused by the trematodes *Fasciola hepatica* and *F. gigantica*, also called “liver flukes”. They infect approximately 17 million people worldwide. Ruminants are the natural hosts of *Fasciola spp*. and infection is found in areas where ruminants are raised and the consumption of watercress is common (38, 44).

Adult flukes reside in the intrahepatic bile ducts, where they release eggs that are passed in the stools. In freshwater, the eggs become embryonated and release the first stage larva “miracidium”, which invades a suitable snail. In this intermediate host, the parasite multiplies and develops through several stages. At the fourth stage, “cercariae” abandon the snail and encyst as infective “metacercariae” on aquatic vegetation.

Ruminants and other mammals, including humans, acquire the infection through ingestion of aquatic plants or water contaminated with metacercariae. Once excysted in the small bowel, the metacercariae penetrate the gut wall and migrate through the peritoneal cavity to the liver. Here they perforate the capsule and start an intrahepatic migration.

The biliary or chronic phase, represented by the migration into the biliary tree, begins after 1 - 6 months. The worms finally enter the intrahepatic bile ducts and develop to adults in 2-3 months when they start to produce eggs. Occasionally, the larvae migrate to other organs or pass through the diaphragm and cause ectopic fascioliasis (45).

Clinical presentation

Clinically, an acute and a chronic-latent stage are distinguishable. During the acute stage, which is associated with the intrahepatic migration of the larvae, manifestations are typically

an acute febrile eosinophilic syndrome, with abdominal and allergic symptoms. These can last several months and include fever, hepatosplenomegaly, upper-quadrant abdominal pain, urticaria, arthromyalgia and cough. Dyspepsia is prominent, and fatigue and weight-loss are sometimes striking. The chronic-latent phase, caused by adult flukes in the bile ducts, occurs after approximately 3 months and can persist for years. The symptoms are generally discrete and reflect biliary obstruction, inflammation and bacterial superinfection. They include upper abdominal discomfort, intermittent jaundice and fever, loss of weight.

Diagnosis

Fascioliasis is suspected by typical symptoms and diagnosis proved by visualization of eggs in stool and serological testing. Laboratory findings include marked eosinophilia, hypergammaglobulinaemia, elevated liver enzymes and anaemia. Elevated liver enzymes and bilirubin are common. Serological tests that detect antibodies against *Fasciola* excretory-secretory antigens become positive 2–4 weeks following infection and are consequently useful in the diagnosis of acute fascioliasis, when no eggs have been produced yet and during the chronic phase, because the shedding of eggs is intermittent and stool examination can give false-negative results. Antibody titres return to normal within 1 year of successful treatment. False-positive results can result from cross-reactivity with schistosomiasis or other parasites.

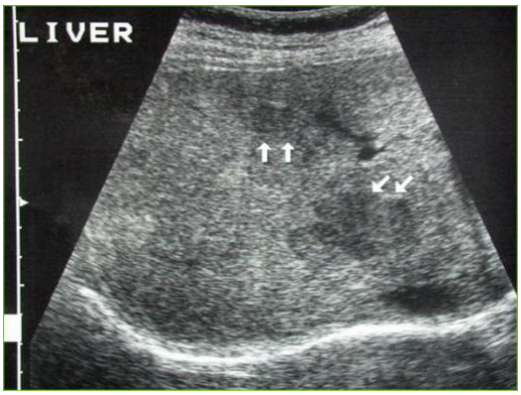
Ultrasound

In the acute stage, imaging techniques such as ultrasound and CT usually reveal a non-specific hepatosplenomegaly, which is sometimes accompanied by a small amount of ascites (38, 39, 46-48). Hypoechogenic “migrating” lesions with ill-defined margins should be present. Contrast enhanced ultrasound (49) is better at delineating the number, size and shape of the lesions [Figure 10 and 11] (38).

Figure 10 Ultrasound appearance of hepatic fascioliasis. Note the hypoechogenic lesions with ill-defined margins, one of which is adjacent to the liver capsule (entry point

of the fluke) (a) and the cyst-like nodules that progress from the liver capsule with a footprint-like pattern (b).

a



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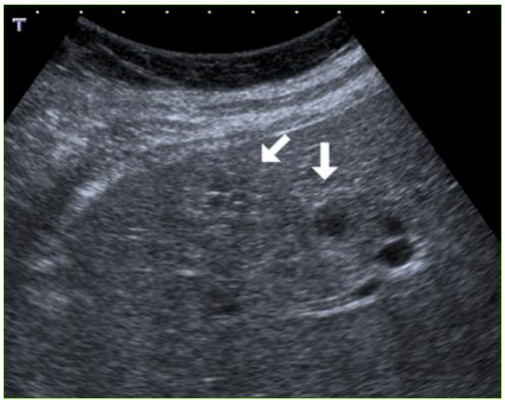
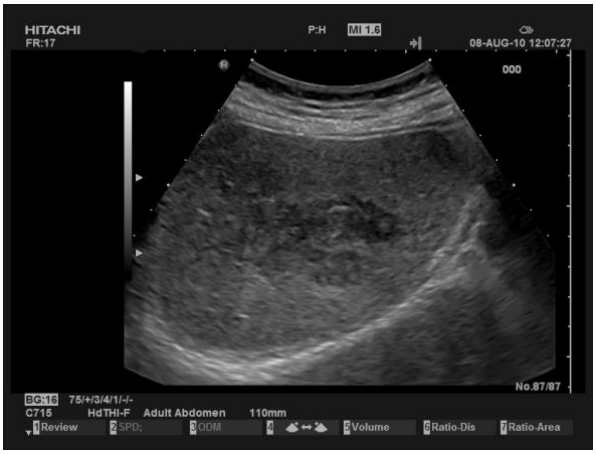


Figure 11 Acute fascioliasis shown by B-mode imaging (a) and contrast enhanced ultrasound (b) with liver abscess formation.

a



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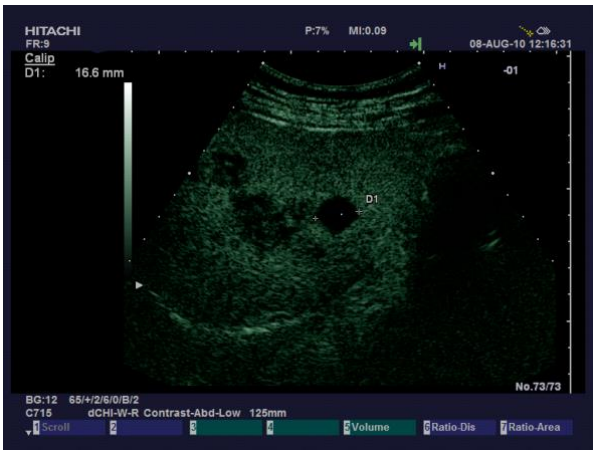
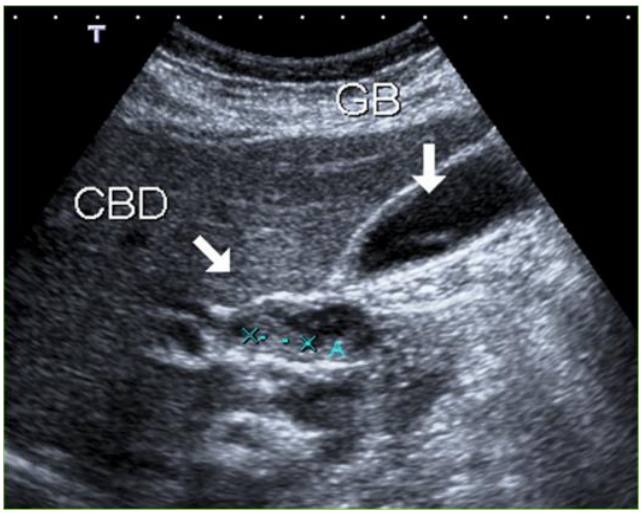


In the chronic stage, adult flukes may be seen inside the dilated biliary ducts or the gallbladder as single or multiple elongated filamentous/leaf-like echoic structures a few centimetres in length [Figure 12]. Spontaneous movement may be observed. Other ultrasound findings include thickening of extra-hepatic bile ducts and gallbladder walls, common bile duct dilation, cholelithiasis, small calcifications of the liver parenchyma, cystic necrotic lesions, liver abscesses due to superinfection [Figure 11] and hepato-splenomegaly. Periportal lymphadenopathy has been observed as a sensitive but non-specific sonographic finding (39, 46-48). Intrahepatic biliary dilatation was detected in 17 patients (46%). Oedema and dilatation of common bile duct was observed in 12 patients (32%) (48). Long-term complications include secondary sclerosing cholangitis.

Figure 12 Ultrasound scan of enlarged common bile duct (CBD) with a *Fasciola* obstructing its lumen and another *Fasciola* floating in the gallbladder (GB) lumen (a). A CT scan of a liver from a patient with acute fascioliasis. A subcapsular hypodense lesion and two other elongated lesions are seen in the right lobe (b). CBD fasciola is shown also in (c, arrows).

a



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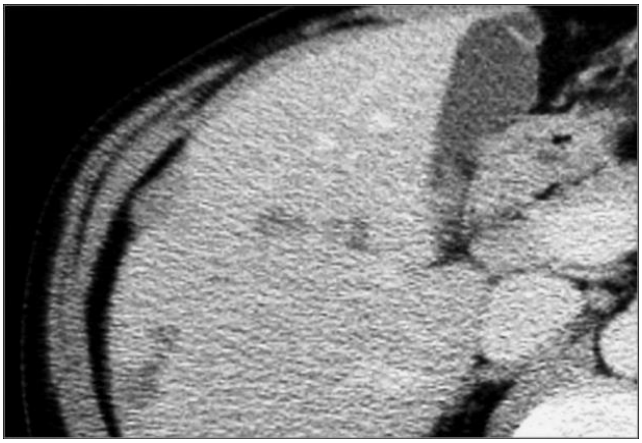

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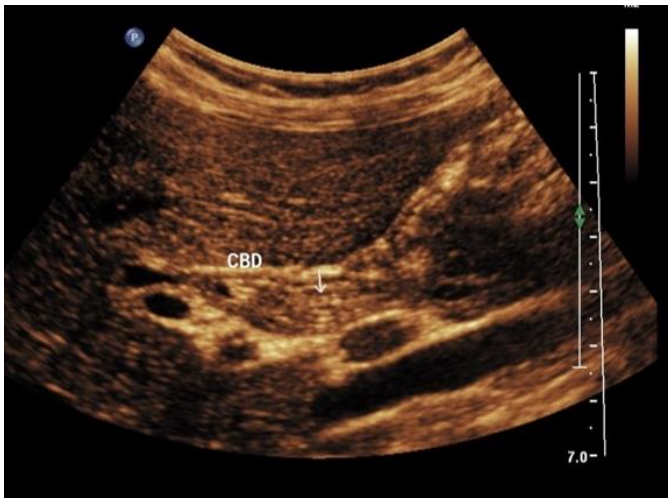


Other imaging modalities

Small necrotic lesions form along the migratory paths of juvenile flukes. The lesions can be seen as hypodense or hypointense small lesions by CT or MRI. The lesions do not coalesce and are typically arranged along serpiginous tracts, from the surface of the organ to deep within the hepatic parenchyma. They can change in quantity and location over time. This particular lesion arrangement can be helpful in the differential diagnosis of tumours, pyogenic abscesses and other visceral *larva migrans* (50).

Differential diagnosis

The differential diagnosis includes other flukes, tumours, pyogenic abscesses and other visceral *larva migrans* (47). (37).

Prognosis

In contrast to Asian trematodes species *Clonorchis sinensis* and *Opisthorchis spp*, *Fasciola spp* tend to cause less fibrosis and the risk of developing cancer seems to be much lower.

Treatment

The treatment of fascioliasis is relatively difficult, because the fluke has a thick cuticula, which is not easily penetrated by drugs. Therefore, praziquantel, otherwise the drug of choice in trematode infections, is of little use in fascioliasis. Triclabendazole in a dose of 10 mg/kg body weight or bithionol are recommended (51). Triclabendazole is usually given as single dose after a meal. In severe infections, a second dose should be given after 12 hours. However, triclabendazole is not licensed for use in humans in many countries. Endoscopic or surgical interventions may be necessary in complicated cases. In case of concomitant cholangitis and liver abscesses, antibiotics such as ceftriaxone and metronidazole are required to treat bacterial superinfections. If dead worms obstruct the bile ducts, papillotomy and endoscopic drainage (ERCP) might be required.

Small Asian liver flukes

Introduction

Clonorchis sinensis (Chinese or Oriental liver fluke), *Opisthorchis viverrini* (Southeast Asian liver fluke) and *Opisthorchis felineus* (Cat or Siberian liver fluke) are food-borne trematode parasites that reside in the human bile ducts and can cause different hepatobiliary diseases with varied images in US. *C. sinensis* is endemic in Korea, China, Taiwan, Vietnam and far-eastern Russia with 200 million people at risk and more than 15 million infected (52). *O. viverrini* is endemic in the countries bordering the Mekong, namely Thailand, Laos, Cambodia and Vietnam with about 90 million at risk and more than 10 million infected (53). *O. felineus* is endemic in northern Eurasia with more than 15 million at risk and incidence rates up to 500/100.000 population in Western Siberia (54). The three parasites share a similar life cycle. After contact with freshwater, the eggs hatch and the first-stage larvae (miracidiae) are ingested by a suitable snail as first intermediate host. Within the snail the asexual reproduction takes place, with development of cercariae that are shed into the water and penetrate actively the skin of freshwater fishes belonging to the family Cyprinidae. They are the second intermediate hosts, in which larval development to the infectious metacercariae occurs. By eating raw or undercooked fish, humans or other fish-eating mammals such as dogs, cats, rats and pigs, get infected as the definitive hosts. After ingestion, the metacercariae excyst in the duodenum and the juvenile worms migrate through the ampulla of Vater into the biliary tree. Adult parasites can survive up to 30 years in humans. They measure 7-10 mm in average and reside in the intrahepatic and occasionally extrahepatic bile ducts, where they start to shed embryonated eggs, that are passed in the faeces, approximately 1 month after infection (44).

Clinical presentation

Clinical manifestations of clonorchiasis and opisthorchiasis depend more on the intensity and duration of the infection than on the species of the liver flukes that are involved. In general, the acute infection is harmless and for example in the case of *O. viverrini*, in 90-95% even asymptomatic (55). Nonspecific symptoms such as mild abdominal pain, dyspepsia, fatigue,

fever, skin rash, constipation or diarrhoea may occur, but no specific correlate in clinical imaging for an acute infection is currently known.

Diagnosis

Raised liver enzyme levels and eosinophilia are common laboratory findings. The definitive diagnosis is made by the detection of eggs in stool microscopy. In general, the formalin ethyl-acetate concentration technique (FECT) is often used for detection of ova, and multiple stool sampling increases the sensitivity. The eggs of *C. sinensis* and *Opisthorchis spp* may look similar but the geographic exposure can suggest which species are most likely involved. In endemic regions, additionally, minute intestinal flukes (MIF) may be also found, the eggs of which look also very similar. Therefore, further diagnostic methods such as serological testing could be necessary.

People in endemic regions get regularly re-infected and danger arises from the chronic infection that can lead to cholangiocarcinoma (CCA). In later stages of the CCA, patients present with (obstructive) jaundice, cholangitis, often accompanied by right upper quadrant pain, fever, night sweats and weight loss. Both *C. sinensis* and *O. viverrini* have been classified as a group I biological carcinogen by the International Agency for Research on Cancer (56) and in some endemic countries CCA is the most common cancer (e.g. in the male Thai population (57)). The dismal prognosis of CCA is due to its silent clinical development, difficult early diagnosis, and limited therapeutic approaches.

Ultrasound

Chronic infection can lead to a wide range of features like periductal fibrosis, dilated bile ducts, gallbladder and intrahepatic duct stones, cholecystitis, recurrent pyogenic cholangitis and liver abscesses, all clearly visible on US [Figure 13, 14] (58).

