**CLINICAL VIGNETTE**

# Fever and Abdominal Pain in a 44-Year-Old Man Returning from East Africa

Donald E. Dietz IV, MD and Christopher Tymchuk, MD

***Case***

The patient is a 44-year-old man with no significant past medical history who presented with persistent fevers and abdominal pain after a recent trip to East Africa.

The patient was born in Minnesota but had also lived in Iowa and Kansas, prior to moving to Los Angeles twenty years ago. He works as a musician and lives alone in an apartment with two cats. He reported sexual activity with multiple women. He denied substance abuse, including intravenous drug use. He was up to date on screening exams, including HIV testing. Tuberculin skin testing in 2000 was negative.

Recent history was remarkable several months prior for an episode of severe constipation, for which he was evaluated with abdominal x-ray and prescribed multiple laxatives and suppositories for five days and eventual normalization of bowel movements.

The patient visited Kenya and Tanzania for 2 weeks in August. He was on safari in several national parks and slept in tents with mosquito nets, ate mostly cooked food, and drank bottled water. However, he did eat some sliced raw fruit and salad. He denied physical contact with animals or swimming in open water. He reported stepping in feces, presumed to be from a buffalo, while wearing boots, but he denied touching the feces with his hands. He reported multiple insect bites. No other travelers were noted to be ill during the safari. Prior to his trip, he had received vaccines for typhoid (oral), yellow fever, and measles-mumps-rubella. He was previously vaccinated against hepatitis A. He took atovaquone-proguanil for malaria prophylaxis during his trip. He remained asymptomatic throughout the duration of his travels and returned to the United States feeling well in mid-August.

Four days after his return, he developed fevers, chills, night sweats, diffuse abdominal pain, poor appetite, and alternating diarrhea and constipation. After 2 days, he was evaluated at an urgent care clinic, where bloodwork was obtained, including tests for malaria, West Nile virus, and Zika virus, all of which were negative. His fevers persisted and he was evaluated by an infectious disease specialist two days later, who repeated basic laboratory testing and felt his symptoms were consistent with a non-specific viral infection, for which no medications were prescribed. He continued to have fever and presented to an emergency room where a repeat malaria exam was negative and labs were notable for alkaline phosphatase of 170 and elevated inflammatory markers, with C-reactive protein 33 and sedimentation rate 96. Blood and urine cultures were negative. He was discharged from the emergency room.

The patient continued to have fevers and two days later reported to the UCLA-Santa Monica emergency department. On admission, signs were: temperature 101.2F, heart rate 75, blood pressure 114/67, respiratory rate 18, oxygen saturation by pulse oximetry 96% on room air. Physical exam revealed minimal abdominal tenderness without guarding or rebound.

Labs included leukocytosis to 16.2, anemia to 12.9, and a platelet count of 377. Chemistry panel was notable for sodium of 128, elevation in alkaline phosphatase to 268 with normal renal function and coagulation panel.

Chest x-ray showed no evidence of consolidation but did reveal a solitary lingular nodule, consistent with a calcified granuloma. Computed tomography of the abdomen and pelvis revealed a 10 cm multiloculated complex cystic mass areas of enhancement at the root of the mesentery extending to the upper pelvis, partly encasing the vessels in portions of duodenum without significant mass effect. The patient received acetaminophen, ceftriaxone, and normal saline. He was then admitted to the hospitalist service for further management.

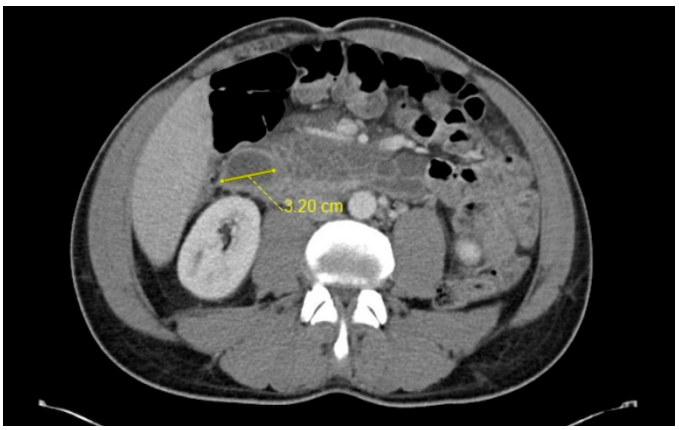
Given the highly unusual findings on CT abdomen/pelvis, with findings concerning for Echinococcal disease, infectious diseases consult was obtained. Serologies were sent for *Echinococcus*, human immunodeficiency virus, and schistosoma, as well as interferon-gamma release assay. All of these eventually resulted negative. The patient was continued on ceftriaxone and initiated on albendazole, both for empiric treatment of possible parasitic infection, as well in preparation for possible diagnostic biopsy. Given the size of the lesion and concern for possible non-infectious etiologies, such as malignancy, surgical consult was also obtained.

