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Case Report

Management of serology negative human hepatic hydatidosis (caused by *Echinococcus granulosus*) in a young woman from Bangladesh in a resource-rich setting: A case report

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ABSTRACT

Human cystic echinococcosis (hydatidosis) is a parasitic zoonosis with almost complete worldwide distribution. *Echinococcus granulosus*, the dog tapeworm, causes hydatidosis which accounts for 95% of human echinococcosis. Although this tapeworm is found in dogs as a definitive host and a number of intermediate hosts, humans are often infected from close contact with infected dogs. Humans are not part of the parasitic lifecycle and serve as accidental hosts. Hydatidosis is an important consideration in the differential diagnosis of hepatic cysts in individuals from endemic areas. Clinicians should be aware of the long incubation period, the high frequency of negative serological tests, and the possibility of intraoperative evaluations of the cyst aspirate being non-diagnostic. We describe a case of serology negative hydatidosis that came to medical attention as an incidental finding in a young woman from Bangladesh. The patient underwent imaging and was then started on albendazole. After several weeks of albendazole, the cyst was punctured, aspirated, injected with hypertonic saline, re-aspirated, and then fully excised. Diagnosis was confirmed by microscopic evaluation of the cyst aspirate. Serological tests for hydatidosis may be negative in patients with early disease and thus should not be used to rule out this disease. Consideration of this diagnosis allows clinicians to avoid the catastrophic spillage of cystic contents risking an anaphylactic reaction, which might prove fatal. Despite World Health Organization hydatidosis staging being based on ultrasound, radiologists in resource-rich setting may prefer MRI in the management and staging of cystic echinococcosis.

Introduction

Human cystic echinococcosis is a parasitic zoonosis caused by the larval form of *Echinococcus granulosus*, the dog tapeworm, which accounts for 95% of human echinococcosis cases. *Human cystic echinococcosis* is present worldwide except in Iceland, Ireland, and Greenland, and remains highly endemic in many rural communities [1]. In developed countries, such as the United States, this is mainly a disease of immigrants although there has been reported local transmission to humans in California, Arizona, New Mexico, Utah and Alaska [2,3]. Cystic echinococcosis has a mortality of 2–4% and may be more common in the United States than generally recognized, in part because the disease is not reportable [4,5]. Worldwide, echinococcosis causes an estimated annual loss of US $194,000,000 or 285,000 disability-adjusted life years [1].

Hydatidosis is usually transmitted by the unintentional ingestion by humans of food or water contaminated with fecal material from infected canines. The tapeworm inhabits the small intestine of canines, the definitive host, and may release thousands of embryonated eggs in the feces each day. The viability of these eggs may exceed 1 year when deposited into a cool, moist environment. When ingested, these eggs hatch in the small intestine releasing an oncosphere which matures into a metacestode. The metacestodes penetrate the bowel wall and migrate via the circulatory system to a number of organs including but not limited to the liver [6–8]. In the liver, or other organ to which the parasite migrates, a cyst develops, enlarges, becomes filled with protoscoleces and daughter cysts and undergoes a predictable evolution over a number of years with characteristic imaging

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features [9]. The cysts tend to increase in size by about 1–5 cm per year with calcification occurring 5–10 years post infection, but this development varies depending on the individual infected as well as the particular genotype of the infecting parasite [10,11].

In areas of the world where hydatidosis is endemic, control programs have been established to eradicate it by interrupting the zoonotic cycle, through the use of health education, meat inspection, dog testing, dog treatment, and in some cases large-scale canine culling [12]. Although "Island" control programs have been successful in Iceland, New Zealand, Tasmania, Falklands and Cyprus, outcomes for "Continental" control programs, in Africa, Asia and South America, have not been as favorable. If the efficacy and feasibility of canine vaccination, which is currently being tested, are established, "Continental" programs will have an increased chance of success [13,14].