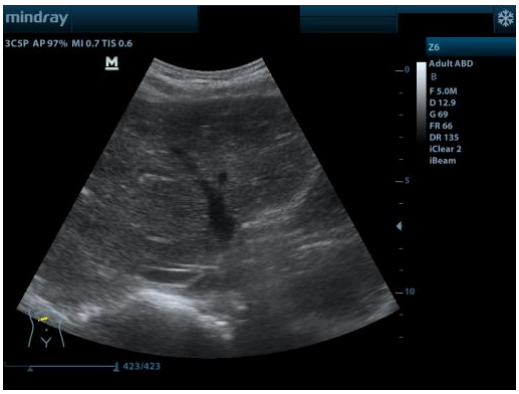
Liver

US can be a useful tool to detect CCA in early stages, particularly as to date there is no diagnostic marker of CCA. A progressive periductal fibrosis occurs as a consequence of chronic inflammation of the biliary tree. Advanced periductal fibrosis, as well as bile duct dilatations, can be a precursor of CCA and in such cases (59, 60). Therefore, a close follow-up with US is

reasonable. On the contrary, US follow-up is not useful in verifying the success of antiparasitic therapy or in the differentiation between chronic and acute infection, as the pathological changes of the bile ducts can persist for years.

Figure 13 Periductal fibrosis can be seen as 'starry sky' appearance of the liver parenchyma (diffuse echogenic foci, mainly in the periphery of the liver)

a



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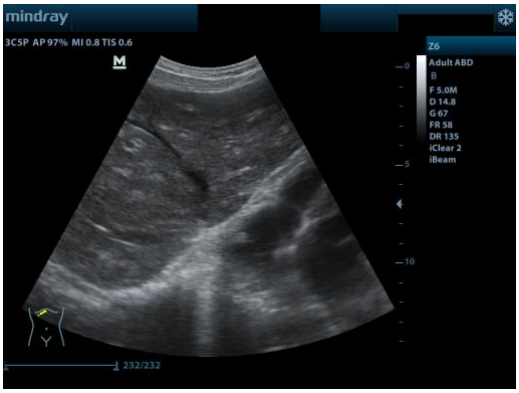
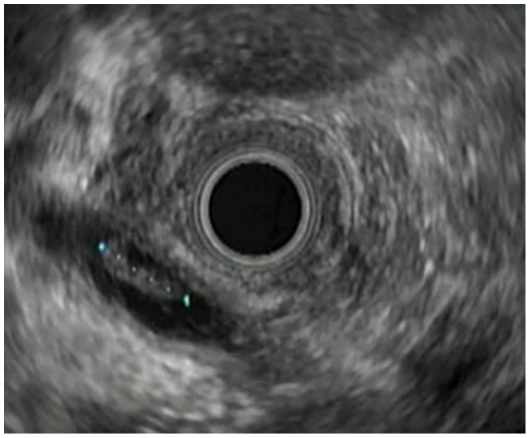


Figure 14 Endoscopic ultrasound showing *Opisthorchis* spp. (between calipers) in a dilated common bile duct (freeze – frame from a video recorded by Dr. William Brown

and edited by Dr. Franklin Kasmin, Beth Israel Medical Center, New York City, NY.)



Other imaging modalities

In the case of infection complications, such as pyogenic cholangitis, liver abscesses, pancreatitis or a lesion that is already suspicious for CCA, CT/MRI are recommended. For the confirmation of CCA, these imaging techniques might not be conclusive and histological proof is the gold standard.

Treatment

Praziquantel is the drug of choice for the treatment of these flukes, coupled with endoscopic or surgical interventions in complicated cases. In endemic areas, mass drug administration (MDA) (61) is common practice with a dosage of 40 mg/kg body weight one or two times per year. Interestingly, the role of praziquantel for MDA is under discussion as it might induce the expression of fibrogenetic factors and enhance the carcinogenetic pathway when administered repeatedly (62, 63).

Echinococcosis

Human echinococcoses are zoonoses caused by the larval forms (metacestodes) of *Echinococcus spp.* tapeworms. Four species of *Echinococcus* cause pathology in humans, of

which *E. granulosus sensu lato*, causing cystic echinococcosis, is by far the most widespread. *E. multilocularis*, the second most frequent species, causes alveolar echinococcosis and its distribution is limited to the northern hemisphere. *E. vogeli* and *E. oligarthra,* occurring in Central and South America, cause neotropical echinococcosis and only a few human cases have been reported.

Carnivores are the definitive hosts of all *Echinococcus* species (canids for *E. granulosus*, *E. multilocularis* and *E. vogeli*, and felids for *E. multilocularis* and *E. oligarthra*), which have various mammals as the intermediate hosts (ungulates for *E. granulosus* and rodents for the other species). The adult tapeworms reside in the small intestine of the definitive host. Mature eggs containing the infective larva (oncosphere) are released with the faeces and can be ingested by a suitable intermediate host. Here the eggs hatch and the oncospheres penetrate the intestinal wall and migrate through the bloodstream to various organs where they develop into the cystic larval form containing protoscoleces (infective tapeworm heads). The definitive host becomes infected by ingesting the cyst-containing organs of the intermediate host. After ingestion, the protoscoleces evaginate, attach to the intestinal mucosa, and develop into the adult stage. Humans are accidental intermediate hosts, who acquire the infection by ingestion of infective eggs.

Cystic echinococcosis

Introduction

Cystic echinococcosis (CE) is caused by the metacestode of *E. granulosus s.l.* species complex. Although less clinically severe than alveolar echinococcosis in most cases, it is the most geographically widespread and therefore medically and economically important infection caused by cestodes of the genus. Human CE is highly endemic in pastoral communities worldwide, where there is close contact between humans, livestock and dogs. CE causes more than 95% of the 2–3 million estimated cases of echinococcosis worldwide. Most cases are asymptomatic or oligo-symptomatic and may remain as such indefinitely. Yearly incidence of human disease arriving to clinical attention may be up to 50 cases per 100,000 inhabitants in highly endemic areas, where the prevalence can be up to 10% in humans and over 50% in

livestock. In published work, case fatality rate of CE is reported at 2–4% or higher in symptomatic patients

The liver is the organ most frequently infected, followed by the lungs. The metacestode develops into a well-defined cyst that grows concentrically at a variable rate (reportedly 0.5–1.5 cm/year, but in most cases very slowly). Each protoscolex developed inside the cyst can, in case of cyst rupture, generate a new cyst, in a process called “secondary infection”. Within the cyst, daughter cysts may also develop.

Clinical presentation

Approximately 60–75% of patients with CE are asymptomatic and the infection is usually discovered during an imaging exam carried out for other reasons. Morbidity depends on the number, size and developmental status of the cysts, the organ involved, and the location within the organ. Clinical symptoms usually occur when the cyst compresses or ruptures into neighbouring structures. Patients with hepatic CE can present with upper-quadrant abdominal pain or discomfort and hepatomegaly. In case of rupture or leakage of cystic material, recurrent allergic symptoms (rash, urticaria or bronchospasm) and in some cases anaphylactic shock can occur. Other complications include rupture of the cyst into the biliary tract, with associated symptoms of cholangitis and biliary obstruction, or, less frequently, portal hypertension caused by compression of the caval vein or venous thrombosis. Mass effect, rupture and allergic reactions are the basis of the CE-related symptoms even in the case of thoracic localisation.

Diagnosis

The diagnosis of CE is based on imaging techniques complemented by serology when imaging is inconclusive. Parasitological confirmation may be achieved by cytological or histological examination of cyst material obtained by percutaneous puncture or surgery, with visualization of protoscoleces or their components and/or the characteristic laminated layer of the cyst wall. Haematochemical parameters are generally unaltered, with the exception of increased cholestasis indices in case of biliary involvement. Eosinophilia is often absent. Serology can be useful to confirm the diagnosis of CE in doubtful cases, but is hampered by its variable sensitivity (false-negative results are very frequent in case of young or inactive cysts, and cysts

located in organs other than the liver). Moreover, serology at present has no role in indicating the viability of CE cysts or in the follow-up after treatment, as positivity may persist for years even after surgical removal of cysts.

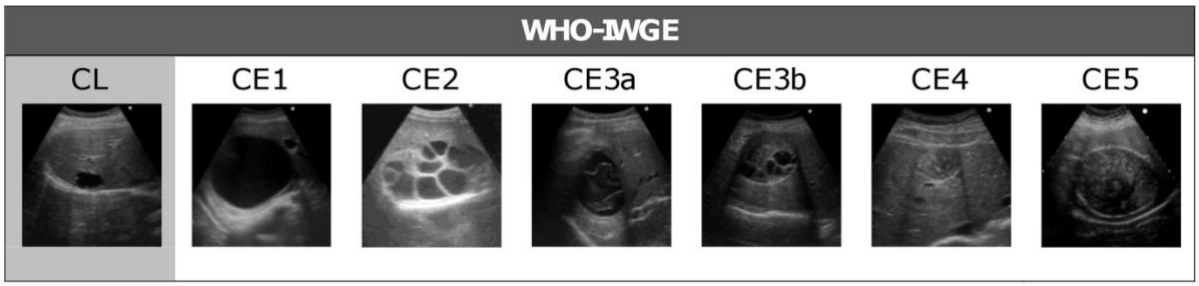
Ultrasound

Ultrasound is the basis of the diagnosis and follow-up of CE in the liver and other US-accessible localizations. Other radiological techniques are useful to complement an initial ultrasound exam, in case of extra-hepatic abdominal locations and extra-abdominal locations of suspect CE lesions, when cysts are not accessible by ultrasound, and before surgery to assess the relative topography of cysts and surrounding structures.

CE cysts may evolve through morphologically different stages, corresponding to different cysts' activity states. Importantly, clinical decision-making for uncomplicated liver CE is based on ultrasound staging of CE cysts. In 2003, the WHO-IWGE (Informal Working Group on Echinococcosis) published a standardised classification that divided the cysts into three activity (i.e. evolutive) groups: active (CE1, uniloculated and CE2, with daughter cysts), transitional (CE3) and inactive (CE4, with solid content and CE5, solid content with egg-shell wall calcifications) (64). CE3 transitional cysts were then differentiated into CE3a (with detached inner parasitic layers) and CE3b (predominantly solid with daughter cysts) (65). In terms of viability, CE1, CE2, and CE3b are viable; CE3a have variable viability; CE4 and C5 are not viable or have low viability. CE1 and CE3a are early stages, and CE4 and CE5 are late stages [Figure 15], see also (66) for further illustrations.

Figure 15 WHO-IWGE ultrasound classification of echinococcal cysts. CL=Cystic Lesion; this is an unilocular cyst without pathognomonic signs of CE, which is therefore only

suspect of echinococcosis and requires additional workup for etiological diagnosis (67).



A number of elements are important in the differentiation of echinococcal from non-parasitic cysts [Figure 16 and 17].

Pathognomonic features of CE include: i) double wall sign (CE1); ii) regular, avascular "septations", which are actually the juxtaposed walls of the daughter cysts (CE2); iii) continuous hyperechoic thin and regular "membrane" (parasitic layers) floating in the cyst (CE3a); iv) heterogeneous avascular solid content with hypoechoic folded structures (parasitic layers) forming the so-called "ball of wool" appearance with one or more daughter cysts in the mass (CE3b), without daughter cysts (CE4), and with cyst wall calcification (CE5). In non-parasitic lesions [Figure 16] a single thin, irregular wall may be visible, septations, if present, are grossly irregular or interrupted, can have a fuzzy appearance due to the presence of fibrin the mass or septa may be vascularized in neoplasms.

Figure 16 Non-parasitic, biliary cyst, characterized by absence of clear wall, irregular shape, and thin, often interrupted septae (a). CE1 stage echinococcal cyst, identified by a "double wall" (inner hyperechoic parasitic layers and outer hypoechoic fibrous adventitial layer from the host) (b). CE1 stage echinococcal cyst developing into a CE3a stage cyst, as shown by the detachment of the parasitic layers (arrows); floating echoes can be observed in echinococcal cysts, caused by protoscoleces and brood capsules (hydatid sand). Different appearance of CE2 stage echinococcal cysts; in all cases CE2 cysts are identified by the presence of daughter cysts. "Septae" in echinococcal cyst are not real septations but the walls of adjacent daughter cysts. The number of daughter

cysts may vary, either filling the entire "mother" cyst (D – E) or with the presence of daughter cysts adjacent to the mother cyst wall (F – IMPORTANT NOTE: in this image the wall of the "mother cyst" is poorly visible, but it must be visualized in a live exam) (d-f). CE3a stage echinococcal cyst, identified by the detachment of parasitic (thin, regular, and continuous) layers floating in the cyst's liquid content (g). CE3b stage echinococcal cyst, identified by the presence of daughter cysts in a solid matrix in which hypoechoic folded parasitic layers can be seen (arrow) (h). CE4 stage echinococcal cysts. The cyst content is solid with variably heterogeneous appearance, but in all cases a CE4 cyst is identified by the presence of hypoechoic folded parasitic layer is a heterogeneous hyperechoic matrix (h-k). CE5 stage echinococcal cyst, identified by the presence of substantial eggshell calcification of a CE4 stage cyst (i.e. the folded parasitic layer should be identified to attribute the lesion in this stage to *E. granulosus* on the basis of imaging) (l, m). CEUS of an echinococcal cyst (in this case in CE3b stage) showing no contrast enhancement (n).

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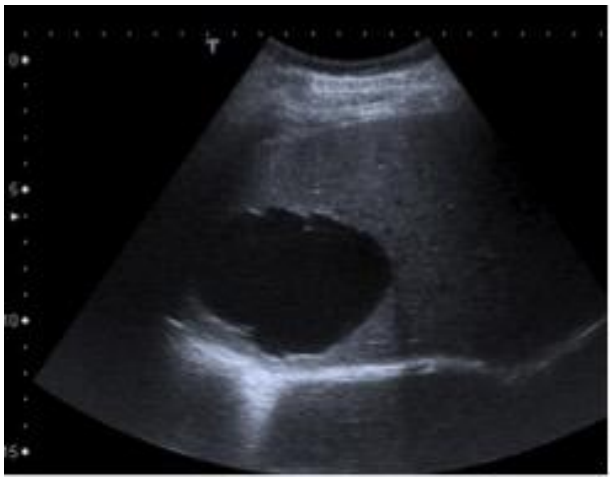

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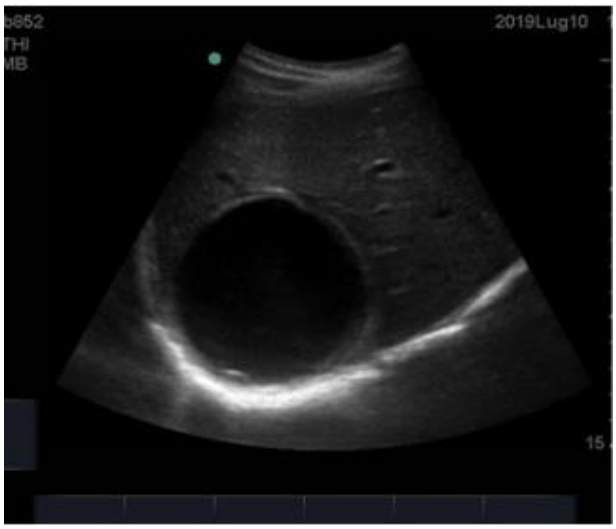

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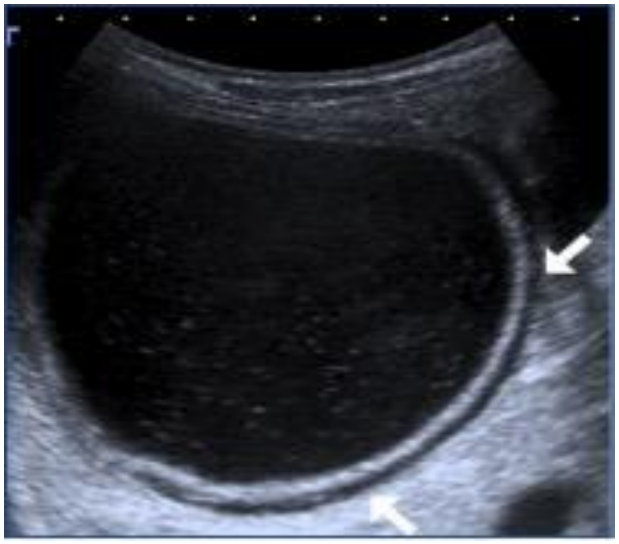

