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Clinical review of liver hydatid disease and its unusual presentations in developing countries

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Abstract

Human hydatid cyst disease is an international public health issue that particularly affects the developing countries. In this article, we discuss the epidemiology of hydatid disease in third world countries, the life cycle of *echinococcus granulosus* and how to make the clinical diagnosis of the disease, including laboratory tests and imaging modalities as well as uncommon presentation of this entity that we have encountered at the American University of Beirut Medical Center (AUBMC). We emphasize on the new World Health Organization classification of hepatic echinococcosis with examples from our clinical practice at AUBMC, and finally we describe the treatment, including medical and interventional therapies.

Key words: Hydatid—Echinococcus—Third world—Middle east—Liver—Parasites

Human hydatid cyst disease is an international public health issue that particularly affects developing countries. It is caused by an infection with any of four species of echinococcosis, of which the most prevalent worldwide is the tapeworm *Echinococcus granulosus* responsible for cystic echinococcosis [1, 2]. Other species of Echinococcus are responsible for rare clinical presentations. *Echinococcus Multilocularis* for example is the larval stage of the fox tapeworm and is responsible for alveolar echinococcus which usually presents as a space occupying lesion that infiltrates the liver and spreads to other organs [3]. *Echinococcus vogeli* or *Echinococcus oligoarthritis* are the species responsible for polycystic Echinococcosis which presents as multiple cysts on almost any organ. It is usually asymptomatic unless complications develop [4].

Cystic echinococcosis can involve any visceral organ in the body including the kidney, lungs, and brain, but due to the bowel venous drainage system, it tends to favor the liver where hepatic infection accounts for two-third of all cases.

Echinococcus granulosus worms (2–7 mm in size) consist of a scolex with suckers and hooks, as well as three or more proglottid segments which have both male and female sexual organs and can produce eggs 30–40 μm in size containing embryos (oncospheres).

Dogs act as definitive hosts for *E. Granulosus*, and are responsible for transmitting the disease to humans. Sheep act as intermediate hosts, and areas where sheep are raised tend to have the highest rates of endemic disease. Humans are incidental hosts for the parasite, and up until today there are no human to human-reported cases. When infected, humans develop visceral Echinococcal cysts, which are fluid-filled structures limited by a parasite-derived membrane, which contain a germinal epithelium [5].

Hydatid disease of the liver is associated with a number of complications such as biliary tree obstruction with superimposed infection resulting in cholangitis or other superimposed infections that might lead to the development of abscesses. Other important and dangerous complication includes intraperitoneal leakage causing peritonitis and in extreme cases anaphylactic shock leading to death. Therefore, it is important to strictly abide by treatment guidelines to decrease the rate of possible complications [6].

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Epidemiology

The global burden of hydatid disease is estimated at 1 million cases at any one time [7]. Most of these cases are cystic (*E. granulosus*) and especially prevalent in areas with a temperate climate, notably the Mediterranean regions, southern and central parts of Russia, central Asia, China, Australia, and South America [1]. Although better diagnostic methods and surveillance programs are being employed, epidemiological studies and surveys are not available in all the areas endemic to hydatid disease [8], which results in an underestimated overall prevalence of echinococcal infection in general.

Regardless, the number of recognized cases is increasing, which may be due, in part, to better diagnostic technology and surveillance programs [2, 4]. The prevalence of hydatid cyst disease in animals varies between the different geographic areas of the middle east and North Africa region. The prevalence as well as the yearly human incidence in some of the endemic countries are summarized in Table 1 as it is reported in available epidemiology studies. [6, 8–17].

Life cycle of echinococcus

The transmission cycle of Echinococcus includes an intermediate host (such as sheep or pigs) and a definitive host (such as dogs). Humans are incidental hosts. The adult worm is usually found in the small intestine of dogs (the definitive host). The gravid proglottid segments can release up to thousands of eggs daily which end up being expelled in the feces of the host and are subsequently ingested by an unsuspecting intermediate host (usually sheep) or accidental host (humans). Once in the intestine of the intermediate/accidental host, the eggs hatch to release onchospheres that penetrate into the circulation through the intestinal mucosa. Once they reach the liver or other visceral organs they develop into cysts that enlarge and produce protoscolices. As the definitive host ingests the infected organs, the protoscolices attach to the intestinal mucosa and develop into adult worms as the life cycle starts anew [5, 14, 18]. (Fig. 1).

A complete life cycle takes 4–7 weeks. The transmission of the disease requires both a definitive host for the adult worms and an intermediate host for the eggs to hatch and cysts to grow. For this reason, human-to-human transmission is not possible [14].