Imaging often plays a large role in the diagnosis of this disease, but despite the greater than 90% sensitivity of ultrasound for hepatic hydatidosis there often is a challenge in distinguishing between an echinococcal cyst and a simple liver cyst [15]. A number of serological tests are available for echinococcal disease including IgG ELISA, but these tests have less than optimal sensitivity and issues with specificity [16,17]. Accurately distinguishing an echinococcal cyst from a simple cyst is critical in the management of these infected patients because approximately 10% of the time, the accidental leakage of hydatid cyst contents into the abdominal cavity results in an often fatal anaphylactic reaction [18,19].

Case presentation

A 29-year-old immigrant from Bangladesh was admitted to Long Island Jewish Hospital in February 2013 with fever, abdominal pain and chills. This young woman was married with two young children and had a past medical history of migraines treated with sumatriptan as needed, a benign ovarian cyst, and a prior episode of nephrolithiasis. She had grown up in rural Bangladesh where her family raised livestock. She moved to the United States in 2008, at the age of 24 years, and had returned to Bangladesh only once when she visited her family in January 2010. The patient reported contact with her family's dogs while in Bangladesh. Upon admission, she was diagnosed with influenza B on the basis of symptoms and a positive polymerase chain amplification test from a respiratory viral panel test. Although the patient's immediate symptoms resolved after several days without any specific therapy, an abdominal computed tomography (CT) scan was performed as part of the evaluation of her abdominal pain.

The abdominal CT scan revealed a heterogeneous hypoattenuating mass in the liver (8.4 cm × 5 cm × 5.2 cm) (Fig. 1). A magnetic resonance imaging (MRI) scan of the liver suggested that this was a complex cyst, without surrounding edema, showing numerous serpiginous septations. The MRI was read as most likely an echinococcal cyst (Fig. 2). After several days in the hospital the patient was discharged from the acute care setting and was scheduled for follow-up care in the outpatient setting. A number of tests were ordered including an echinococcal ELISA.

The patient was seen in the outpatient clinic several weeks later, in the beginning of April, and noted to have a negative echinococcal IgG ELISA. Despite this negative test the clinical suspicion was high enough that the patient was started on albendazole and a repeat imaging test was ordered. In the beginning of May, a repeat MRI was performed that documented no change in the liver cyst.

The patient was admitted for surgery following the second MRI. The cyst was punctured and the fluid aspirated. A portion of the fluid was sent for immediate microscopic evaluation, performed at the time of surgery, and the remaining fluid was sent to the diagnostic parasitology division of the NSLJHS Core Lab. The cyst was injected with 20% hypertonic saline and then, after a 10-min dwell time, reaspirated. The cyst was then opened and explored. At the time of surgery, only a simple cyst was evident with no septations; no smaller cysts and no obvious daughter cysts were noted. The cyst was then fully excised with no complications. The patient tolerated the procedure well and was discharged to home after her hospital stay to complete a several month course of albendazole. Evaluation of the cyst contents in the parasitology lab revealed numerous hooklets in the aspirated fluid confirming the diagnosis of an echinococcal cyst.

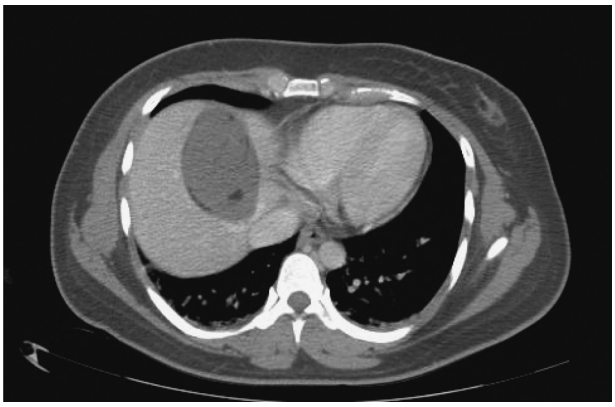

Fig. 1. Abdominal computed tomography scan. This is a representative slice from the CT performed during the initial patient hospitalization with the following details. Procedure date: February 23, 2013. Findings: there is a heterogeneous hypoattenuating mass in the liver (8.4 cm × 5 cm × 5.2 cm). Impression: benign versus malignant neoplasm versus hamartoma versus adenoma, less likely hepatocellular carcinoma, no cirrhosis.