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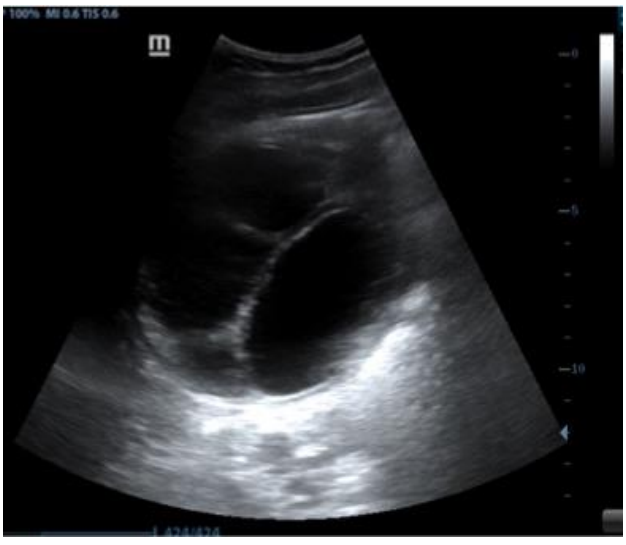

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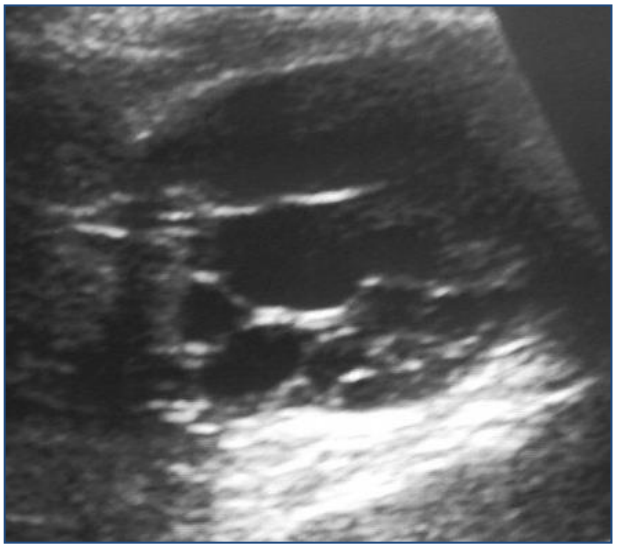

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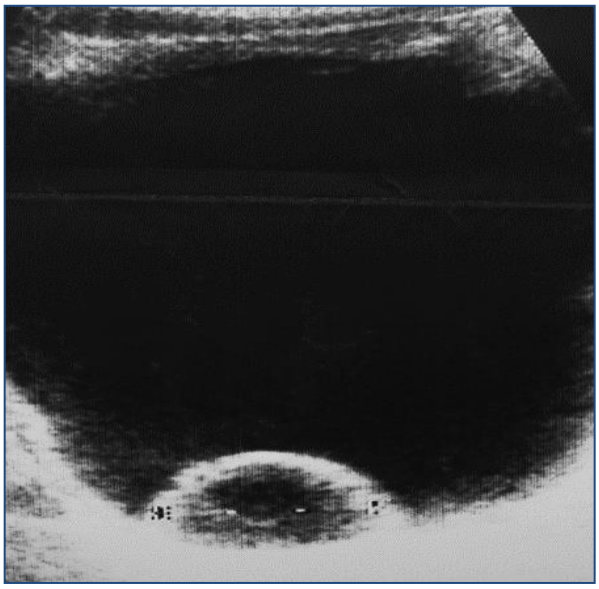

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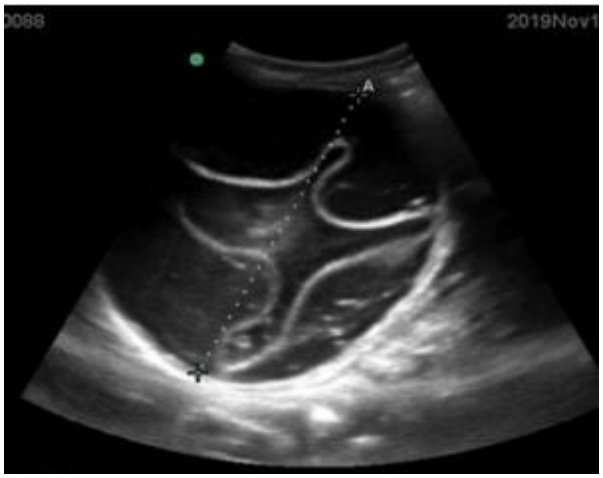

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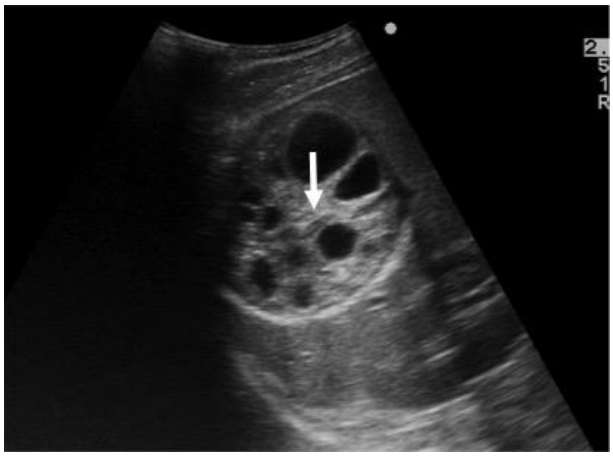

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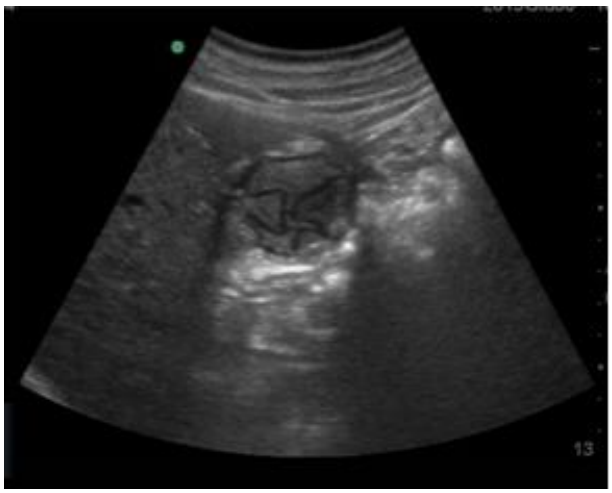

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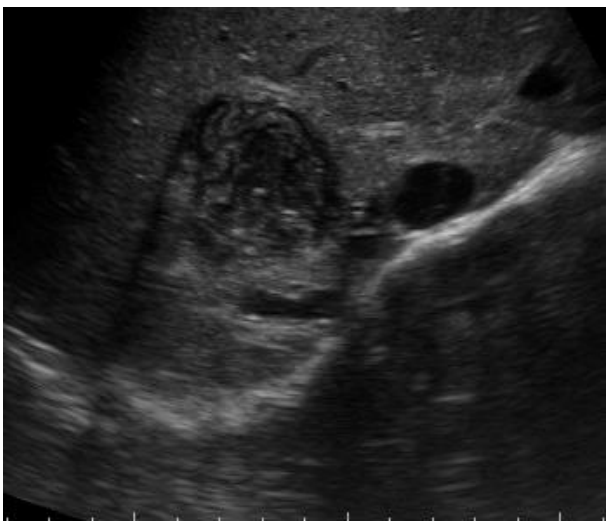

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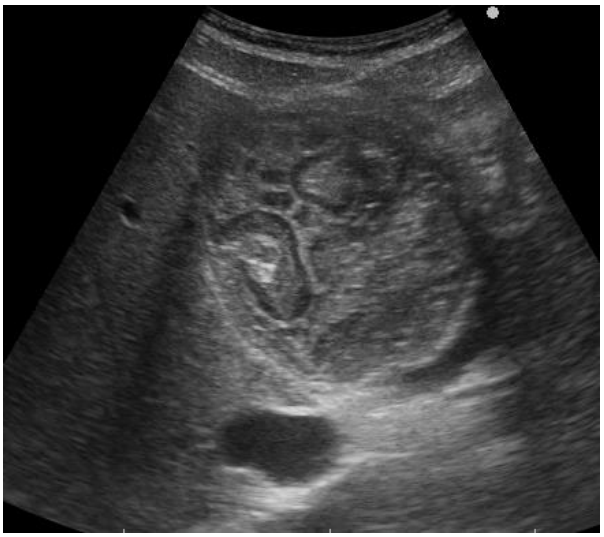

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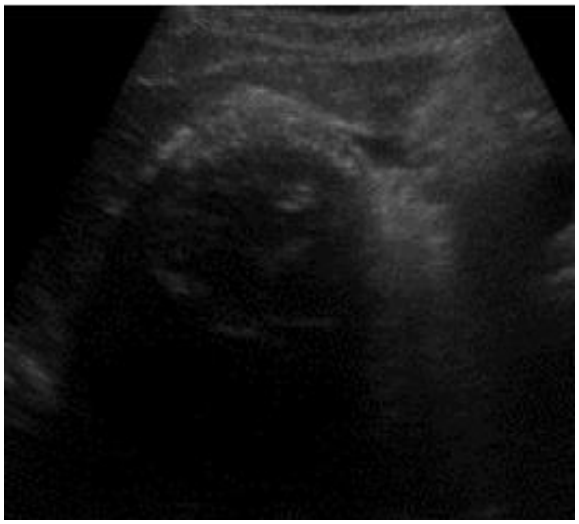

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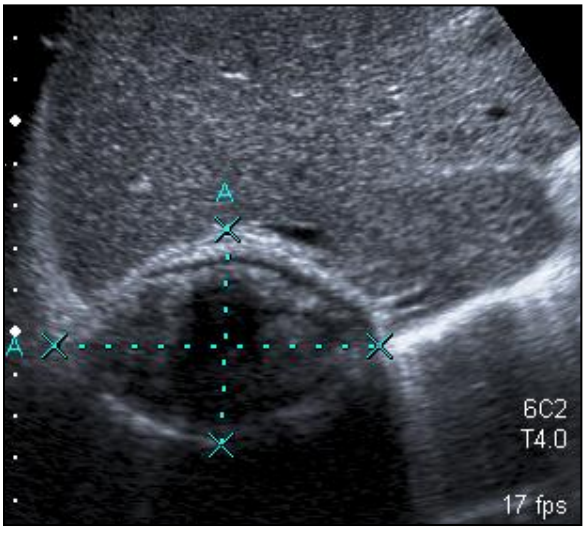

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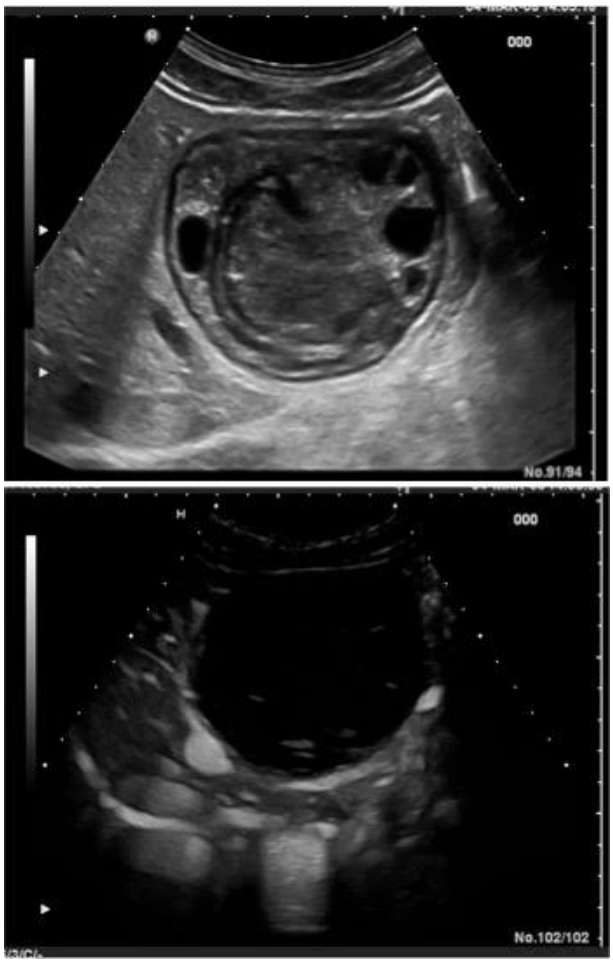
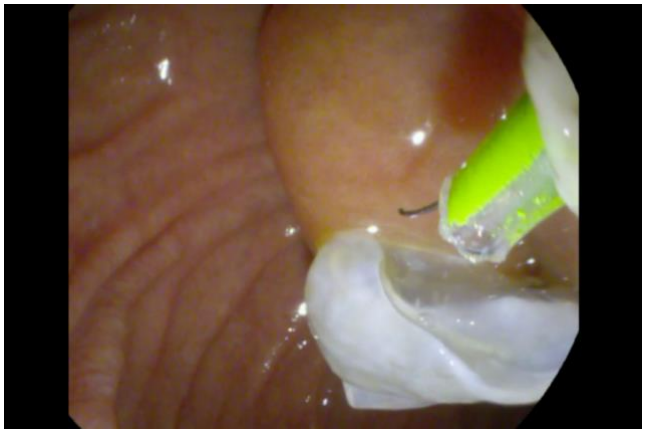


Other imaging modalities

Lung, bone, and brain cysts have to be imaged by CT or MRI. MRI shows most typical features of CE better than CT, and is therefore preferable. For the abdominal field, US is the primary imaging modality. However, clear visualization of multiple or multiorgan cysts and calcified cysts, or cysts in obese patients, may need CT or MRI (68). Cysts containing air (ruptured or infected) may need evaluation with CT. Cysts with biliary communication may be imaged with MR-cholangiography. Daughter cysts are usually better seen by US. Endoscopic ultrasound (EUS) is the best imaging modality and in combination with endoscopic sphincterotomy the best treatment option for common bile duct involvement [Figure 17]. EUS also allows high resolution imaging of liver cysts [Figure 18].

Figure 17 **Endoscopic and endoscopic ultrasound view of hydatid cyst disease of the common bile duct. Side view endoscopy with large papilla and protruding whitish parasitic material (a). Endoscopic sphincterotomy was performed and the parasite removed from the common bile duct (b). The corresponding EUS view is shown as well (c).**

a



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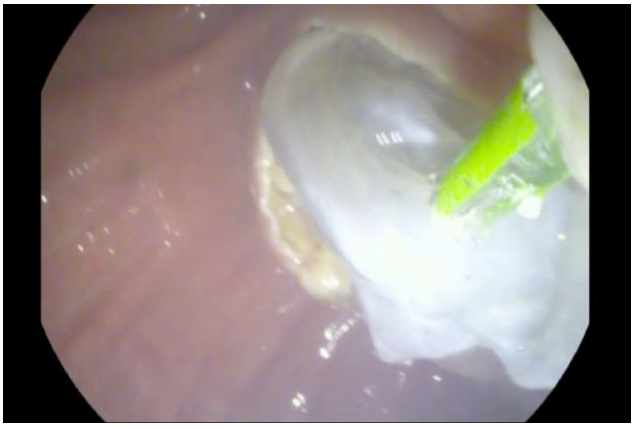

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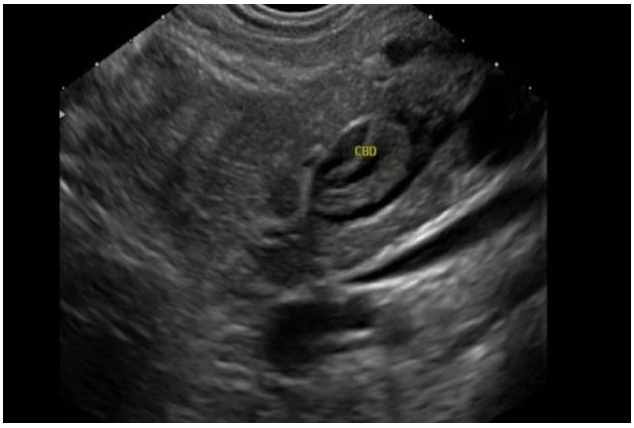

Figure 18 Endoscopic ultrasound view of hydatid cyst disease of the liver with different stages. EUS is performed to confirm and treat bile duct involvement.

