Recurrent amebic liver abscesses despite metronidazole treatment: A rare case report

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August 22, 2023

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Key words: Entamoeba histolytica; Liver Abscess, Amebic; Amebiasis; Paromomycin; Parasitic Diseases

Word Count: 1205

Figures : 2

Tables: 1

Acknowledgments: none

Funding sources: None

Author reports no conflicts of interest.

All authors consent to publication

Key Clinical Message:

Amebic liver abscesses should be considered in adult males with fever, right upper quadrant pain, and weight loss with a history of travel to endemic areas. Effective treatment includes metronidazole followed by paromomycin.

Background:

Amebiasis is an intestinal infection with fecal-oral transmission caused by *Entamoeba histolytica* , a parasitic amoeba. Infection is asymptomatic in 80% of cases but can present with abdominal pain, diarrhea, or constitutional symptoms. Extraintestinal manifestations of amebiasis can occur from invasive infection, with amebic liver abscess (ALA) being the most common complication.[1] While rates of asymptomatic amebiasis are equal in both sexes, ALAs are more prevalent in men.[2] Risk factors for infection include travel to endemic areas with poor sanitary conditions, usually from contaminated food or water. Clinical manifestation of the disease typically occurs 8-20 weeks after exposure but can occur decades after initial exposure.[3] The length of stay during endemic areas is not associated with an increased risk of amebic liver abscess, underscoring the importance of a complete travel history.[3]

Individuals with ALA often present acutely with fever, right upper quadrant pain, and, occasionally, cough. Subacute anorexia and weight loss are also reported, with diarrhea notably absent.[1,4] Radiographically, ALAs are variably-sized solitary collection in the right hepatic lobe, resultant from preferential portal circulatory system of the right colon.[5] Common complications of ALA include transudative pleural effusions or abscess rupture leading to pleuropulmonary amoebiasis with a possible misdiagnosis of bacterial pneumonia.[5] Rarely, the mechanical compression and inflammation of amebic liver abscess cause hepatic vein and inferior vena cava thrombosis.[6]

Diagnosis of ALA is challenging and relies on imaging and serological*E. histolytica* testing in the appropriate clinical context. Polymerase chain reaction (PCR) of liver aspirate may be helpful, as stool PCR can be negative without concurrent amebic colitis.[1] Treatment of ALA includes a ten-day regimen of metronidazole 750 mg orally three times a day followed by an intraluminal amebicide, such as a ten-day regimen of paromomycin 10mg/kg orally three times a day. Decompression is not required but may be helpful to confirm the diagnosis or if there is a concern for rupture or lack of response to medical therapy. [7]

Case Summary:

A previously healthy 66-year-old man was admitted to the hospital for workup of recurrent culture-negative liver abscesses refractory to meropenem therapy. He presented with his fifth occurrence of hepatic abscess over the past five years (**Figure 1)** . The patient lives independently in urban Nevada, with no exposure to animals or engagement in outdoor activities. There is no history of housing instability or incarceration. His sexual history included insertive vaginal intercourse with barrier protection with female partners. His only travel outside the United States was an uneventful five-day trip to Mexico 30 years ago. Several months before his first liver abscess, he used subcutaneous synthetic analogues of growth hormone-releasing hormone (GHRH) for muscle building. His index presentation was a subacute history of fever, chills, and fatigue, where he was found to have a liver abscess and treated with 14 days of ertapenem.

One month following ertapenem therapy, he presented with similar constitutional symptoms and was found to have recurrent hepatic abscess formation. He was treated with six weeks of meropenem. Serum*Entamoeba histolytica* antibody was positive, and he completed a ten-day course of metronidazole 500 mg orally thrice daily. It is unclear whether he completed paromomycin after that.

Three years after his second episode, he was hospitalized with fever, chills, fatigue, and severe dyspnea. He was found to have methicillin-resistant Staphylococcus aureus (MRSA) bacteremia and empyema. Cross-sectional imaging revealed recurrence of a liver abscess, which was aspirated with MRSA. Following percutaneous drainage, a 4-week course of intravenous vancomycin was administered with radiographic improvement. Studies for Entamoeba were not sent as it was believed his liver abscess was pyogenic from MRSA.

One year later, he was found to have recurrence of culture-negative hepatic collection. Despite completing ertapenem for six weeks and current treatment of meropenem for three weeks with patent percutaneous

drains, serial cross-sectional imaging demonstrated a previously drained right lobe abscess cavity, a new right lobe abscess, and a thrombus of the anterior segment right hepatic vein (**Figure 2**).