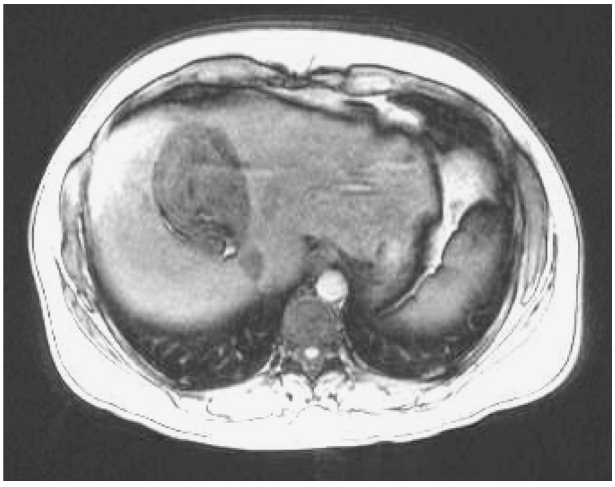

Fig. 2. Magnetic resonance scan of upper abdomen with and without contrast. This is a representative slice from the MRI performed during the initial patient hospitalization with the following details. Procedure date: February 24, 2013. Findings: there is a nonenhancing complex cystic lesion in segment 8 of the liver, which contains numerous serpiginous internal septations, small foci of fat and fluid. No additional lesions identified. There is no evidence of intra or extra biliary ductal dilation. The gall bladder is normal. The pancreas, adrenals, and kidneys and spleen are unremarkable. No contrast extravasation into the cyst is seen on the hepatocyte phase images. There is no mesenteric or retroperitoneal lymphadenopathy. The visualized bowel is unremarkable. Impression: cystic liver lesion containing small foci of fat is most likely an echinococcal cyst.

Discussion

There are a number of features of this case of human hepatic hydatidosis that make it both interesting and challenging for the

clinician. The travel and exposure history, the negative serology and the negative microscopic evaluation of the cyst contents reported during the time of surgery are three aspects that deserve a bit more attention.

Since certain parasitic diseases are characterized by long incubation periods between exposure and disease or diagnosis, an extensive travel and exposure history is required to be taken by the clinician in order to introduce infection with *E. granulosus*, the dog tapeworm, into the differential diagnosis. On initial history this patient was noted to be a young woman living in the urban environment of Queens, New York, with no travel within the last 3 years and no exposure to pets or other animals. A deeper exploration of this woman's past history revealed that she was born and raised in a rural part of Bangladesh where her family was involved in animal husbandry and she was exposed to dogs. This woman had moved out of this environment 5 years previously, but just over 3 years prior to this liver cyst coming to medical attention she had traveled back to visit her family in the endemic area. With the very variable course of *E. granulosus* it is not possible to be certain whether her infection was acquired during her return to Bangladesh in January 2008 or whether this was acquired prior to her emigrating to the US, although the stage of the cyst would favor infection during her January 2008 visit. In addition to the long period between exposure and diagnosis is the fact that this woman falls into the identified high-risk group of international traveler termed traveler visiting friends and relatives (VFRs). Even an adventurous traveler to a destination is unlikely to have the exposure that this woman had upon visiting her family's home and directly interacting with the family dogs.