Diagnosis

The vast majority of cases are diagnosed incidentally by imaging. In the case of a symptomatic patient, after obtaining a detailed medical history (focused on contact with dogs or wild life, living in endemic areas…) and conducting a proper physical exam, the diagnosis of hydatid disease is achieved through a combination of imaging and serology. A typical diagnostic scenario would start with a patient presenting with non-specific symptoms such as epigastric and/or right upper quadrant pain, nausea, vomiting, or malaise/fatigue. The clinical interview should include exposure to risk of hydatid disease (contact with wildlife, improperly washed vegetables, history of travel to endemic areas, etc.) especially in endemic areas. When the history is suggestive, a vigilant physician should ask for an ultrasound examination of the abdomen, where a cyst would be usually found in affected patients. If the history and the radiological findings are very suggestive, most physicians will proceed to treatment and refrain from additional tests. However, when in doubt, some dedicated assays are available. Detection of *E. Granulosus*-specific antigen and immune complexes with ELISA usually confirms the diagnosis with a sensitivity and specificity of 93.5% and 89.7%, respectively. In the rare cases where imaging was inconclusive and ELISA was negative but the history is very suggestive, US-guided percutaneous biopsies can be performed to collect some cystic fluid and test it for *E. Granulosus* antigen 5 (Ag5) and antigen B (AgB). However, the risk of secondary hydatid cyst formation due to spillage is high and so oral Albendazole must be administered 4 days before the procedure and continued for a month following the intervention, which also serves to decrease the risk of anaphylactic shock during the aspiration procedure [19]. We will focus on the imaging aspect of diagnosis and the use of ultrasonography, CT, and MRI in the diagnostic imaging of hydatid disease and the characteristic findings [20].

Table 1. Incidence and animal prevalence of CE in the Middle Eastern region

	Humans (Per 100,000)	Cattle (%)	Sheep (%)	Dogs (%)	Goats (%)	Camel (%)	Other (%)
Lebanon	3.82 [9]	41.5 [9]	6.6–22.1 [9]	20–33 [9]	6.6–22.1 [9]	–	–
Libya	4.2	5.4 [12]	12.7 [12]	11.8–40.3 [12]	1.5 [12]	39.8 [12]	–
Tunisia	0.4–15 [13]	12–68 [12]	0.1–70 [12]	30–68 [12] 21 [15]	1–16 [12]	10.1 [14]	–
Jordan	2.9–8.2 [6]	0.9 [10]	12.9 [10]	11.1–15 [8] 9.7–14.5 [6]	12.7 [10]	11 [10]	Donkeys: 16.9 [11]
Turkey	3.77–4.4 [12]	25.9 [12]	30.6 [12]	0.9–40.5 [12]	12.7 [12]	–	–
Kuwait	1.6–3.6 [16]			23 [17]			

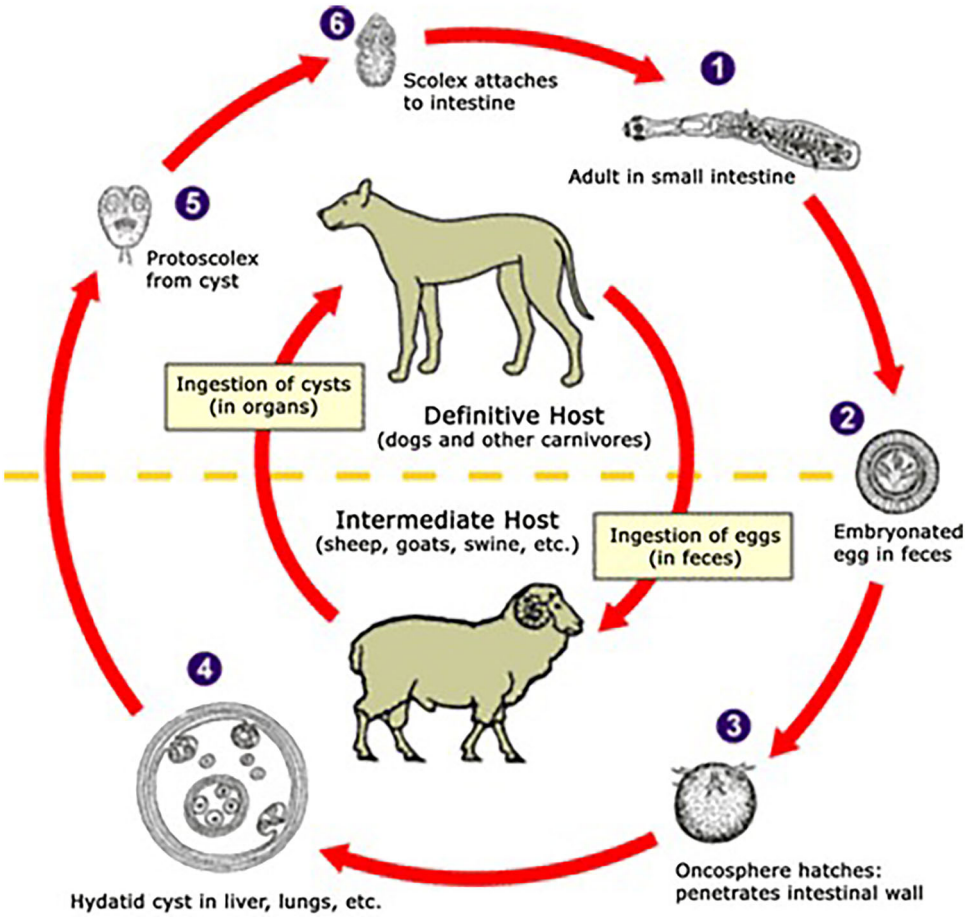

Fig. 1. Life cycle of Echinococcus.