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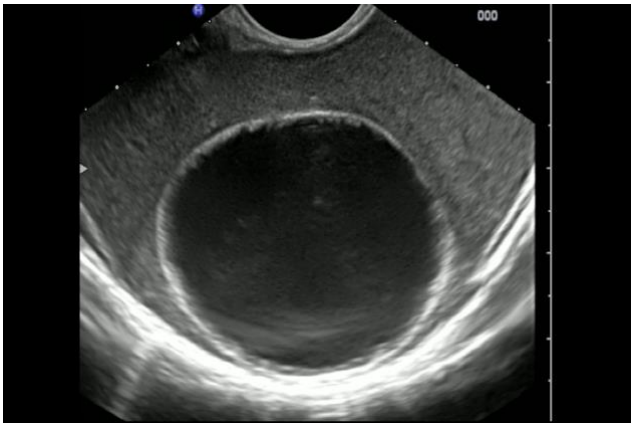

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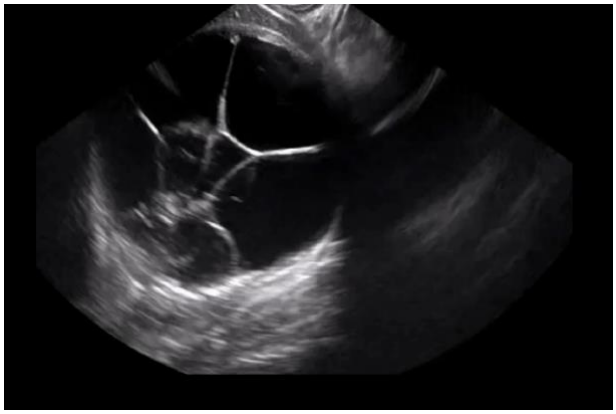

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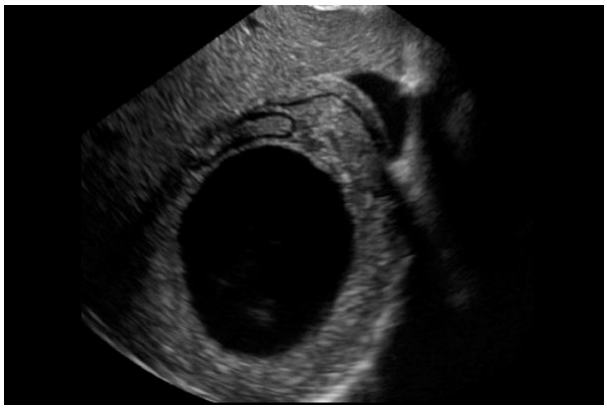

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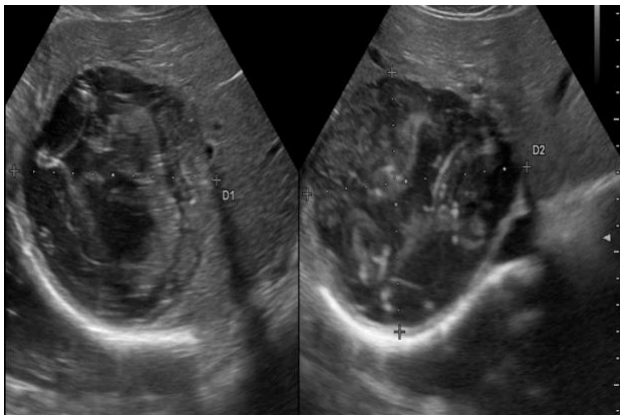

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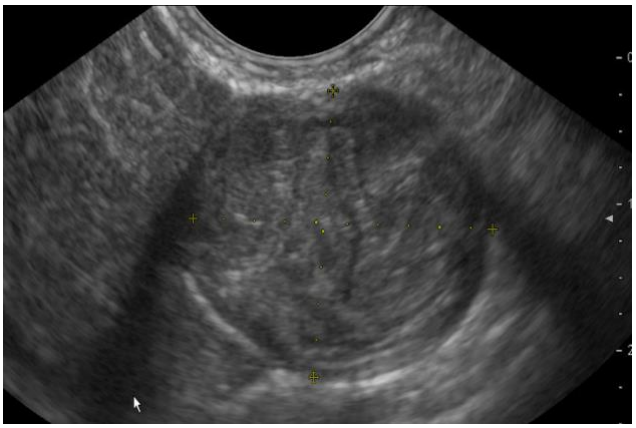

Treatment

The characteristics of cysts and patient, and the availability of resources, are all important parameters to take into consideration when choosing a therapeutic approach. In reference to the ultrasound classification only, asymptomatic hepatic CE1 and CE3a cysts may be treated with albendazole (generally for 3–6 months continuously) or percutaneous interventions; CE2 and CE3b cysts are generally candidates for surgery as they are less responsive to medical and standard percutaneous treatments; CE4 and CE5 inactive cysts do not require treatment, and must only be followed with ultrasound over time, generally for 5-10 years (“watch and wait” approach); in all cases of invasive procedures, albendazole prophylaxis must be associated. Reactivation of inactive cysts is rare if solid stage is reached spontaneously (13). Surgery is the first therapeutic choice in complicated cysts, in case of poor response to other treatments or when these treatments are contraindicated.

Alveolar echinococcosis

Introduction

Human alveolar echinococcosis (AE) is an orphan zoonosis caused by the larval stage of the fox tapeworm E. multilocularis (66). AE primarily affects the liver and is silently- growing but with malignant behaviour and infiltration to adjacent tissue, organs, lymph nodes and the potential to metastasise (67). Therefore AE is regarded the most dangerous parasitic zoonosis in Europe; left untreated, it has a very high mortality rate (68). AE-prognosis was poor until the 1970's, but has improved with the introduction of benzimidazole (BMZ) –treatment in the 1980's (69-71). A good prognosis has been reported large case series from Switzerland, France and Germany (72-74). Echinococcus multilocularis is restricted to the northern hemisphere with cool and moderate climate. Expansion of the "old" Central European endemic area has been observed (75, 76). The cycle of transmission in Central Europe is mainly based on the red fox as the definitive host and the vole as intermediate host of E. multilocularis (77). Humans become infected by ingesting tapeworm eggs and are therefore accidental intermediate hosts. Risk factors identified by case control studies in Europe (78, 79) and meta-analysis were owning a dog or cat, having a kitchen-garden and being a farmer amongst others (80).
Human AE is increasing in incidence in Europe and spreading to areas not previously affected (81-85). If the trend persists, more human cases can be expected in the near future and might pose a challenge for health care (86, 87). Data from the French AE- database, support the suspicion of increased AE- occurrence in immunocompromised patients (88). Worldwide the main burden of AE is not in Europe, but in rural communities of Western-China (89). The consensus recommendation of the WHO Informal Working Group on Echinococcosis suggests that patients should be treated in specialised centres by multidisciplinary teams (90).

Clinical presentation

The diagnosis of AE remains a challenge, even for experts. In its initial phase, the infection is usually asymptomatic. The time from infection to development of a typical liver lesion is thought to be between 5 to 15 years in immunocompetent individuals (69). In Western Europe, most patients become symptomatic when older than 50 years (70). However, there is also a significant group of patients who are diagnosed with AE around the age of 20 years. In

patients diagnosed with AE, a slight preponderance of female gender is seen (71-73). In immunocompromised patients, the course of AE is different with shorter asymptomatic period and atypical presentation of the disease (74).

First symptoms and signs may include abdominal discomfort or pain, mostly in right upper quadrant or epigastric. Non-specific symptoms like fatigue and weight loss may occur. Symptoms depend on the size and location of the parasitic lesion. More liver-specific symptoms are caused by the growth behavior of the AE lesion with frequent involvement of liver vessels and bile ducts. Symptoms like cholestasis, jaundice or recurrent cholangitis occur when the parasitic lesion involves central hepatic structures, often in later disease stages. Cholestasis with or without jaundice is seen in around one third of patients at first presentation. Budd-Chiari like appearance is common if hepatic veins or inferior vena cava is involved. In advanced parasitic liver-lesions, due to poor vascularization, a necrotic cavity develops with a significant risk of bacterial superinfection. In Europe, due to widespread use of imaging techniques, especially ultrasound, between a third and a half of AE liver lesions are diagnosed by chance (70, 73). Abnormal laboratory data such as elevation of liver-enzymes, inflammation marker, serum IgE levels or hypergammaglobulinemia can lead to the diagnosis of AE. The final diagnosis is achieved by positive echinococcosis serology or biopsy when imaging suggests a possible diagnosis of AE (75)**.**

Diagnosis

AE presents a significant diagnostic challenge in clinical practice, due to the rarity of the disease, especially in non-endemic areas. According the WHO-IWGE, the diagnosis of AE is based on clinical findings and epidemiological data correlated with imaging techniques (75)**.** Diagnostic imaging plays a crucial role in work-up of suspected AE. The final diagnosis is achieved by the combination of serology *and* imaging techniques such as ultrasound (US), computerized tomography (CT) or magnetic resonance imaging (MRI). For serology, a two-step approach using a high sensitivity screening test confirmed by a specific confirmatory test is recommended, resulting in both high sensitivity and specificity of 95% – almost 100% (75, 76)**.** Tests based on specific *E. multilocularis* antigens (e.g. Em2-ELISA) allows discrimination of *E. granulosus* and *E. multilocularis* in up to 95 % of cases (76-79).

Despite the use of highly specific antigens for *E. multilocularis* like Em2- and Em18-antigens, there might be a cross-reactivity resulting in misdiagnosis, so finally serology *and* history (possible exposure to *E. multilocularis* eggs) *and* imaging are *all* pieces of the puzzle for the diagnosis of AE (70, 76, 78-80). Confirmation of AE diagnosis can be achieved by histopathology and immunohistological staining using the *E. multilocularis*-specific monoclonal antibody Em2G11 and detection of parasite nucleic acid in a clinical specimen (76, 78). Monitoring of specific serology profile in the follow-up of patients with AE after surgery and/ or benizimidazole therapy is useful (81, 82).

According to the WHO-IWGE criteria, AE cases can be classified as “possible”, “probable” or “confirmed”. A “possible AE” case has a positive serology OR a slowly growing liver lesion and a compatible medical/epidemiological history. “Probable AE” includes any patient with clinical presentation and epidemiological history and suitable imaging findings AND a serology positive for AE. Finally “confirmed AE” refers to any patient with histopathology compatible with AE and/or detection of *E. multilocularis* nucleic acid sequence(s) in a clinical specimen (75). “Possible AE” cases with only a positive serology for AE were identified in seroepidemiological screening of rural communities in AE-endemic areas in Germany and France (83, 84). Most of these cases never developed an active AE (85).

Only early diagnosis, based on diagnostic imaging and serological markers, can increase the rate of curative resections. Early diagnostic imaging therefore takes on decisive importance (73).

Ultrasound

The widespread use of imaging modalities has led to an increase in the detection of unsuspected liver masses in asymptomatic patients. US is the current method of choice for the diagnosis of AE, but CT-scan is more specific particularly in the presence of calcified lesions (86). Typical calcifications with dorsal acoustic shadow can be seen in around three quarters of AE-cases. There is a wide variety of patterns of liver lesions where AE is a potential differential diagnosis. The primary appearance of hepatic AE lesion is *not* a simple cyst, but irregular lesions, with a solid part, and mixed echogenicity. 60-70% of patients with AE have a solitary lesion. The majority of lesions are localized in the right hepatic lobe. Involvement of

both hepatic lobes is rare. Vascular infiltration (e.g. portal vein thrombosis) and bile duct involvement occurs frequently.

Liver

On US, AE liver lesions are irregular with mixed echogenic pattern, indistinct margins and often calcification. The review of clinical data and US findings of 185 patients with AE revealed five typical patterns in the US morphology of hepatic AE lesions. The most common sonomorphological pattern is the "hailstorm pattern" seen in 54% of patients. Less common are the pseudocystic and ossification patterns, while the hemangioma-like and metastasis-like patterns are rare. Around 5% of the lesions could not be assigned to one of these five sonomorphological patterns (87). The typical hailstorm pattern is characterized by a heterogeneous, hyperechoic lesion with indistinct and irregular boundaries, with or without dorsal acoustic shadow (88). Pseudocystic lesions have, in contrast to simple liver cysts, an irregular and heterogeneous rim, often more than 10 mm thick, which does not appear vascularized on power Doppler and color-coded duplex ultrasonography. In the center of the lesion is a necrosis zone, which is hypo or anechoic, often non-homogeneous as it may contain hyperechoic material. Pseudocystic lesions in AE can be huge and involve an entire hepatic lobe. Hemangioma-like AE lesions are often difficult to distinguish from atypical (*e.g*. partially thrombosed) hemangiomas. Sonomorphologically, the lesions present as a relatively clearly demarcated non-homogeneous tumour that appears hyperechoic in comparison with the surrounding hepatic parenchyma. Echogenicity ranges from slightly and non-homogeneously hyperechoic to strongly and homogeneously hyperechoic. In terms of size, both the "hailstorm" and hemangioma-like lesions are larger than those of the ossification type. The ossification pattern presents with solitary or grouped, mostly sharply delineated lesions with dorsal acoustic shadow. In terms of their differential diagnosis, these lesions are often difficult to distinguish from hyperechoic metastases of various carcinomas. Metastasis-like lesions of AE are mainly hypoechoic and show typical characteristics compared to hepatic metastases. Eventually there is a central, hyperechoic, non-homogeneous scar. These metastasis-like AE lesions represent the greatest diagnostic challenge, finally confirmed by PCR or histopathology from US -guided liver biopsy or diagnostic liver resection. Metastasis-like AE lesions are often multifocal. Using CEUS, there is no enhancement in AE liver lesions, because the parasitic larval tissue is not vascularised.

The importance of US in hepatic AE lies primarily in the opportunity for early diagnosis. AE must be part of the differential diagnosis if an irregular-appearing liver lesion with mixed-echogenic pattern, calcification and undefined margin is detected [Figure 19]. Further imaging as CT scan or MRI and performing serology for echinococcosis is recommended as the next step. The US patterns can allow an earlier diagnosis, but cannot determine the therapeutic management. For treatment planning, staging according the PNM classification has to be done (88).