Despite the history and other features of the case being so compelling, the negative serology for echinococcal disease is an important feature in this case. A number of the neglected diseases (NTDs), less common in the developed world, have diagnostic assays lacking the high level of sensitivity of many ELISAs commonly ordered in these areas. A negative serology does not rule out cystic echinococcosis (CE) as clearly demonstrated in this case. Not only may a patient have an echinococcal cyst with a negative serology, but there may also not be a consistent relationship between the extent of the infection and serological results [20,21]. In some series 30–40% of patients with hepatic

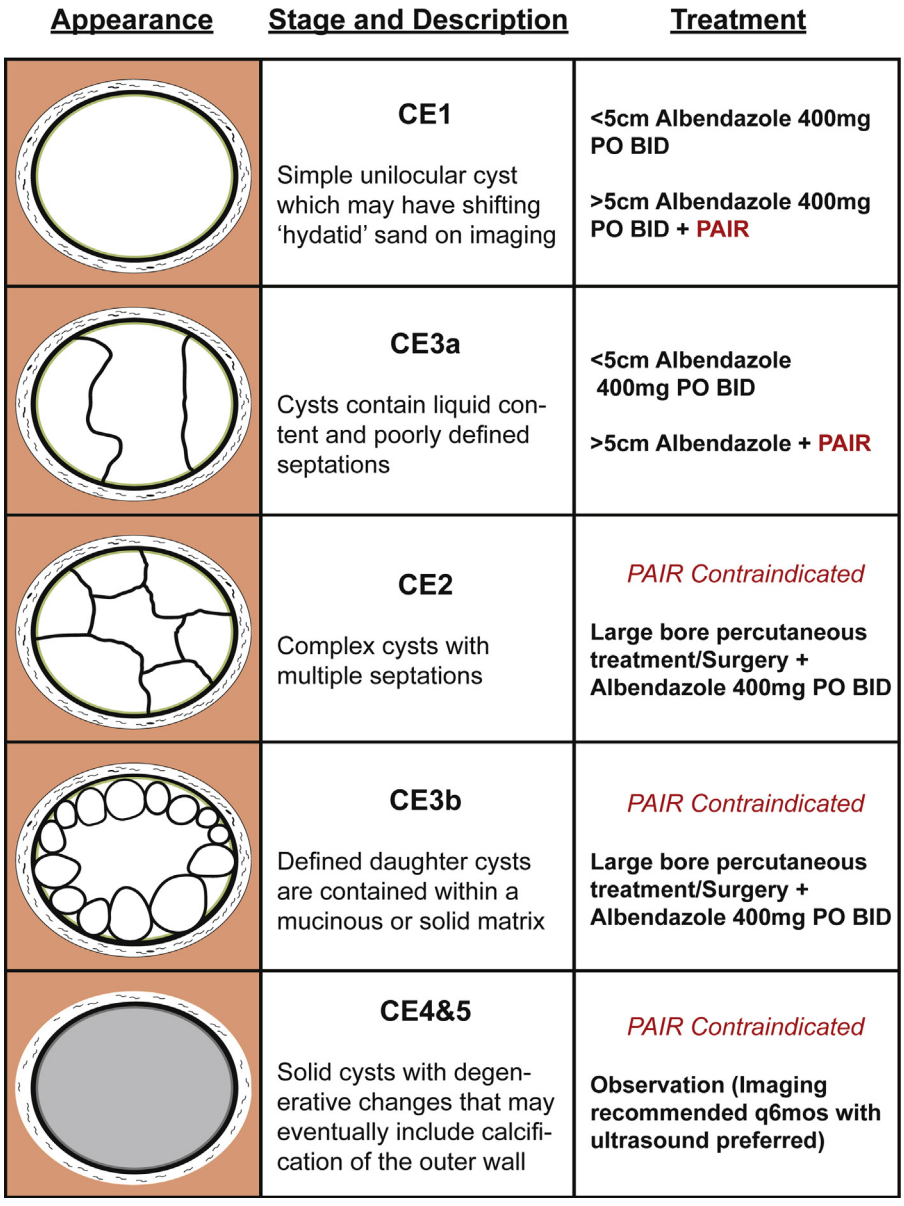

Fig. 3. Appearance, classification of cyst stage, cyst stage description and recommended treatments for echinococcal cysts.

cystic echinococcosis are antibody negative and this may be due to the ability of *E. granulosus* antigens to inhibit B cell activity and proliferation [22]. Although the sensitivity of serological testing is not clearly dependent on the extent of disease, it does appear to be dependent on cyst stage. Patients with cystic echinococcosis can be staged according to the WHO criteria and may fall in the spectrum between CE1 and CE5 (Fig. 3) [23]. Patients with early or inactive cyst stages may only have positive serologies as little as 54.8%, and patients with simple cysts staged at CE1 may only be positive 73.7% of the time [24]. The sensitivity of the ELISA increases for patients with active disease staged as CE2 and CE3.