Imaging

Ultrasound imaging provides a fast and accurate method of capturing liver lesions with a sensitivity reaching 90–95% [21]. Hydatid cysts commonly have the appearance of a simple fluid-filled cyst on ultrasound but they can vary in appearance and characteristics depending on the developmental stage of the disease. The WHO classified the different types of cysts based on these variations in ultrasound features, each with a tailored treatment regimen [20]. The different features are outlined in the next section.

CT scan and MRI are more sensitive and specific in the detection and characterization of hydatid disease. However, these relatively expensive procedures are not always required for the diagnosis of hydatid disease and are more essential in cases of extrahepatic involvement [22]. CT scan has an additional advantage in the rapid diagnosis of cyst rupture with exact delineation of the location and type of rupture, prompting surgical intervention in emergency situations [23].

Classification

The World Health Organization 2001 classifies hepatic hydatid cysts based on ultrasound features.

CL Unilocular anechoic cystic lesion without any internal echoes and septations. (Fig. 2)

CE 1 Uniformly anechoic cyst with fine echoes settled in it representing hydatid sand. (Fig. 3)

CE 2 Cyst with multiple septations giving it multivesicular appearance, rosette appearance, or honeycomb appearance with unilocular mother cyst. This stage is the active stage of the cyst. (Fig. 4)

CE 3 Unilocular cyst with daughter cysts with detached laminated membranes appearing as water lily sign. This is the transitional stage of the cyst. (Fig. 5)

CE 4 Mixed hypo and hyperechoic contents with absent daughter cysts, these contents give an appearance of ball of wool sign indicating the degenerative nature of the cyst. (Fig. 6)

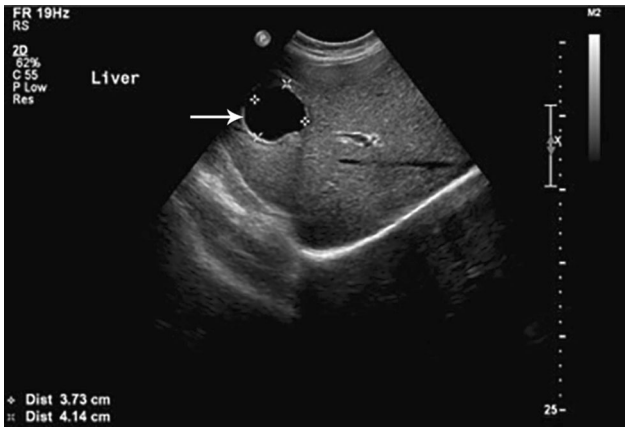

Fig. 2. CL Cyst. A 29-year-old male patient presenting for right upper quadrant discomfort. Ultrasound of the liver showed, anechoic cystic lesion measuring 3.7 × 4.1 cm without echoes or septations (arrow) consistent with CL cyst given the positive Hydatid Titer. The patient was treated with 9 months of albendazole and remains stable since last follow-up with the cyst having changed to a CE4 type (considered cured).

CE 5 Arch like thick partially or completely calcified wall. This stage of cyst is inactive and infertile. (Fig. 7)

Uncommon presentations

Liver hydatid with intrahepatic venous thrombosis

Intrahepatic venous thrombosis secondary to liver hydatid is an uncommon occurrence that seems to be more common in areas endemic to hydatid disease but remains a rare finding. On MR imaging, it tends to present as an exophytic mass that appears hypointense on T1-weighted images and hyperintense on T2-weighted images with a hypointense rim. The mass effect of the cyst on the IVC or hepatic veins, in combination with inflammation response, can lead to thrombosis. (Fig. 8) [24].

Pancreatic hydatid

Pancreatic hydatid disease is a very rare presentation of the disease with incidence no more than 2% in endemic areas. These cysts vary in their location between the head of the pancreas, body, and tail. The imaging characteristics of hydatid disease are rarely present in cases of pancreatic presentation and one must keep a high index of suspicion for cystic lesions in the pancreas in endemic areas (Fig. 9) [25].