Figure 19 **Different appearance of AE lesions on ultrasound, "hailstorm" pattern: characterized by a non-homogenous, hyperechoic lesion with indistinct, irregular boundaries, with or without dorsal acoustic shadow (a + b). AE pseudocystic lesions have an irregular and inhomogeneous rim, often more than 10 mm thick, which is not vascularized on power Doppler and color-coded duplex ultrasonography. In the center of the lesion is a necrosis zone, which is hypo or anechoic, often non-homogeneous as it may contain hyperechoic material (c +d + e). AE hemangioma-like lesions present as a relatively clearly demarcated non-homogeneous tumor that appears hyperechoic in comparison with the surrounding hepatic parenchyma (f). AE: ossification pattern (g). Metastasis-like (h + i).**

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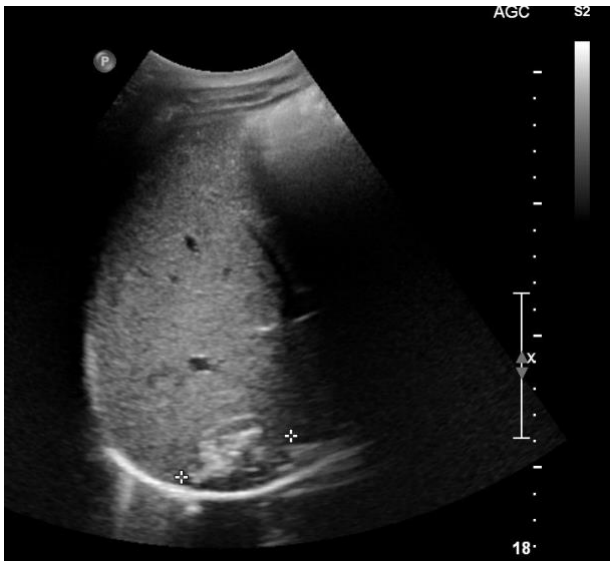

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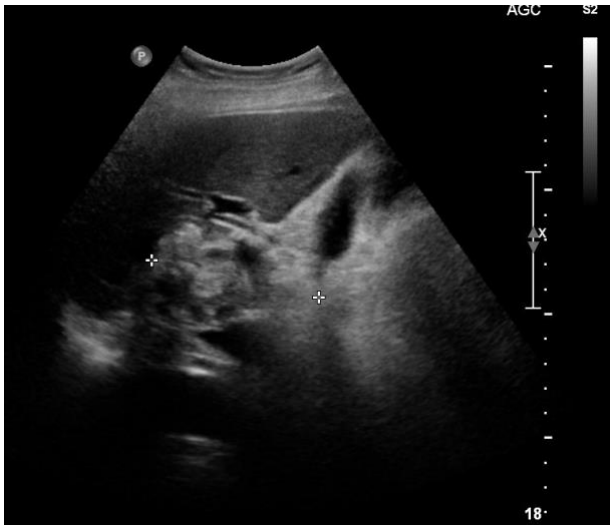

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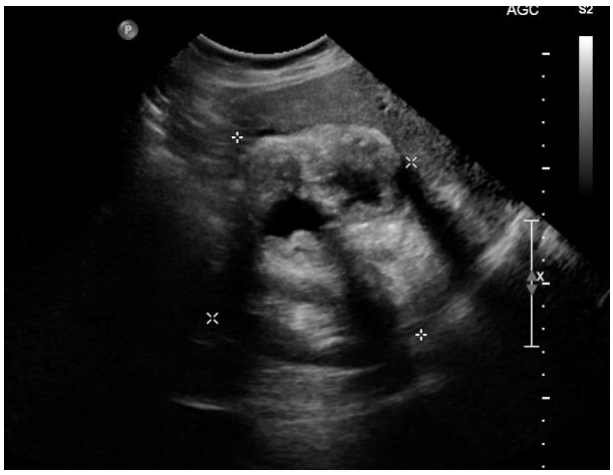

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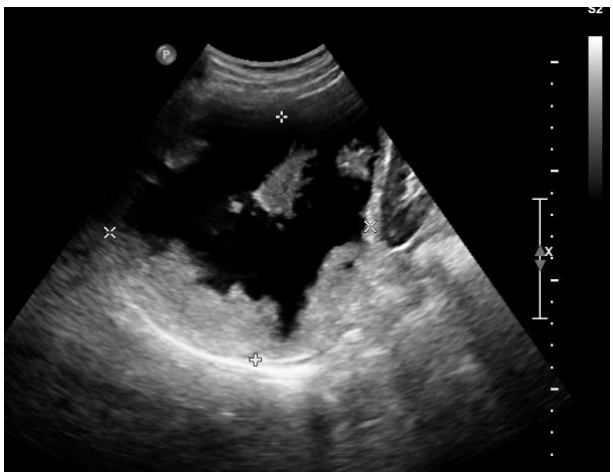

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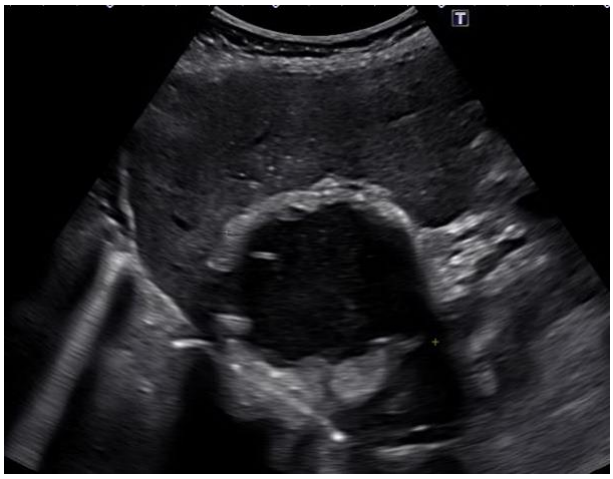

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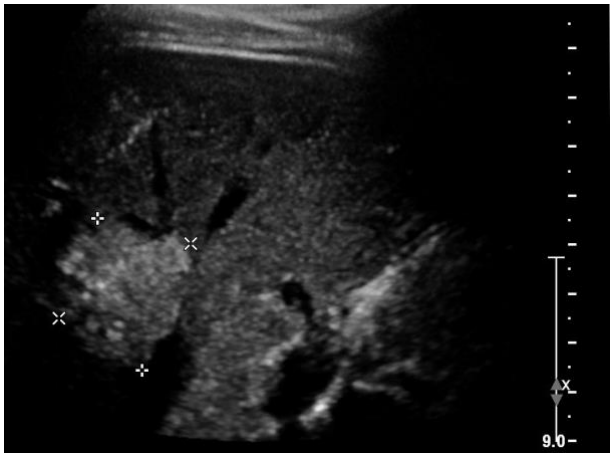

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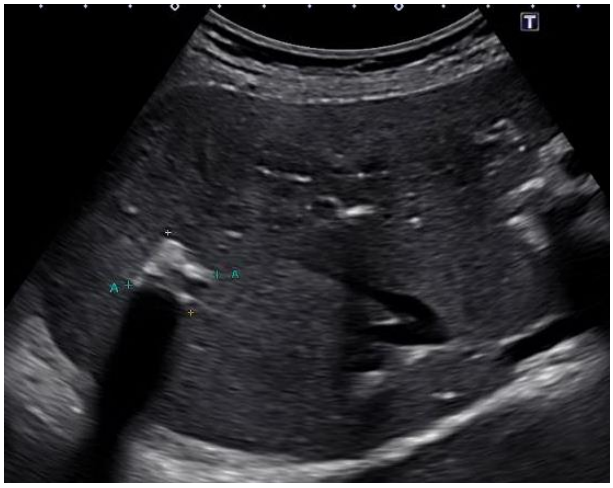

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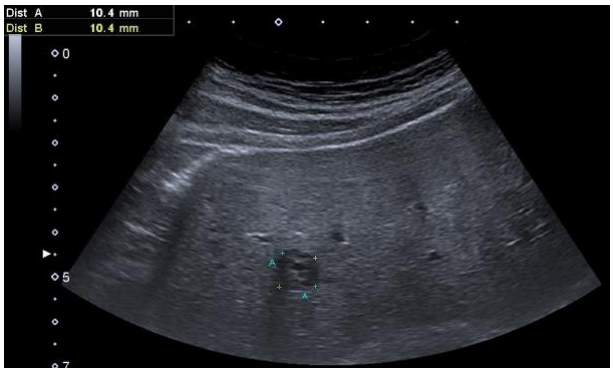

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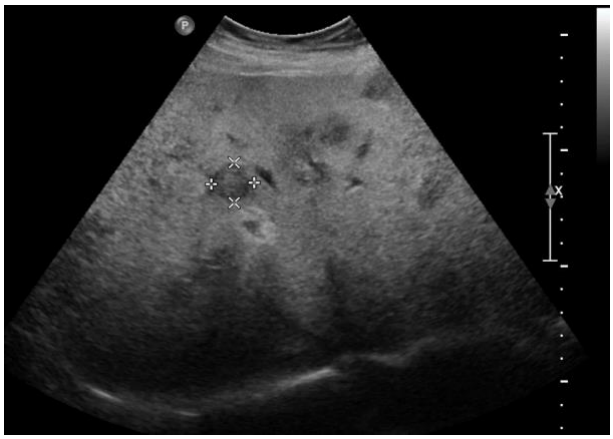

Other imaging modalities

CT represents the imaging method of choice among the currently available diagnostic methods, especially for heavily calcified lesions (86, 89). [18F]-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) is a sensitive and specific tool that uses [18F]-fluorodesoxyglucose (18F-FDG) metabolism to estimate the metabolic activity of hepatic AE lesions; FDG enrichment around AE lesions is interpreted as larval metabolic activity (90). Assessment of the vascularisation of hepatic AE lesions with contrast-enhanced ultrasound (CEUS) correlates with their metabolic activity assessed using combined ^{18}F-FDG-PET-CT and can better delineate the spatial extent of hepatic AE lesions. Lesions characterized by vesicles and small cysts show a high degree of correlation between ^{18}F-FDG-PET and CEUS findings (91).

In 2003 Kodama et al. (92) introduced a five part classification (type 1 to type 5 lesions) for assessing hepatic AE with MRI. Type 1 (multiple, small, round cysts without a solid component)

and Type 2 (multiple, small, round cysts with a solid component) lesions are supposed to represent the most "active" lesions, and correlation between micro-cysts on MRI with hepatic AE with elevated FDG-metabolism in PET has been shown (93).

The *Echinococcus multilocularis* Ulm Classification for Computed Tomography (EMUC-CT) presented by Graeter in 2016 (94) provides a basis for the systematic description of hepatic lesions caused by *E. multilocularis*, thus improving diagnostic investigation and allowing a direct comparison of CT findings. It distinguishes five primary morphological types. Type I: diffuse infiltrating; Type II: primarily circumscribed tumour-like; Type III: primarily cystoid (IIIa – intermediate, IIIb – widespread); Type IV: small cystoid/metastatic; Type V: mainly calcified. The subcriteria 'with/without cystoid portion' for types I and II, and 'with/without solid portion at the edge' for type III, additionally characterise the primary morphologies. With the exception of type V 'mainly calcified', each primary morphological type is allocated to one of six separately defined calcification patterns, allowing a comprehensive description of the lesion. The calcification pattern 'with a central calcification' is a feature only of type IV. The EMUC-CT has established the term 'cystoid' for the confluent hypodense areas of the lesions. The picture of a "normal" cyst is not seen in AE, but has to be carefully separated from small "micro-cysts" which represent the proliferating part of the larval tissue, the "alveoli" in alveolar echinococcosis. Using the delayed PET scan, measuring the FDG metabolism after 3 hours (instead of 1) increased the sensitivity for active parasitic lesions (95)**.** In active AE lesions, a diffusion restriction in diffusion weighted MRI has been shown and is useful in determining the activity of the disease (96). In Austria, the first patients were investigated by PET-MRI, but its value in AE needs further evaluation (97). In addition to the infiltrative growth of the larval tissue in AE, there can also be metastatic involvement of other organs or lymph nodes (98) and this is reflected in the PNM classification introduced by the WHO-IWGE. Location and size of the larval lesions at diagnosis are described using the PNM classification (99), a modification of the TNM classification for malignant tumors (P, parasitic mass in the liver; N, involvement of neighbouring organs; M, metastases). PNM staging can be best achieved by combined PET-CT scan from head to lower limb [Figure 17].

Figure 20 Other imaging modalities (CT, MRI, PET CT) for AE. Images a-k showing different imaging modalities with typical appearance of parasitic liver lesions of hepatic

AE. CT scan showing different aspects of typical AE lesions with calcification or pseudocystic appearance (a). [F18] FDG PET CT with typical periparasitical FDG uptake surrounding a zone with non- FDG metabolism (b). MRI T1-WI and T2-WI showing liver lesions with cystoid aspect "microcysts" (c). Intraoperative surgery is shown as well (I).

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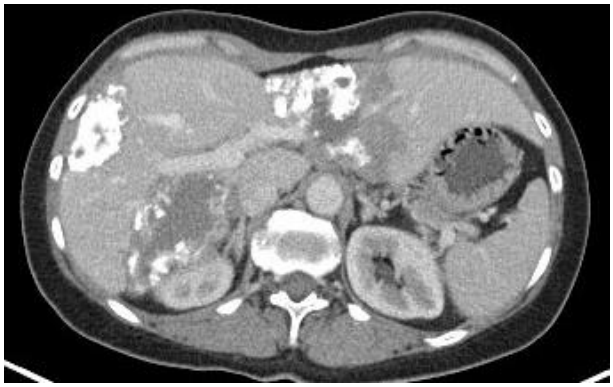

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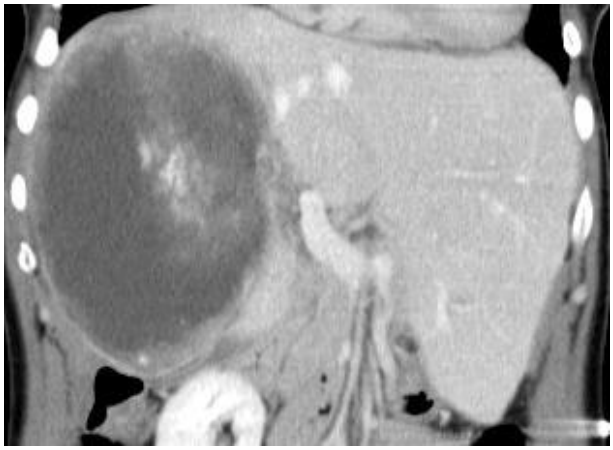

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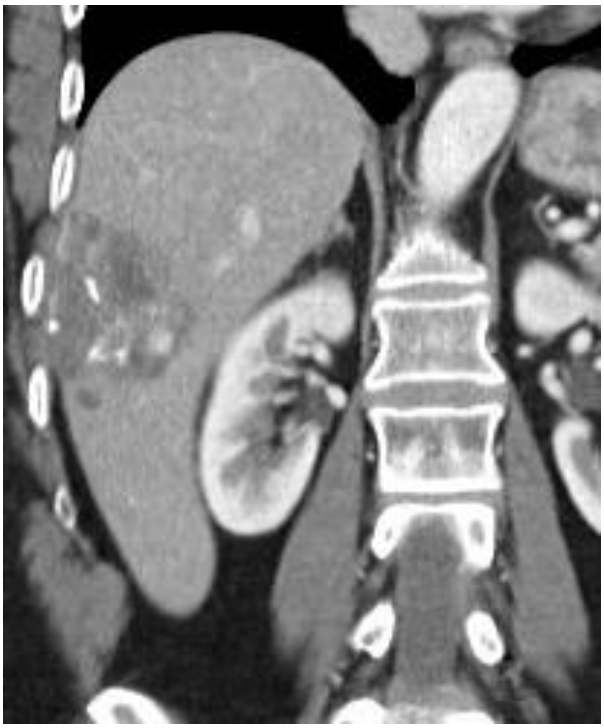

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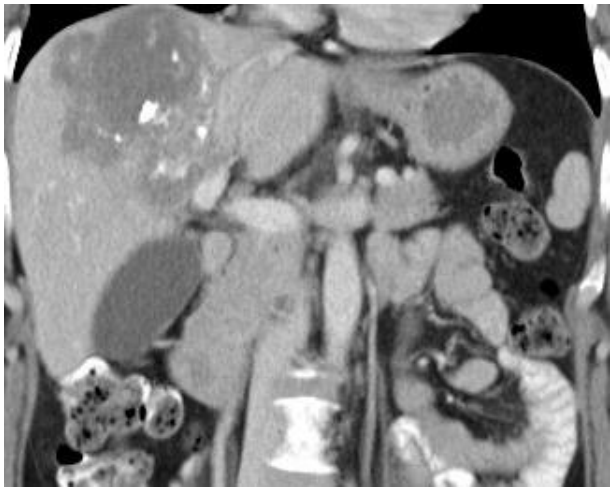