We used an echinococcal IgG ELISA, which in our lab reflexes to a confirmatory Western blot when positive. This test has perhaps the highest positive predictive value among the available serological tests, but unfortunately may only have a negative predictive value of <90% [20]. One possible approach to a compelling clinical case with negative IgG ELISA is to perform several serological tests using different modalities such as indirect hemagglutination, latex agglutination, immunoelectrophoresis, or radioallergosorbent testing. It has been demonstrated that since the size, location and clinical stage of the cyst affect the accuracy of the various serological tests, a combination of several tests can improve diagnostic accuracy [20]. One might also consider repeating the same serological test at different laboratories as change in sensitivities can occur due to the batch-to-batch variation in the prepared antigens [25]. Due to the limitations of current serological assays, a number of researchers are actively investigating the use of specific echinococcal peptides and echinococcus protoscolex soluble somatic antigens (PSSAs). The use of specific echinococcal peptides and echinococcus PSSAs may increase our sensitivity and specificity and even allow staging of the disease with serological rather than imaging tests [26]. In our case, we chose to proceed with a clinical diagnosis of cystic echinococcosis despite the negative serology, considering that further testing would not have changed our planned management.

In this woman's case, microscopic fluid evaluation during the surgical procedure was unrevealing and there was no reported visualization of protoscoleces, hooklets or fragments of laminated membrane. Visualizing diagnostic hydatid elements in wet, unstained mounts of cystic fluid sediment is challenging and time consuming; thus researchers are searching for potentially superior techniques such as rapid antigen detection assays [27,28]. Our Institution's access to a parasitology laboratory with technicians experienced in the identification of hydatid fluid sediment was critical for the correct diagnosis and appropriate management of this patient. At institutions without access to a parasitology lab, clinicians should refer patients with possible hydatidosis to a center with such access if hydatidosis diagnosis would be critical in the proper care of the patient.

Critical to the successful outcome in this case was that, despite the distant history of exposure, the negative serology, and the negative microscopic examination during the time of surgery, the patient was still optimally treated. The patient was pretreated with albendazole, the cyst was properly aspirated without leakage, a protoscolicide (hypertonic saline) was injected, with an appropriate dwell time, and then the cyst was re-aspirated prior to surgical removal. Optimal management of cystic echinococcosis is guided by cyst stage and an expert consensus for guiding the clinical management of these patients has been generated under the aegis of the World Health Organization Informal Working Group on Echinococcosis (WHO-IWGE) [23]. The appearance, classification of cyst stage, description and recommended treatments are presented in Fig. 3. Every effort should be made to prevent protoscolex spillage and sterilize the germinal layer as the mortality rate of 2–4% usually seen in cases of cystic echinococcus may be increased if patients are improperly treated. Spillage of viable protoscoleces from a cyst may result in anaphylaxis, secondary cystic echinococcus or death.

Despite the staging of echinococcal cysts being based on ultrasound characteristics of the identified cysts, in developed countries, CT scans and MRI scans may be selected by the clinicians responsible for the management of these patients. Following an initial CT, this patient underwent two MRI scans, the first to further characterize the cyst and the second to evaluate any change in the cyst. It is suggested that MRI is superior to CT in reproducing the ultrasonic features and heavily T2-weighted MRI series may even be superior to ultrasound for certain cyst location or patient-specific reasons [2].

Conflict of interest

The authors declare no competing financial interests.

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