The patient was admitted to the hospital for evaluation of this new liver abscess with adjacent thrombus. The patient noted 60 pounds of weight loss throughout the last five years but had no abdominal pain, diarrhea, bloody stools, nausea, or vomiting. Physical examination was non-contributory. Laboratory investigations were only significant for normocytic anemia and mildly elevated alkaline phosphatase. Aspiration of the enlarging hepatic collection was negative for bacteria, acid-fast bacilli, and fungus. Doxycycline was added to meropenem for acellular coverage. Esophagogastroduodenoscopy, colonoscopy, and magnetic resonance enterography did not demonstrate evidence of malignancy or inflammatory bowel disease. Polymerase chain reaction (PCR) of stool and the liver abscess were positive for *Entamoeba histolytica* . Antibacterials were discontinued, and the patient was discharged with a ten-day course of metronidazole 750 mg orally thrice daily, followed by ten days of paromomycin 1000 mg orally thrice daily. Repeat stool PCR four weeks after treatment was negative for stool ova and parasites.

Discussion:

There are several possible considerations for the recurrent nature of the patient's liver abscesses. The initial treatment with metronidazole at 500 mg thrice daily may have been subtherapeutic as current guidelines recommend dosing at 750 mg thrice daily. Moreover, metronidazole therapy alone is insufficient without a subsequent luminal agent to treat asymptomatic colonization (Table 1).[8-10] One study in India found a recurrence rate of 9% within two years among patients not treated with a luminal agent.[11] Another study showed a 72% prevalence of asymptomatic luminal colonization of *E. histolytica* at initial presentation of ALA. Of these patients with concomitant intestinal infection, treatment with metronidazole was insufficient to eradicate intestinal infection in greater than 50% of patients despite resolution of the liver abscess.[12] *E. histolytica* has also been shown to develop metronidazole resistance in vitro, but the rates of resistance in practice are unclear.[13] Another possibility considered for the patient's recurrence was close contact with an asymptomatic carrier, such as his family. However, the patient's family tested negative for the stool *E. histolytica* antigen.

It is uncertain when the patient was initially infected with *E. histolytica.* While his use of exogenous GHRH preceded his first liver abscess, it remains unclear whether GHRH increased his susceptibility to ALA recurrence, particularly as he continued to have recurring episodes of abscesses without repeated travel to endemic regions. It is possible that while the patient may not have cleared his initial infection, his exogenous GHRH use may have contributed to the number of relapsing liver abscesses. Endogenous male hormones such as testosterone may contribute to these gender differences as mice models show testosterone level determines susceptibility to ALA.[14] The relationship between GHRH and ALA has not been studied, but it may play a role similar to testosterone in increasing susceptibility.

Conclusion:

We describe a case of recurrent amebic liver abscesses in a patient previously treated with metronidazole without repeated travel to an endemic area. Despite treatment with a 10-day course of metronidazole four years ago for ALA, the patient developed three additional episodes of liver abscesses, ultimately found to be from amebiasis. This case highlights the importance of using appropriately dosed metronidazole, followed by an intraluminal agent for effective treatment of ALAs. Imaging and serology are necessary for diagnosis, but PCR testing of stool and abscess fluid is helpful. Drainage is not necessary but may be helpful in complicated amebic liver abscesses.

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Figure 1. Representation of liver abscess recurrences.

Figure 2. CT abdomen and pelvis with contrast from patient's fifth episode of recurrent liver abscess. This shows a large abscess (red arrow) within the liver dome, measuring 8.2 cm. There is a heterogeneous abnormal signal within the right hepatic lobe inferior to the liver dome abscess, corresponding to the previously drained abscess cavity; the percutaneous drainage catheter is noted within this region (blue arrow).

Author	**Age and sex at first presentation**	**Initial treatment**	**Treatment for recurrence(s)**	**Duration between recurrence(s)**	**Risk factors for reinfection**
Creemers-Schild et. al	23-year-old male	10 days metronidazole then 10 days diloxanide furoate	1st recurrence: drainage + initial treatment 2nd recurrence: drainage + 10 days metronidazole then 10 days paromomycin	1st recurrence: 4 years 2nd recurrence: 3 years	1st recurrence: travel to Nepal and Bangladesh 2nd recurrence: travel to Thailand and China
Hwang et. al	63-year-old male	10 days metronidazole 750 mg TID then 10 days paromomycin 1 g TID	Drainage + 3 days tinidazole 2 g then 20 days iodoquinol 650 mg TID	1 year	No travel or sick contacts

Author	**Age and sex at first presentation**	**Initial treatment**	**Treatment for recurrence(s)**	**Duration between recurrence(s)**	**Risk factors for reinfection**
Ramiro et. al	38-year-old male	10 days metronidazole then unspecified luminal antiameba treatment	1^{st} recurrence: same as initial treatment 2^{nd} recurrence: same as initial treatment	1^{st} recurrence: 18 months 2^{nd} recurrence: 12 months	Residence in Mexico

Table 1 . Other reports of recurrent amebic liver abscesses.