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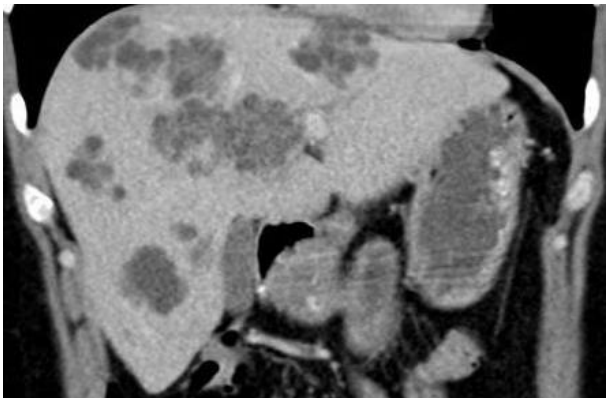

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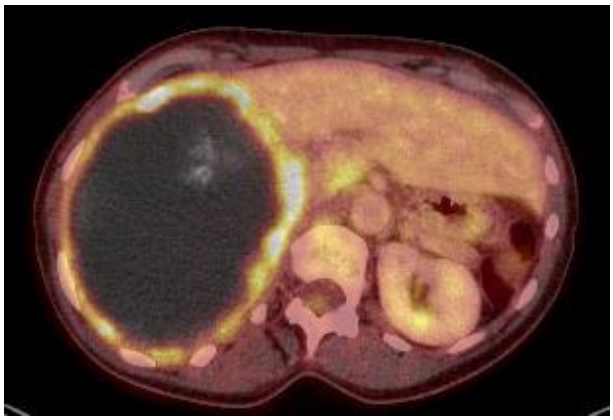

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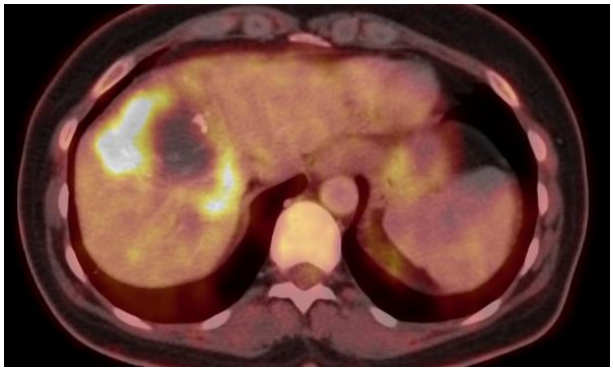

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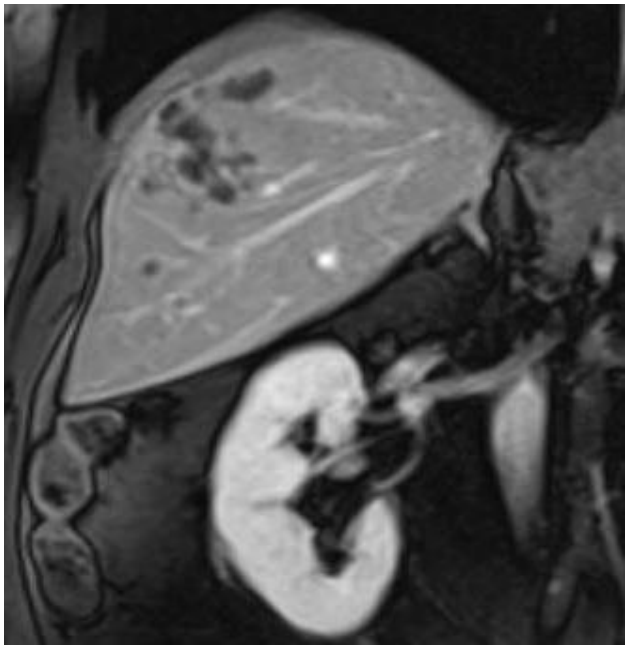

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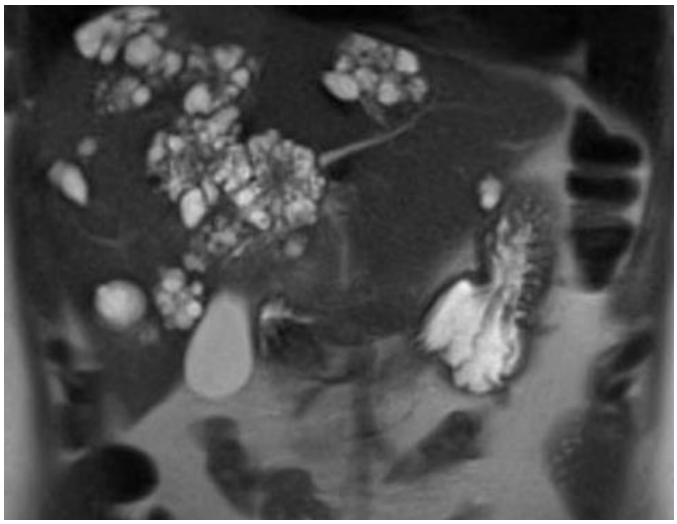

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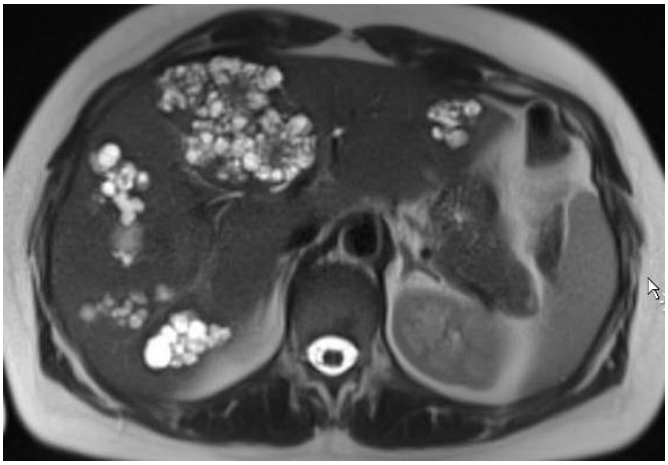

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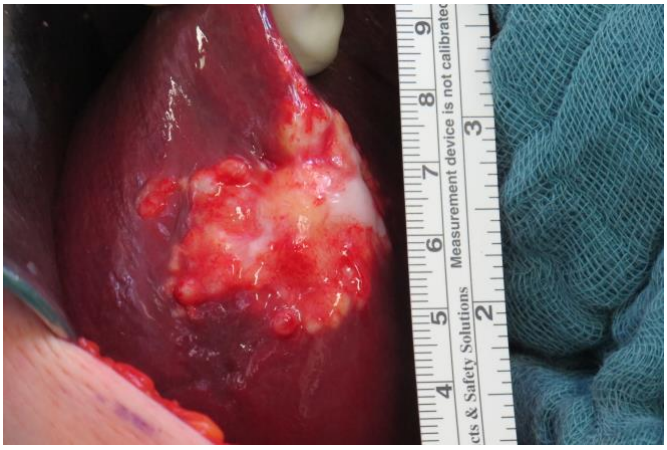
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cts & Safety Solutions

Other organs

Extrahepatic AE manifestations should be sought, therefore staging as for malignancies is recommended, with at least CT- scan of thorax and head, as recommended by the WHO-IWGE. Lungs can be involved either by direct infiltration when the larval mass grows through the diaphragm or by metastasis, the latter often appearing as multiple small nodules, often partially calcified (70, 73). Brain lesions often show surrounding edema. Bone lesions in AE typically involve the spine, often by continuous growth of hepatic lesions (100). Other primarily extrahepatic AE manifestations are reported with involvement of the retroperitoneum and spleen (101).

Differential diagnosis

The differential diagnosis of AE includes all primary and secondary liver malignancies with a morphological pattern similar to AE. Cholangiocellular carcinoma or Klatskin-like-tumour are examples. Small cystoid lesions might appear as liver metastasis and also liver haemangioma can have a similar appearance, but usually can be distinguished. Especially for pseudocystic lesions, cystic echinococcosis is mentioned as differential diagnosis, and bacterial or amoebic liver abscesses can have a similar morphological, but a different clinical appearance. However, AE, as well as other hepatic incidentalomas, such as regenerative nodules, and angiomyolipomas remain a diagnostic challenge for all imaging modalities. Frequently a final diagnosis is only made upon histopathological examination of material obtained with liver biopsy or resection.

Treatment

The treatment of AE requires a multidisciplinary approach. Treatment should follow the WHO-IWGE recommendations (75). The backbone of AE treatment is benzimidazole (BMZ) - therapy, with albendazole (ABZ) as the most effective drug. Benzimidazoles are recommended for all patients with probable or confirmed AE. Mebendazole (MBZ) seems less effective but is sometimes used in case of ABZ-associated liver toxicity as a good alternative. Despite the manufacturers recommendation for cyclic medical treatment, the continuous BMZ-therapy is clearly recommended by the WHO-IWGE (102).

The introduction of benzimidazole treatment in the 1980's is called a revolution in the treatment of human echinococcosis. Long-term application is necessary for non-resectable AE, because BMZ are effective, but not able to kill the parasites in most patients. In all patients receiving BMZ, either ABZ or MBZ, monitoring for toxicity is mandatory. Blood chemistry, hematology and BMZ plasma levels should be monitored during treatment. Treatment effectiveness should be also monitored by imaging and serological/immunological tests. The FDG-PET has been validated for the follow-up evaluation of parasitic activity (103). The start of specific therapy early after diagnosis is relevant for patients outcome (73).

Radical surgery, aiming to completely remove all lesions including satellite (metastatic) lesions followed by a 2-year BMZ administration is the standard treatment aiming for cure, but the majority of patients are inoperable and need long-term BMZ-treatment (73). After liver resection, surgical specimens should be graded as complete resection (R0), or incomplete or palliative resection (R1: microscopic residuals at resection margins; R2: macroscopic residuals). Adjuvant post-surgical medical treatment is recommended even after complete resection (R0) for at least at least 2 years using ABZ (2 x 400 mg daily) (104, 105). Recent data show good cure rates when resection margin is > 1mm and support the indication for adjuvant BMZ treatment after surgery (106, 107). Palliative surgery for parasitic mass-reduction is not recommended and often results in late biliary complications (108, 109). Evidence for initiating preoperative ABZ treatment is lacking, but the experience at our center in Ulm shows remarkable regression of AE liver lesions under strict BMZ treatment, allowing complete surgical resection after months or even years. Cure can only be assumed, when parasitic lesions remain undetectable after surgery and after long-term follow up, recommended to be for at least 10 years after surgery (110). Structured treatment interruption can be a goal for patients also with non-resectable lesions, but strict preconditions should be used and careful monitoring in an experienced center is necessary (73, 111, 112). In patients with no surgical option, ABZ treatment is recommended indefinitely. Praziquantel has no effect on human AE. Case series from China with ex-vivo liver resection and auto transplantation have been published. Orthotopic liver transplantation is rarely used in Europe. It is important that ABZ-treatment is given early after surgery, especially after liver-transplantation, to avoid -relapse resulting from immunosuppressive treatment (113, 114).

Prognosis and concluding remarks

The prognosis of AE depends on the localization of the lesion. Involvement of hilar structures is a poor prognostic sign. Age and comorbidity of the patient also have an impact. The treatment response in human AE with long- term benzimidazol treatment is good, with ~ 90% long term survival and good quality of life [(72-74)]. Biliary complications are common in AE and occur in 10-30 % of patients diagnosed with AE, and especially late biliary complications (>3 years of treatment) are associated with high mortality in human AE [(126, 130, 131)].
Management of AE is complex and based on expert opinion; prospective studies to guide evidence-based therapy are lacking. A multidisciplinary approach in specialized centers is recommended. Human AE is increasing and spreading to new geographical areas. Additionally human AE as an opportunistic infection in patients with immunosuppressive treatment has to be taken in account and seems to have increased in recent years.
Ultrasound is important as a screening tool, due to it is widespread use. Therefore, the possible appearance of AE lesions should be known by all ultrasound users and the further steps in AE diagnostic (echinococcosis serology and further imaging like CT and MRI) should be known as well. Early diagnosis of human AE is shown to influence the cure rates, by detecting parasitic lesions when local resectable.

Schistosomiasis

Human schistosomiasis, also known as “bilharziosis”, is a highly prevalent disease caused by the trematode worms of the genus *Schistosoma*. *S. mansoni*, *S. haematobium* and *S. japonicum* are the most common species affecting humans, whereas *S. mekongi S. intercalatum* and *S. guineensis* have been described more recently. More than 230 million people are estimated to be infected with *Schistosoma spp.*, and over 20 million suffer from severe disease, with an estimated mortality of 15,000–20,000 deaths per year.
Eighty five percent (85%) of cases occur in Africa, where prevalence can exceed 50% in hyperendemic communities. *S. haematobium* is responsible for approximately 60% of all infections, with approximately 120 million people infected in Africa and the Middle East. Recently, autochthonous transmission of *S. haematobium* infection has been observed in South Eastern Corsica, France (115). *S. mansoni*, which is endemic in Africa, the Middle East,

Latin America and the Caribbean, infects an estimated 67 million people. *S. japonicum* is present in China and Southeast Asia, where it infects an estimated 1 million people (116).
The other four species have a more localised distribution; *S. mekongi* in Cambodia and Laos, *S. malayensis* in Malaysia, *S. intercalatum* and *S. guineensis* in parts of Central and West Africa. Humans are the most important definitive hosts for *S. mansoni*, *S. haematobium* and *S. intercalatum*, but rodents, baboons and monkeys can be infected as well. *S. japonicum* and *S.mekongi* are the cause of zoonotic diseases with various animals including rodents (*S. japonicum*), dogs (*S. mekongi* and *S. japonicum*) and cats, goats, horses, pigs and water buffalos (*S. japonicum*) as possible definitive hosts (117).
Adult worms reside in the mesenteric veins (*S. mansoni* and *S. japonicum*) and in the venules of the bladder (*S. haematobium*). Here the females release eggs that move progressively towards the lumen of the intestine or the bladder and ureters, and are eliminated with faeces or urine. In the water, the eggs hatch and release the first stage larva “miracidium” which actively swims to and penetrates a suitable snail. In the intermediate host, the larva undergoes multiplication and maturation to the cercarial stage. The cercariae are then released from the snail and use their bifurcated tails to swim until they reach the skin of the definitive host. Penetrating the skin, the larvae lose the tail to become schistosomulae. These juvenile worms then migrate through the host’s body until they reach their final destination in the portal and perivesical veins, depending on the species, and begin to produce eggs approximately 2 months after infection. Embryonated egg are released with faeces or urines; contamination of freshwater with faeces and urine containing worm eggs perpetuates the parasite cycle.

Clinical presentation

Acute infection in travellers to endemic areas can present with an acute cercarial dermatitis immediately after exposure (“swimmer’s itch”) and an acute hypereosinophilic febrile syndrome after several weeks (“Katayama fever”), characterized by fever, chills, gastrointestinal symptoms, hepatosplenomegaly and eosinophilia. In inhabitants of endemic areas, the acute stage is often asymptomatic or oligo-symptomatic and patients are usually seen in the chronic stage of the disease.
Chronic pathology is caused by a granulomatous inflammatory reaction to eggs that are trapped in the intestinal wall and in the liver (for *S. mansoni, S. japonicum, S. intercalatum* and

S. guineensis) or in the wall of the ureters and bladder (for *S. haematobium*). This inflammation eventually leads to fibrosis.

Hepatic and intestinal schistosomiasis

Symptoms are non-specific, with abdominal discomfort, diarrhoea and sometimes blood in stools. Later, portal hypertension develops and sudden life-threatening haemorrhage can occur as a result of the rupture of gastro-oesophageal varices, which is the most common complication of portal fibrosis. Generally, hepatic function is preserved. Hepatic complications are especially severe in patients with associated liver damage due to hepatitis B, C and/or D virus co-infection or nutritional factors. Other complications include portal vein thrombosis, which in turn leads to the cavernous transformation of the collateral veins, and cardiopulmonary schistosomiasis that occurs when ova reach the caval veins through collateral circulation. Ectopic schistosomiasis as a result of erroneous migration of worm pairs can occur in any location including the central nervous system, appendix or breast in females.