Paraspinal hydatid eroding into the vertebrae

Skeletal hydatid disease is another uncommon presentation. Its seen in up to 2% of cases and tends to present clinically with signs of disk disease with neurological compromise. On imaging, they tend to present with lytic lesions with a dense calcified rim. The disk space tends to be spared. A classical daughter cyst in parent cyst appearance is common. With time bone invasion is more likely and if MR imaging is available the parent cyst usually has a signal similar to that of muscle on T1 [26]. (Fig. 10).

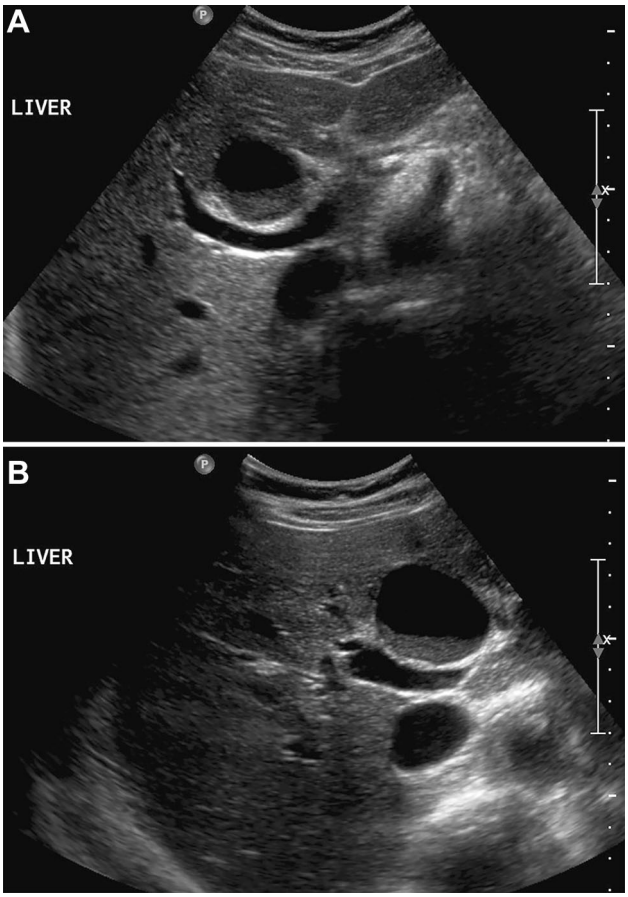

Fig. 3. CE 1 Cyst. A 59-year-old female presenting with fatigue. The history was suggestive (lives on a farm with several dogs) and hydatid titers were positive. Ultrasound of abdomen showed a 2.6 × 3.1 cm anechoic cyst with fine echoes representing hydatid sand that gravitated to the dependent portion of the cyst (**A**, **B**) consistent with a CE 1 cyst. PAIR was chosen as therapy and the patient recovered without any complication.

Isolated renal hydatid

A slightly more common presentation (up to 4%) is isolated kidney hydatid disease. The clinical presentation depends on the size and involvement of kidney or neighboring structures. On imaging, it can be tricky to diagnose the disease especially in cases of simple hydatid

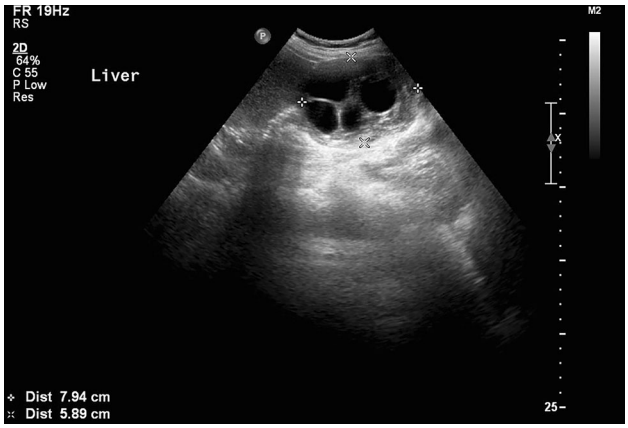

Fig. 4. CE 2 Cyst. A 43-year-old female presenting with weight loss. Ultrasound of the abdomen showed a 7.9 × 5.9 cm large cyst containing daughter cysts in a honeycomb pattern consistent with a CE 2 cyst. Titers were negative, but due to textbook presentation and obvious imaging results, the patient was referred to surgery, with a successful and uncomplicated cystectomy and a confirmation of hydatid nature after postsurgical pathology results.