Other infectious etiologies, such as schistosomiasis, amoebic abscess, or tuberculosis were considered. There was also concern that the mass represented a cystic lesion, infectious or malignant, with bacterial superinfection. Due to risk of spilled cystic contents causing peritoneal seeding or anaphylaxis in *Echinococcus*, surgical biopsy or excision was deemed too risky. The decision was made to pursue medical management.

The patient was discharged on hospital day 3 on albendazole, ciprofloxacin, and metronidazole. He followed up in infectious

disease one week later. He reported absence of fever or abdominal pain, improved appetite, and normalization in bowel habits. Repeat laboratory studies of complete blood count showed persistent leukocytosis with neutrophilic predominance, concerning for ongoing bacterial infection. Repeat serologic tests were negative except for mildly elevated *Entamoeba histolytica* antibody, which was felt to be falsely positive. Repeat CT of the abdomen and pelvis two weeks after discharge showed, interval decrease in size of a mixed cystic and solid infiltrative mesenteric lesion, with resolution of most of the previously seen cystic foci and decreased but persistent infiltrative soft tissue encasing the superior mesenteric artery and vein, likely representing an improving infectious process given interval antimicrobial therapy. In light of this rapid improvement, Echinococcal disease was felt to be unlikely, and albendazole was discontinued. The patient was switched to amoxicillin-clavulinate and trimethoprim-sulfamethoxazole. He was also seen in surgery and surgery was deferred indefinitely given improvement with medical therapy.

The patient was seen in followup 6 weeks after discharge. Repeat CT abdomen and pelvis showed: "Further interval decrease in size of the complex mesenteric lesion, now with no visible cystic components and a small amount of amorphous soft tissue remaining within the mesentery." He was continued on empiric antibiotics for further 4-week course with a plan to obtain interval ultrasounds to ensure complete resolution of lesion.




***Discussion***

The differential diagnosis for fever and abdominal symptoms in a patient with recent travel to East Africa is broad and includes malaria, typhoid (caused by the bacteria *Salmonella typhi*), schistosomiasis, and, if associated with acute hepatitis, hepatitis A. The incidental finding on abdominal imaging in this patient was unexpected and focused the discussion on the possibility of *Echinococcus* or other parasitic diseases. Although *Echinococcus* was later felt to be unlikely, as will be explained below, and the definitive diagnosis remains opaque at this time, we felt this case was an opportunity to review the basic microbiology and clinical manifestations of *Echinococcus*.

*Echinococcus* is a genus of tapeworms that cause infections that can affect many organ systems, most commonly liver and lung. Six species of *Echinococcus* have been identified, but two are most often implicated in human infection: *Echinococcus granulosus* and *Echinococcus multilocularis.* The disease caused by the former is referred to as "cystic echinococcosus," while disease caused by the latter is referred to as "alveolar echinococcosus," although both cause cysts and either can occur in the lung.

These two species share a common lifecycle: adult worms establish residence in the gastrointestinal tract of the definitive host, releasing gravid proglottids into the host feces; embryonated eggs are accidentally ingested by the intermediate host and hatch into oncospheres, which penetrate the intestinal wall and are spread hematogenously to various organs; oncospheres develop into cysts that may contain protoscolices and daughter cysts; the definitive host then ingests the cyst-containing organs of the intermediate host, after which protoscolices develop into adult worms.[1]

The two species have different geographical distributions, different definitive and intermediate hosts, and different but similar clinical manifestations. *E. granulosus* is found in developing countries around the world, particularly South America and sub-Saharan Africa. Dogs and other canines are definitive hosts, while sheep, goats, and other ungulates are intermediate hosts. Cases reported in the United States are usually in seen in immigrants from endemic countries, although some cases of local spread from an infected individual have been reported.[2] *E. multilocularis* is found mostly in the northern hemisphere, especially Europe, Russia, and central Asia, although cases have been reported in northern Canada and Alaska. Foxes are definitive hosts, while rodents are intermediate hosts.[3] Based on the pattern of travel in our patient, he could have been exposed to *E. granulosus* when he stepped in buffalo feces or from other exposure while traveling in sub-Saharan Africa. However, he also could have been exposed to either *E. granulosus* or *E. multilocularis* at an earlier point in his life.