Urogenital schistosomiasis

The most common sign of urogenital schistosomiasis is the presence of blood in urine. Renal impairment can follow the development of hydronephrosis due to fibrosis and strictures of the ureters. Genital involvement can develop in both sexes, and the development squamous cell bladder carcinoma has been related to urinary schistosomiasis. The effects of schistosomiasis during pregnancy include placental involvement and anaemia due to chronic blood loss through urine or stool, which contribute to premature delivery and impaired foetal growth.

Diagnosis

Definitive diagnosis relies on serology and the identification of eggs in stool, urine, seminal fluid or cervical or rectal biopsies. Serology can be false negative during the pre-patent period in the acute stage of the disease. Antibodies persist for years following exposure, which is not helpful in follow-up or in patients from endemic areas (116) but test detecting antigens seem more promising. Egg excretion does not directly correlate with the actual severity of organ involvement.

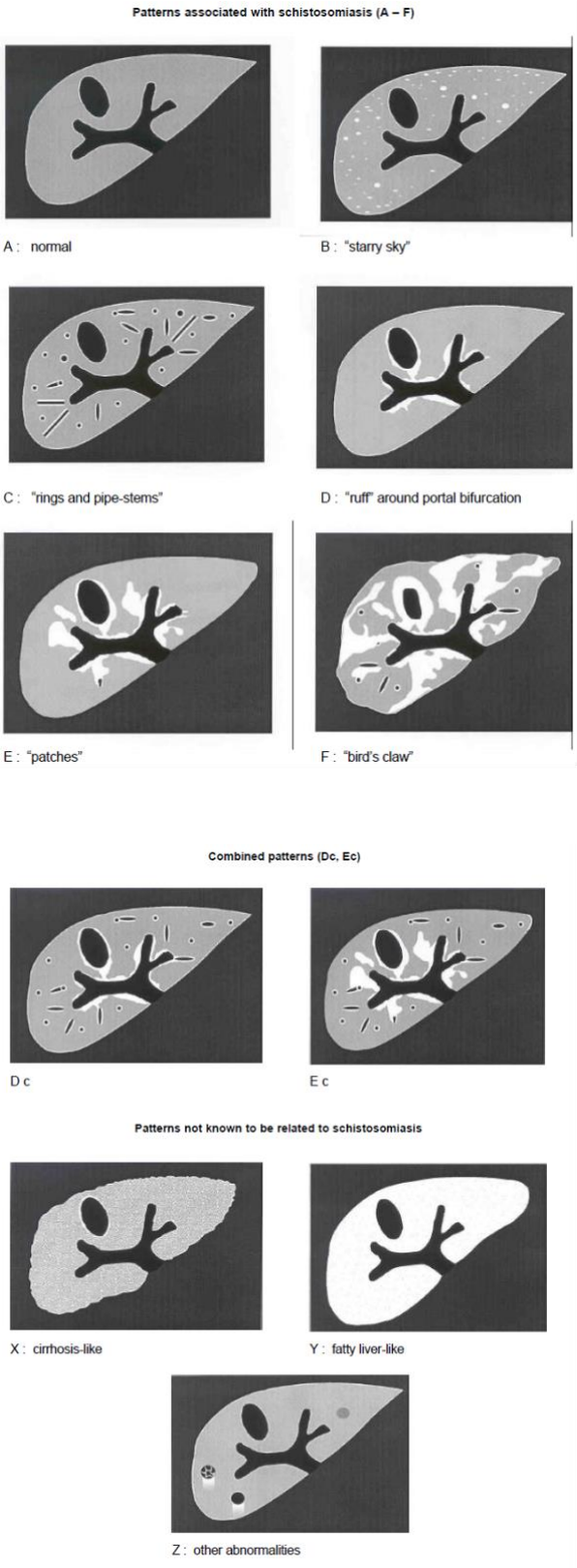
Ultrasound

Liver

Ultrasound is the first-line imaging technique used in the diagnosis and staging of schistosomiasis and, in the follow-up, to detect improvement following therapy or the onset of complications. During acute schistosomiasis, non-specific hepatosplenomegaly with enlargement of the hilar lymph nodes can be observed. These can show an unusual structure, with a hypoechoic halo surrounding a moderately hyperechoic centre (118, 119).

Ultrasound readily detects portal fibrosis and thickening of the walls of portal branches, splenomegaly, and portal hypertension in chronic hepatosplenic schistosomiasis. Portal vein thrombosis and echogenic foci in the spleen can also be observed. Portal fibrosis, also named "Symmer's pipe-stem fibrosis" can be classified into six progressive patterns (118-121) [Figure 21]. These can progress from a "starry sky" appearance, with diffuse echogenic foci, to an increased wall thickness of the portal vein branches: ring-echoes and pipe-stem appearance, echogenic "ruff" around the main portal branches, up to patches and bands that extend from the main portal vein to the liver surface, which induce a retraction of the surface itself. This classification for *S. mansoni* was proposed at a WHO conference in Niamey, Niger in 1996 and subsequently reviewed during a meeting held in Belo Horizonte, Brazil (120).

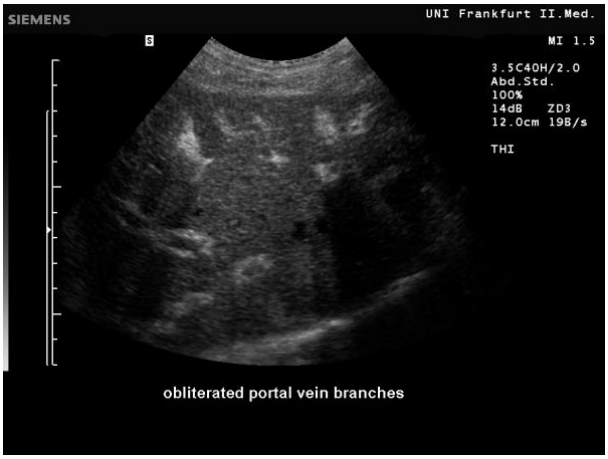
Figure 21 Niamey Ultrasound classification for *S. mansoni* liver involvement.



The liver may be enlarged, normal or shrunken, depending on the stage of liver fibrosis [Figure 22]. Signs of portal hypertension include an increased diameter of the portal vein, presence of varices of the collateral veins, recanalization of the paraumbilical vein and presence of ascites. The wall of the gallbladder can be thickened in *S. mansoni* infection, with occasional external echogenic protrusions (122, 123). In *S. japonicum* infection, a peculiar fibrotic pattern of the liver is observed, with a "network", "fish-scale" or "tortoise-shell" appearance, whereas gallbladder involvement is uncommon [Figure 23].

Figure 22 Schistosomiasis with typical obliteration of portal vein branches in B-mode (a), Power Doppler (b) and continuous Doppler spectral analysis. Velocities below 12 cm/sec indicate portal hypertension (124).

a



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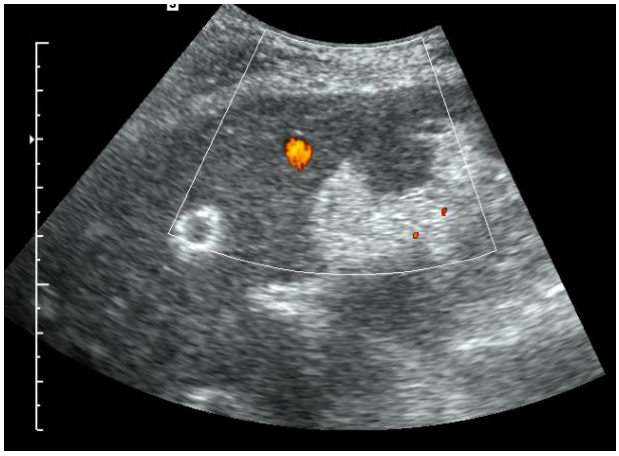

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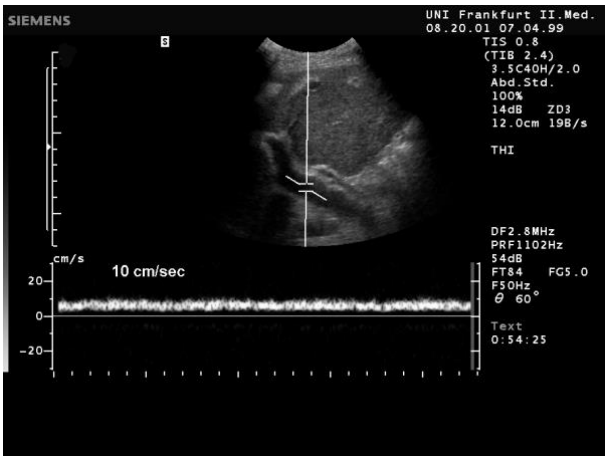
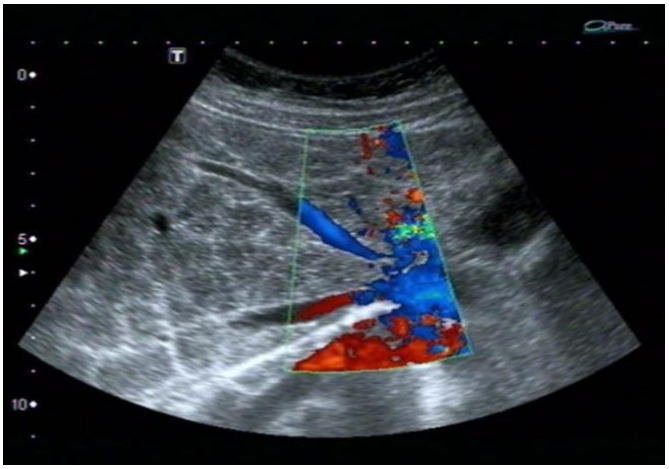


Figure 23 Network-like appearance of *S. japonicum* infection of the liver.



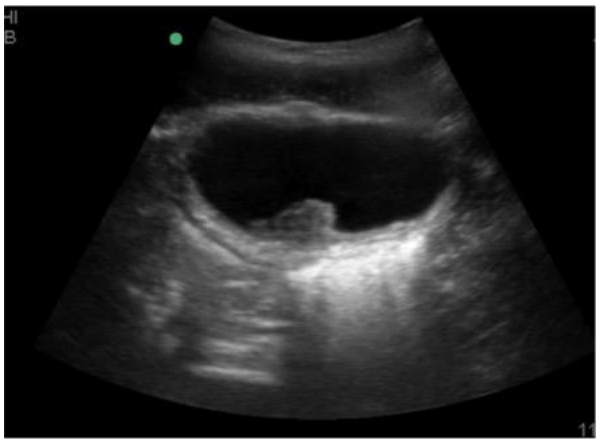
Other organs

In urinary schistosomiasis, ultrasound can show bladder-shape abnormalities, thickening of the wall [Figure 24], presence of intravesical masses, hydronephrosis, and dilation of the ureters. Calcification of the bladder wall is almost pathognomonic, but rarely identified on ultrasound. Ultrasound findings of genital pathology include ulcerations, papillomata, salpingitis, adnexal and pelvic masses, vagino-vesical fistulae, increased uterus volume, hyperechoic patches and pelvic masses in females and scrotal fibrotic masses, fibrotic lesions

of the prostate and seminal vesicles and hydrocoele in males. Schistosomiasis in mothers can result in impaired foetal growth (125).

Figure 24 Schistosomiasis. Asymmetric urinary bladder thickening is typical (a), sometimes with signs of inflammation and hypervascularity (b, arrow).

a



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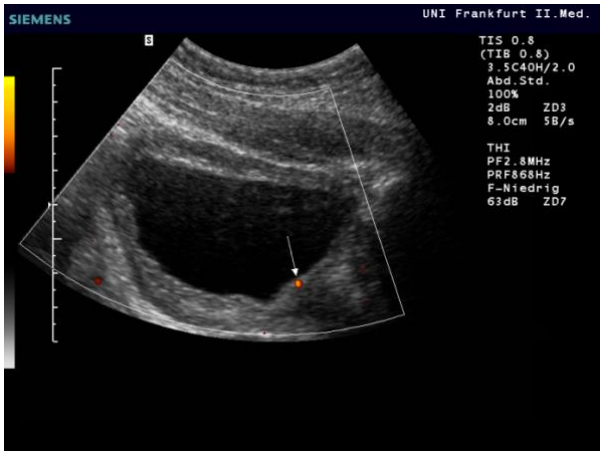


Treatment

Praziquantel is the treatment of choice for schistosomiasis, but it is only effective on adult worms; therefore, the treatment should be repeated after 2–4 weeks to target juvenile forms that are not yet sensitive to the first dose. After therapy, antibodies remain detectable for years, but ultrasound can detect a slow improvement of the organ abnormalities over months,

especially in urinary schistosomiasis, up to their complete resolution depending on the stage and whether re-infection has occurred (121, 126). For proliferative bladder lesions, ultrasound results correlate well with cystoscopy findings; lesions regress within 6 months after successful treatment; invasive exams are indicated in case of persistence.

Melioidosis

Introduction

Burkholderia pseudomallei is an environmental aerobic gram-negative bacterium and the causative agent of melioidosis. The disease affects humans and a wide range of animals and, after inoculation, inhalation or ingestion of the bacteria, the infection can result in a varied clinical picture. The disease is hallmarked by a variable incubation period, from 24 hours to many years, although most patients present relatively soon after exposure. Disease manifestation may be acute or chronic or relapse after long periods of latency. This has led to the nickname ‘tropical time bomb‘. In this era of increasing travel and migration, it should be remembered that a fever of unknown origin can be due to melioidosis even if the stay in an endemic region dates back many years.

Epidemiology

The disease is highly endemic in Southeast Asia and northern Australia, while it is not endemic in temperate climates. A modelling study from 2016 estimated an incidence of 165.000 human cases/year worldwide with a case fatality rate of 54% (~89.000 deaths/year) (127). Of the patients who survive acute melioidosis, 5-28% experience recurrent infection (128). Since the diversity of clinical manifestations needs the isolation and identification of the causative organism for a definitive diagnosis, and the population at greatest risk within endemic areas rarely have access to appropriate health care, the disease is probably far more widespread in the tropics and has probably been grossly underestimated (129). The reported expanding global incidence and distribution reflects the increasing availability of diagnostics, the increase of travelling, as well as an increasing prevalence of underlying diseases that predispose to melioidosis and more frequent severe weather events.

Risk factors

The main risk factors for symptomatic and/or severe disease are: diabetes mellitus, excessive alcohol consumption, chronic renal failure, glucocorticoid use (frequently misused as self-medication in the developing world), leukaemia and lymphoma, chronic pulmonary disease (COPD or cystic fibrosis), congestive heart failure, neoplasms, and occupation as a rice farmer (higher risk of exposure through frequent skin cuts and abrasions). As yet there is no vaccination available, so the only preventive measures available involve reducing exposure wherever possible, for example by minimising direct contact with soil and surface water in endemic regions during the rainy season, particularly amongst those with the above-mentioned risk factors.

Pathogenesis

The pathogenesis is important for the understanding of the clinical manifestations. *B. pseudomallei* can invade, survive, and replicate in a range of phagocytic and nonphagocytic cells. The bacteria can manipulate the host's immune responses and signalling pathways to escape surveillance (128). A distinctive feature of *B. pseudomallei* infection is the formation of multi-nucleated giant cells, which results from cell membrane fusion between infected and uninfected host cells (130, 131). This enables bacterial cell-to-cell spread while avoiding detection by host immunity, and which ultimately contributes to the formation of abscesses.

Clinical presentation

Fever is the most frequent, non-specific symptom, and in approximately 21% of cases the overwhelming picture is that of septic shock (132). As mentioned before, with an overall case fatality rate of up to 40% (SE Asia) and a requirement for specific treatment, melioidosis is an important differential diagnosis in patients with fever and sepsis who have stayed in endemic areas. After inhalation of the organism, the pulmonary manifestations of melioidosis may present as pneumonia, primary lung abscess or multi-focal secondary lung involvement in the setting of sepsis (so-called 'blood-borne pneumonia'). The organism also frequently causes skin or soft tissue abscesses, often at the site of initial inoculation. After haematogenous dissemination theoretically any organ can be affected, but those most frequently involved are

liver, spleen, skeletal muscles and prostate. Eye infections may occur and are usually destructive. Central nervous system involvement is generally rare, although there are geographical differences, with the highest incidence of neurological melioidosis being reported from Australia (approximately 2.6% of cases) (132).