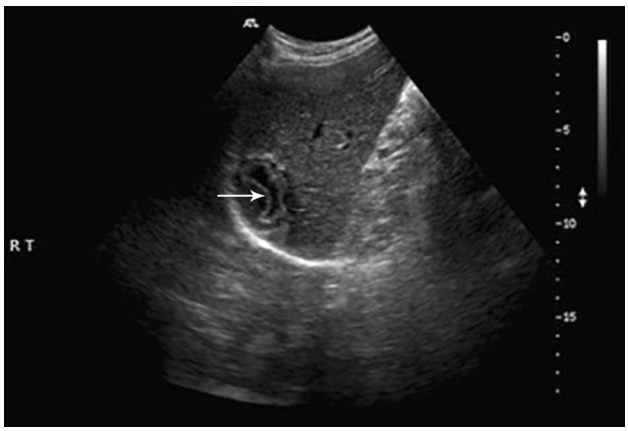

Fig. 5. CE 3 Cyst. A 40-year-old male patient, presenting for vague abdominal discomfort. Ultrasound of liver showed imaging of a CE 3 cyst. Unilocular cyst with daughter cyst (arrow) showing laminated membrane with water lily sign. The patient was advised to undergo 18 months of albendazole therapy to which he agreed but has not followed up since.

cysts due to the similar appearance of a simple renal cyst [27]. (Fig. 11).

Isolated splenic hydatid

Splenic hydatid disease is seen in up to 4% of cases and tends to be insidious in its clinical presentation mainly with some left upper quadrant pain and fullness. On imaging, the lesions tend to be very large because of the late time of presentation and are more commonly simple cysts [28] (Fig. 12).

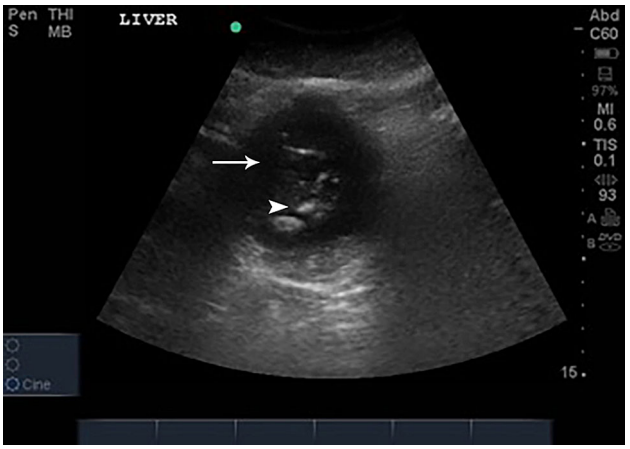

Fig. 6. CE 4 Cyst. A 50-year-old female presenting with epigastric discomfort. Ultrasound liver showed mixed hyper (arrowhead) and hypo (Arrow) echoic content showing the ball of wool appearance consistent with CE 4 cyst. Watch and wait approach was the therapy of choice, however, the patient was lost to follow-up.

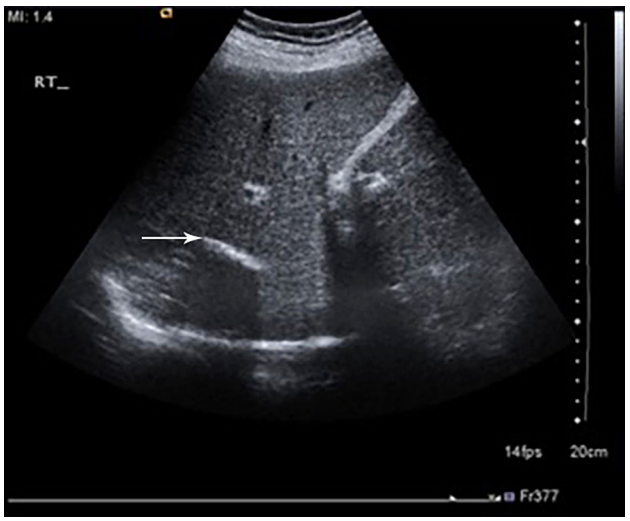

Fig. 7. CE 5 Cyst. Ultrasound imaging of CE 5 cyst in a 29-year-old male presenting for follow-up of a previously diagnosed hydatid cyst in the liver. An arch like partially calcified wall is seen (arrow) with posterior shadowing. Watch and wait approach was the therapy of choice, and the cyst has remained inactive on last follow-up.

Serum assay

In addition to imaging, different serological tests have been developed to establish a diagnosis. Initial screening consists of indirect hemagglutination (IHA) and enzyme-linked immunosorbent assay (ELISA) for IgG, IgM, or IgE antibodies. Then, if necessary, a confirmatory test using specific antigens is carried out. These tests included arc-5 immunoelectrophoresis and immunoblotting [23].