Time course was a key feature of our patient's presentation. The natural history of *E. granulosus* is relatively indolent; many cases are asymptomatic for decades, and symptoms usually arise due to a large cyst causing compression of local structures, blood or lymphatic obstruction, rupture, or bacterial super-infection. In contrast to *E. granulosus* infections, *E. multilocularis* is usually symptomatic, with constitutional symptoms such as malaise and fever, as well as organ-specific symptoms.[4] However, both of these entities usually take years to develop clinical symptoms, so if the the patient's lesion were consistent with Echinococcal disease, it is unlikely to have been acquired on his recent trip to Africa.

Another key feature of the patient's presentation was location. Among *E. granulosus* infections, the liver is affected in two-thirds of cases, while the lungs are affected in one-quarter of cases. Other organs are involved rarely. Among *E. multilocularis* infections, less than 1% occur outside of the liver.[5] Thus, our patient's extrahepatic intra-abdominal lesion would be exceedingly rare for an *Echinococcus* infection.

Ultrasound imaging is used for classification of Echinococcal disease, and the World Health Organization has developed a

staging system that is used to guide treatment.[6] Lesions are characterized from stages I-V, indicating level of activity. Stages I-III are considered active. Stage I indicates a unilocular lesion; those less than five centimeters are treated with albendazole, while those greater than five centimeters are treated with albendazole plus percutaneous drainage. Percutaneous drainage of echinococcal hepatic lesions employs a unique approach termed Puncture, Aspirate, Inject and Reaspirate (PAIR), using a scolicidal agent such as ethanol during the injection phase. This allows for the safe eradication of echinococcus while minimizing the risks of spillage of live cystic contents which can result in anaphylactic shock and seeding of the abdomen with echinococcus.

Stage II indicates a multilocular lesion; regardless of size, they are treated with both albendazole plus surgical excision. Stage III disease is considered transitional, meaning the cyst may already be regressing; again, smaller lesions can be managed medically, while larger ones must be aspirated or surgically excised. Stages IV and V disease are considered inactive and can be observed with serial imaging. This staging system can also be used when diagnosing *Echinococcus* on CT or MRI. Based on this classification, our patient would be considered to have stage CE2 disease, requiring both albendazole therapy and surgical excision. However, the latter was deferred due to inaccessibility of the lesion and lack of certainty about the diagnosis.

Serologic tests, including enzyme-linked immunosorbant assay (ELISA) and direct antigen testings, are available for both species of *Echinococcus*. The reliability of these tests depends on the site of infection. Liver and lung lesions are more likely to result in positive serologic testing than other infection sites. ELISA testing for *E. granulosus* has poor sensitivity, estimated at 60-90%.[7] Testing for *E. multilocularis* is more reliable due to presence of a specific antigen, Em2, that can be used to distinguish between species and can also be trended for resolution of infection.[8] Given the poor sensitivity of serologic testing in extrahepatic disease, our patient's negative serology was not clinically informative.

Medical therapy with albendazole, either as definitive or adjunctive treatment, is usually continued for up to six months in order to achieve resolution of infection.[6] Our patient's rapid improvement within several weeks is not characteristic of an infection with *Echinococcus*. Thus, albendazole was discontinued after the interval improvement on the repeat CT.

Overall, despite the early concern for Echinococcal disease in this patient, his clinical presentation and response to treatment was more consistent with a loculated intra-abdominal cystic lesion of unknown origin, with likely bacterial superinfection. It responded quickly to antimicrobial therapy with both antihelminthic and antibiotic agents, and it continued to improve after discontinuation of the former. There is still no explanation for what might have initiated the formation of this lesion. However, assuming continued resolution on abdominal imaging, he will hopefully avoid the need for a risky intra-abdominal biopsy. In that event, the diagnosis will likely remain speculative.

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