Diagnosis

Diagnosis is based on clinical features and imaging but can only be confirmed by bacterial culture. The isolation and identification of *B. pseudomallei* from blood, sputum, urine, pus, tissues, and wound exudates is the gold standard of diagnostics, although culture is not always available in endemic rural settings. Even when laboratory diagnosis is available, *B. pseudomallei* may be misidentified or reported as "*Pseudomonas* spp" (133). Unfortunately, current serological tests lack sensitivity and specificity and may be misleading, although newer tests using better-defined antigens are being developed. Tests for the detection of antigens directly in patient samples are also under evaluation and show promising results, but PCR is relatively insensitive, especially when performed on blood (128). Early diagnosis and prompt treatment are essential because of the high mortality in septicaemic cases. As laboratory diagnostics are not always available, imaging techniques can play a major role in the diagnostic approach.

Depending on the affected organs, the following features can be detected by ultrasound:

- Lung: abscesses, rarely pleural empyema, pleural effusions
- Head and neck: suppurative parotitis and abscesses, particularly in children in SE Asia (134), neck abscess as a differential diagnosis of tuberculous cold abscess or lymphadenitis
- Cardiovascular (rare): pericarditis with effusion, focal abscesses can lead to myocarditis, mycotic aneurysms
- Cutaneous: cellulitis, subcutaneous abscess, ulcers, rarely necrotizing fasciitis
- Visceral organs (affected in~1/3 of cases): abscesses are most common in spleen and liver, rarely in pancreas. Abscesses of kidneys and prostate gland are probably under-detected (found in 21% of men with melioidosis in Australia, predilection for the peripheral zone resulting from the haematogenous spread of *B. pseudomallei* (135))

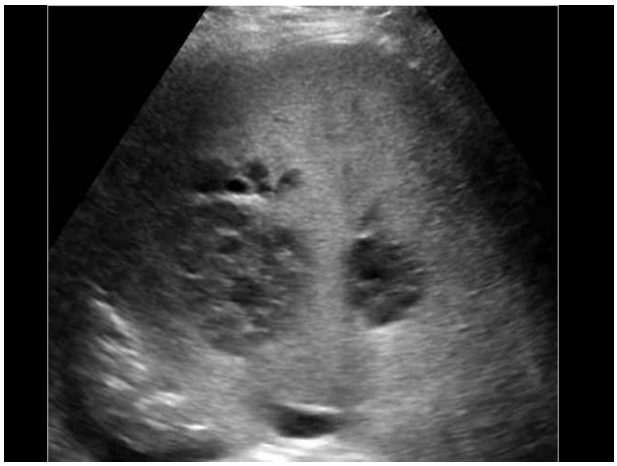
Possible forms of abscesses in visceral organs include:

- Multiple micro-abscesses
- Abscess with satellite abscesses
- Honeycomb type abscesses, usually larger abscesses (> 2 cm)
- Necklace sign abscesses, that is presence of smaller, peripheral abscesses around a larger one (feature at the margin of honeycomb abscesses, usually > 5 cm)

For most of the affected sites, the findings on US and also on CT are non-specific for melioidosis. However, multiple hypoechoic/hypodense, multiseptated, multiloculated lesions in the liver, together with splenic abscesses, are strongly suggestive of melioidosis in at-risk patients who reside in endemic areas (136). The spleen is the most commonly affected organ and the detection of splenic abscesses alone is suggestive of melioidosis, especially in those patients with comorbid diseases or in those who present with fever of unknown origin, abdominal pain or discomfort (137). Usually the splenic abscesses are small (0.5-1.5 cm), single or multiple, multi-loculated, subcapsular collections with or without enlargement of the spleen (138). For the liver abscesses, the honeycomb pattern appears as an imaging marker with a good sensitivity and specificity, increasing with the size of the abscess (139). The necklace sign, concurrent hepatic and splenic involvement, multiple abscesses and residence in an endemic area, can serve as predictors for melioidosis, with the highest sensitivity and specificity ascribed to the necklace sign (140) [Figure 25]. Multiloculated liver lesions are not typical in amoebic or other liver abscesses (141).

Figure 25 Ultrasound (a) and CT (b) of melioidosis liver abscesses. Multiple hypoechoic/hypodense, multiseptated, multiloculated lesions in the liver, together with splenic abscesses, are strongly suggestive of melioidosis in at-risk patients who reside in areas of endemicity [courtesy of Prof. Nittaya Chamadol, Khon Kaen University, Thailand].

a



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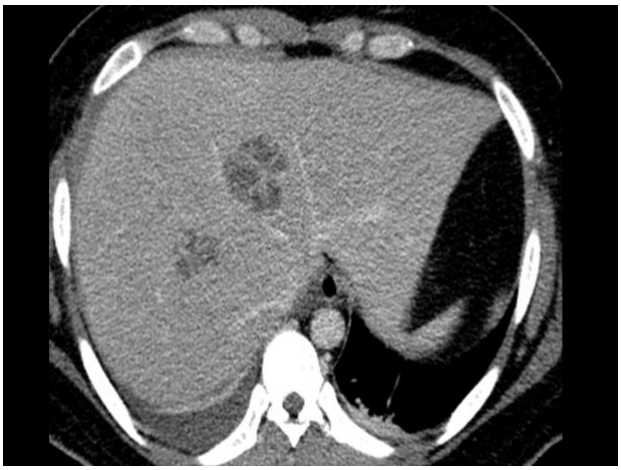


Treatment

A delay in diagnosis can be fatal, since empirical antibiotic regimens used for bacterial sepsis often do not provide adequate coverage for *B. pseudomallei*, which is intrinsically resistant to many antimicrobials. The therapy encompasses an acute phase of treatment for at least 10 days (and often longer), followed by an eradication phase for 12-20 weeks to reduce the risk of relapse. Regimens for the acute phase should contain ceftazidime or a carbapenem. Some physicians add co-trimoxazole in patients with deep-seated abscesses or CNS disease although it is not yet clear whether combinations of treatments in the early phase improve outcomes. Trimethoprim-sulphamethoxazole is the treatment of choice in the eradication phase, except when there is resistance or intolerance, in which case amoxicillin-clavulanate may be used (142).

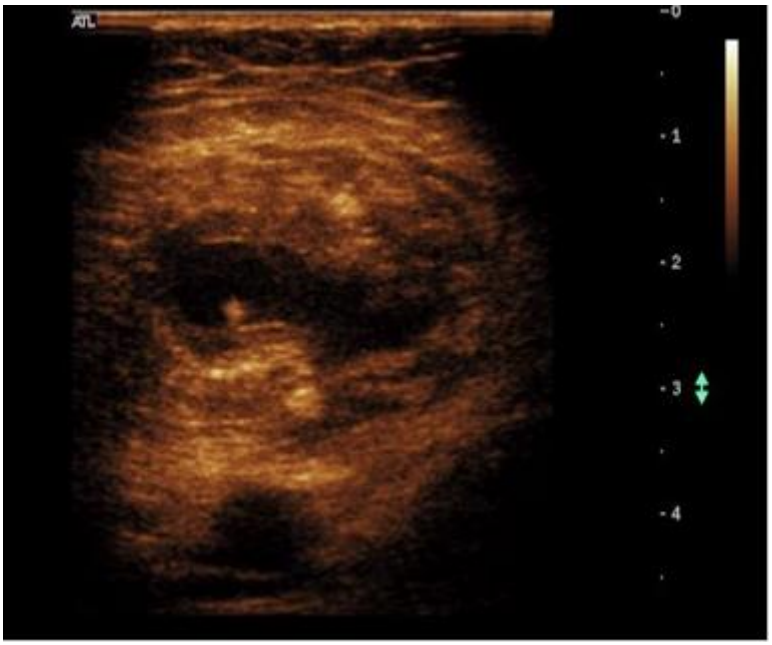
Note: The high mortality rate, extensive distribution in the environment in endemic areas, intrinsic resistance to many antibiotics, lack of a vaccine, and the potential for aerosol spread led to this organism being classified as a category B bioterrorism agent by the Centers for Disease Control and Prevention (143, 144).

Parasitic (worm) diseases with very rare ultrasound findings

Herewith we present parasitic diseases with very rare ultrasound findings, e.g., taenia solium cysticercus [Figure 26] and the Guinea worm Dracunculus medinensis [Figure 27]. Interpretation of such ultrasound findings can only be performed knowing the clinical circumstances. Other illustrating examples from the reader of this chapter are warmly welcome.

Figure 26 **Taenia solium cysticercus. Cysticerosis is the infection with the larval stage of the pork tapeworm *Taenia solium.* In humans, cysts are generally located in the central nervous system (NCC) but occasionally they can be found in other organs like eyes, hearth, lung, liver, muscles and skin. The cyst detected by ultrasound in this figures contains a small hyperechoic body (protoscolex), this finding is pathognomonic for NCC. The diagnosis of NCC is made by combined criteria, which include serology (EITB, enzyme-linked immunoelectrotransfer blot assay) and brain imaging (145). NCC is a neglected complex disease whose diagnosis and treatment needs high expertise. Taenia solium cysticercus in muscle tissue (a), the gastrocnemius muscle (b) in the axillary wall (c) and ocular muscle (d) are shown.**

a



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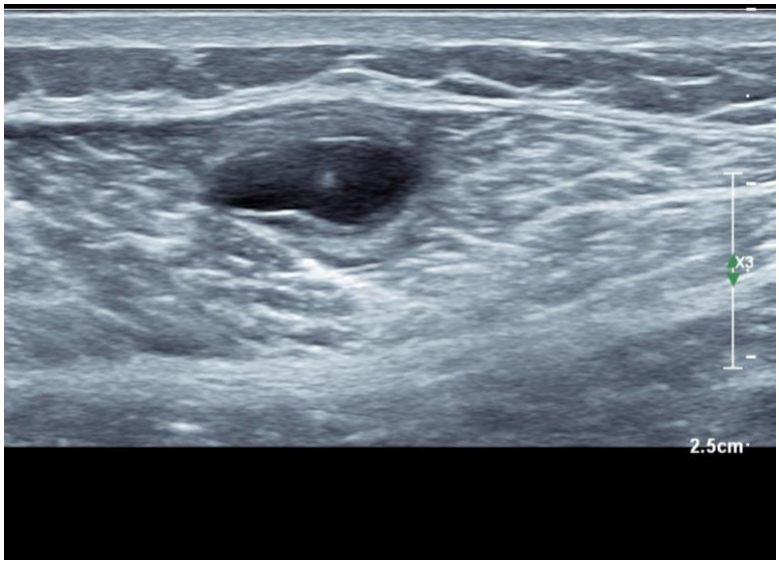

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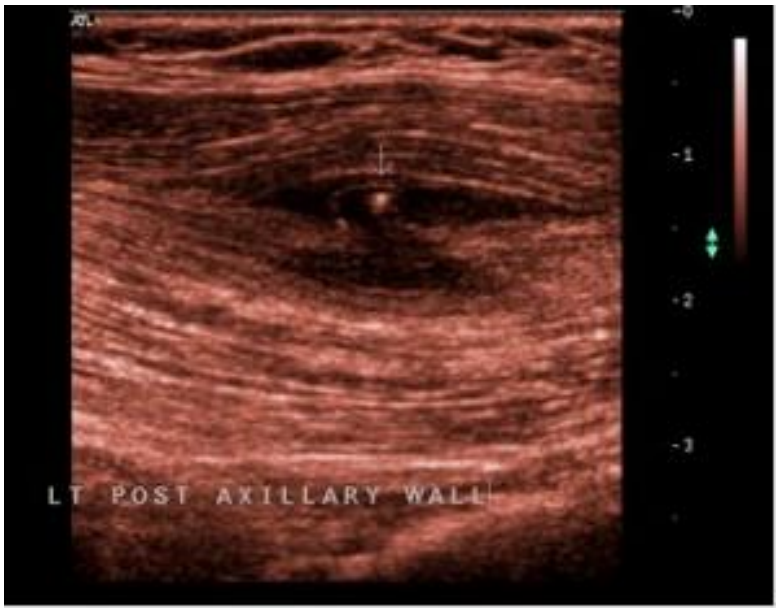

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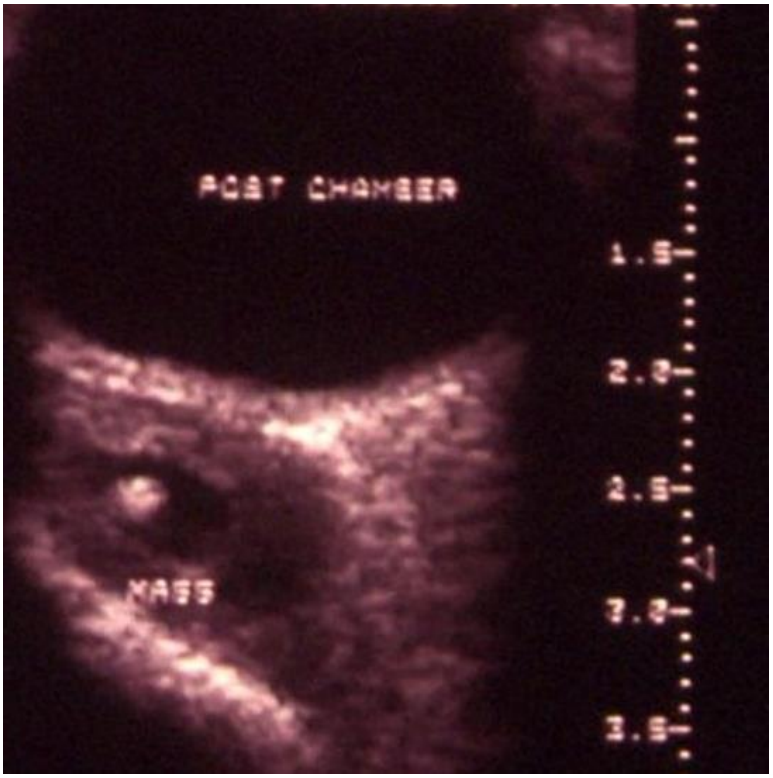
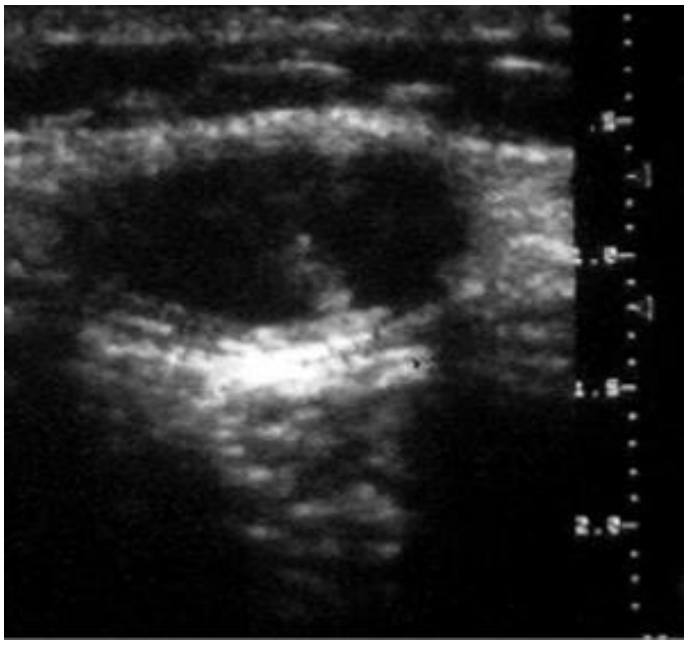


Figure 27 Guinea worm Dracunculus medinensis on abdominal wall (a) and extraction from extremities (b).

a



b

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