PCR is currently used for typing in research, especially in epidemiological studies. It does not serve a

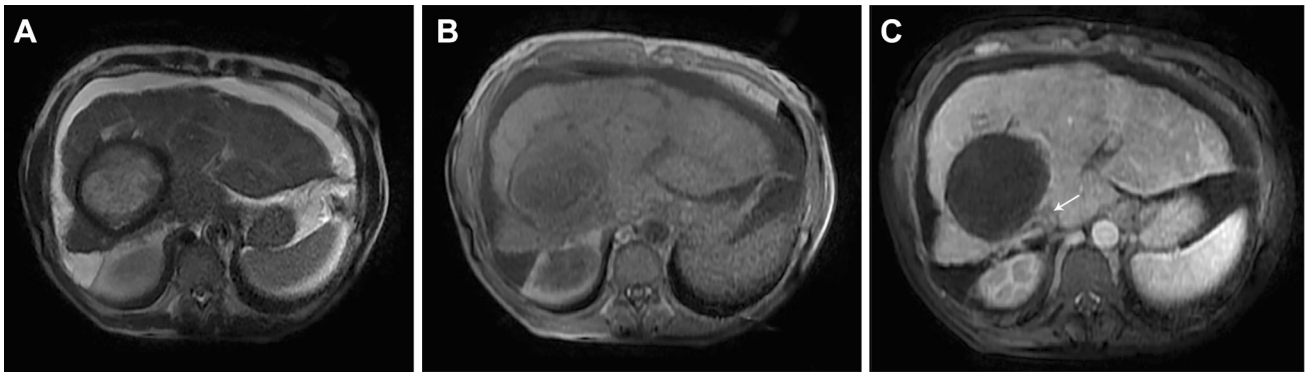

Fig. 8. MR liver with Axial T2-Weighted image (**A**) showing a hyperintense mass with hypointense rim, Axial T1-Weighted image (**B**) showing a hypointense mass and Axial T1 Fat Sat, Post Gadolinium (**C**) Showing the cyst along with lack of flow within the branches of the right hepatic vein (arrow) secondary to external compression.

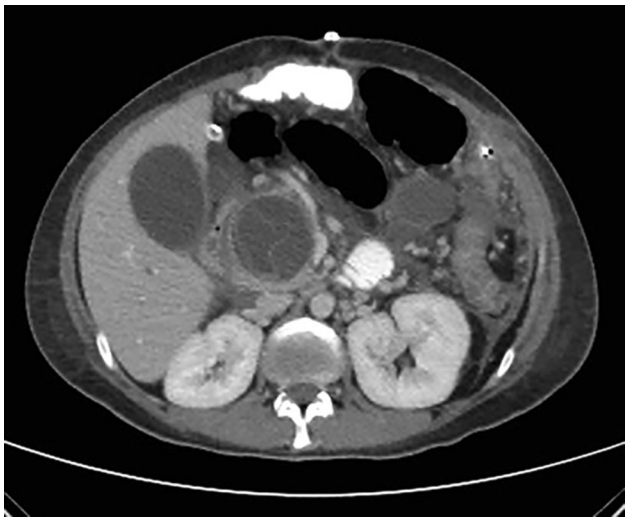

Fig. 9. A 26-year-old female presenting for severe abdominal pain. CT showed a cystic lesion containing daughter cyst within the pancreatic head with a water lily sign. After confirmatory positive titers, these lesions were consistent with hydatid disease of the pancreas. Due to pancreatic involvement, the patient was advised to start albendazole orally immediately hoping the cystic lesion will undergo shrinkage to avoid complication such as biliary obstruction that may lead to a Whipple procedure.

purpose for clinical diagnosis of hydatidosis because echinococcal DNA is not found in the serum or urine of patients with uncomplicated disease [29]. DNA can enter the circulation in the case of ruptured cysts and therefore can only be detected in such cases [29].

Percutaneous aspiration, while not required in most cases, can be done pre-surgically to confirm the diagnosis by direct visualization of the protoscolices under microscopy. This technique carries, albeit not very commonly, the major risk of anaphylaxis due to fluid leakage during the procedure, as well as cyst infection, pneumonia, and hemobilia [23, 30]. Anaphylaxis can be avoided by pretreating the patient with oral Albendazole for 4 days before the procedure, followed by oral Albendazole for a month after the aspiration. However, since one of the treatment interventions for hydatid disease is PAIR (Puncture-Aspiration-Injection-Reaspiration), most protocols consider that once the cyst has been punctured, PAIR should be initiated, as a diagnostic and therapeutic intervention.

Treatment

The treatment can be medical, surgical, endoscopic, minimally invasive, or expectant. The choice of the treatment modality depends on the stage of the cyst, the complications, and the locally available resources [20].

Medical

Antihelminthic chemotherapy has a 30% cure rate, defined as cyst disappearance on imaging [31]. Albendazole is the antihelminthic agent of choice for liver hydatid disease [32]. Short-term therapy is given as a neoadjuvant agent while awaiting surgical or percutaneous treatment [33, 34]. Treatment with Albendazole prior to surgery led to a higher rate of non-viable cysts at the time of surgery [35, 36]. In 2011, an RCT by Shams-Ul-Bari et al. showed that patients who received Albendazole 12 weeks prior and 12 weeks after surgery had no recurrences compared to 17% recurrence in patients with no medical therapy [37]. Medical therapy can also be useful in inoperable cases (multiple lung and/or liver cysts and peritoneal involvement) where it is considered an indication. [38]. Cysts tend to calcify after treatment (Arch like calcifications either partially or completely along the outer border that may progress to involute the inner center with calcification suggestive of inactive and infertile disease. (Fig. 13a, b).

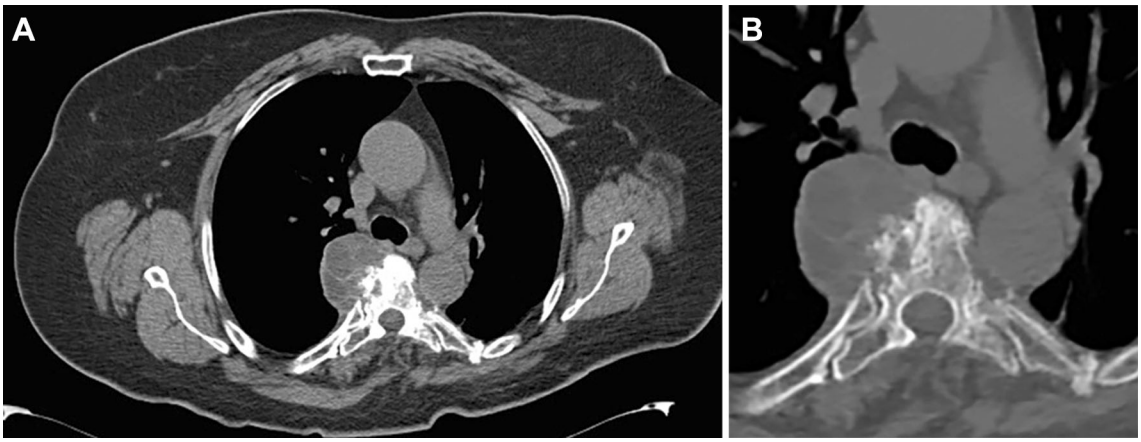

Fig. 10. A 67-year-old female presenting with upper back pain. CT showed a right paraspinal multiseptated cystic lesion with honeycombing appearance with erosion into one of the thoracic vertebral bodies (T6) as seen on regular window (**A**) and Bone window (**B**). Because of the patient's compromised quality of life due to back pain, surgery was immediately performed with confirmatory pathology results obtained on resected specimen.

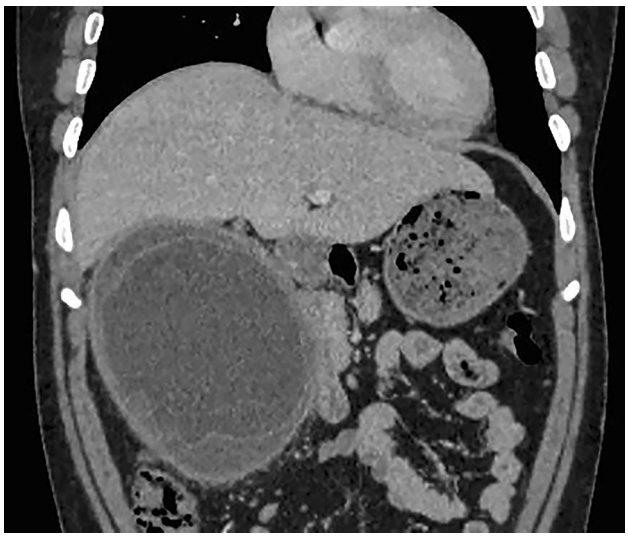

Fig. 11. A 33-year-old male presenting with right flank pain. CT scan of abdomen and pelvis showed a large cystic lesion with detached membranes occupying mostly the right kidney with no other lesion identified in the liver or lung consistent with CE 3 hydatid. Patient failed to follow-up at our institution.

Watch and wait approach

In this approach, inactive uncomplicated cysts can be monitored with ultrasound for changes over time—without administration of treatment. It is a highly stage-dependent method, for which only CE4 and CE5 cysts are candidates. A long-term retrospective study demonstrated that 97.4% of spontaneously inactive cysts remained inactive without treatment [39].

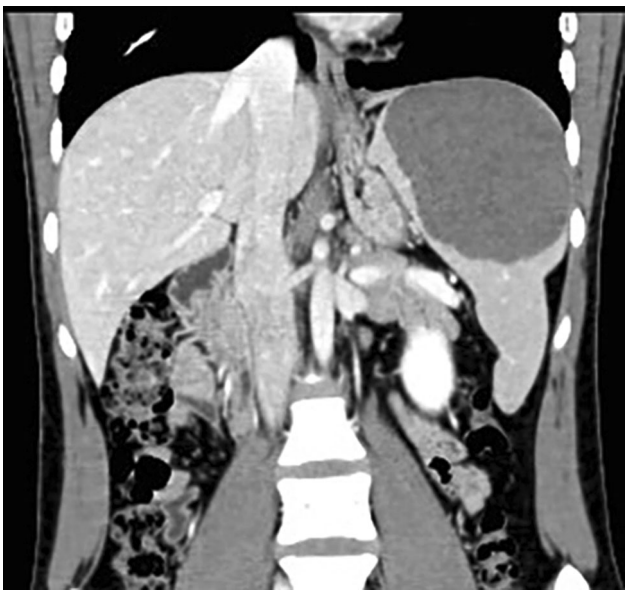

Fig. 12. A 18-year-old male presenting with vague left upper quadrant pain. CT showed a cystic lesion occupying most of the spleen with no other lesion in the liver, lung, or kidney. Titers were positive, consistent with low-grade hydatid cyst (CL or CE1). A 12-month Albendazole therapy proved curative with the cyst having changed to CE4 type and remains stable since last follow-up.

Surgical

The mainstay of hydatid cyst treatment remains surgical [40]. The current WHO guidelines, however, require that surgery be combined with medical treatment for a lower recurrence and seeding rate. Prior to surgery, the patient should be treated with at least 4 days of Albendazole or Mebendazole. Albendazole must be continued for at

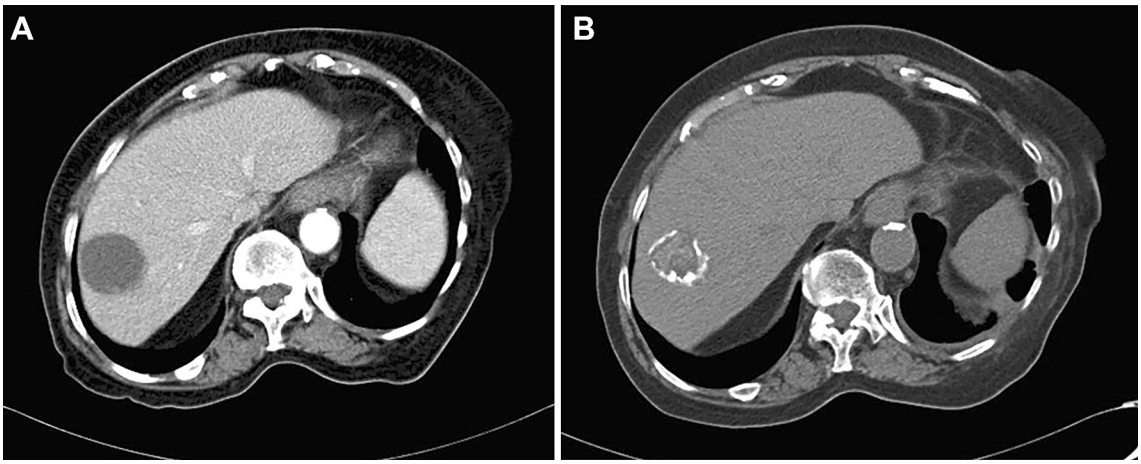

Fig. 13. Pre-treatment appearance of low-grade hydatid cyst (**A**) and Post treatment (**B**) showing decrease in the size of original cyst with peripheral calcification.

least 1 month and Mebendazole for at least 3 months post procedure [38].

It is done through open or laparoscopic approach with no controlled trials comparing the two approaches in the literature. Retrospective studies, however, show that laparoscopy is safe and effective in the resection of hepatic hydatid cysts if it falls in a physically and easily accessible location [40, 41] and it is associated with a significantly shorter hospital stay than open surgery [41].

Percutaneous drainage

Percutaneous treatment can be used as an alternative for surgery in patients with uncomplicated, single compartment cysts (CE1 and CE3a) less than 5 cm in size [20]. Septated complex cysts, cysts communicating with the biliary system, and inaccessible cysts are a contraindication to this procedure. In this method, also called Puncture-Aspiration-Injection-Reaspiration (PAIR), aspiration of the cystic fluid is done under ultrasound or CT guidance using a multipurpose drain catheter. A protoscolicidal agent is then injected into the cavity through the catheter. The contents are then reaspirated about 15 min later [20]. The protoscolicidal solutions of choice in PAIR are 20% NaCl and 95% ethanol [20].

It is recommended that PAIR be preceded by 4 days and then followed by 1 month of Albendazole therapy.

Conclusion

Mediterranean regions and other developing countries are particularly affected by liver hydatid disease.

Echinococcus Granulosus, a tapeworm that is responsible for the disease, has a particular life cycle, with sheep usually acting as intermediate host, dogs as definite host, and humans as incidental recipient.

Diagnosis is done either by serology and/or imaging, with a wide array of treatment options depending on the stage of the disease and the resources available to the managing team. Therefore, each case of liver hydatid disease should be individually classified according to the WHO classification and treated according to the local skills and expertise of the health care team on site.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study, formal consent is not required. This article does not contain any studies with human participants or animals performed by any of the authors.

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