

## CLINICAL CASE OF THE MONTH

# Abdominal Pain in a 39-year-old Man with Recent International Travel

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### CASE PRESENTATION

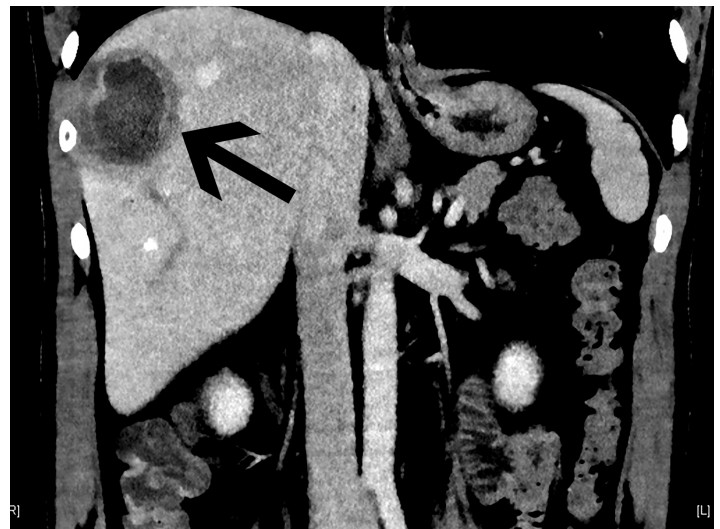
A 39-year-old man presented to the emergency department with a five-day history of right upper quadrant pain, nausea, subjective fevers, fatigue, decreased appetite, myalgias, and pain with deep inspiration. The patient denied any vomiting, constipation, diarrhea, cough, or shortness of breath. Although the patient's symptoms had improved since their onset, the patient was concerned about his ongoing abdominal pain.

The patient denied a history of intravenous drug use. He worked as a bartender, and he admitted to numerous recent sick contacts. The patient also admitted to distant travel to rural Ecuador as a teenager, and more recently, he spent three months in Northern India four months before presentation. Before going to India, the patient attended a travel clinical where he received prescriptions for malaria prophylaxis and azithromycin should he develop severe diarrhea. He also received instructions on food safety in developing countries. The patient stated that he completed his entire course of malaria prophylaxis, and although he only consumed cooked foods and bottled water, he had several episodes of diarrhea during his travels. For the first episode of diarrhea, the patient took his pre-prescribed course of azithromycin, but for subsequent episodes, he obtained unknown antibiotics from local pharmacies. The patient denied any episodes of hematochezia, and he denied noticing worms in his stool.

At the time of presentation, the patient had a pulse of 88/minute, temperature of 98.6 °F, respiratory rate of 21/minute, and blood pressure of 105/64 mmHg. Abdominal exam revealed normoactive bowel sounds and pain with palpation and percussion of the right upper quadrant without rebound or guarding. Murphy's sign and splenomegaly were not appreciated. The lungs were clear to auscultation. The patient's white cell blood count was 17,900 cells/uL (normal range 4,500-11,000 cells/uL) with a normal differential. The patient was mildly hyponatremic at 132 mmol/L (normal range 135-146) and hypokalemic at 3.5 mmol/L (normal range 3.6-5.0). Total protein was elevated at 8.9 g/dL (normal range 3.6-5.2), with a normal albumin at 4.2 g/dL (normal range 3.4-5.0 g/dL). Total bilirubin was elevated at 1.5 mg/dL (normal range <1.3 mg/dL) as was alkaline phosphatase at 135 units/L (normal range 20-120 units/L); both AST and ALT were within normal limits.

Additionally, total serum creatinine kinase, lipase, and lactic acid were all within normal limits. The patient's HIV and acute hepatitis tests were non-reactive.

An abdominal ultrasound revealed an approximately 5 X 4 X 3 cm lobulated echogenic hepatic mass in the right hepatic lobe; the liver was enlarged at 21 cm in length. No biliary duct obstruction or dilation was observed. The mass was further characterized with a triple-phase MRI which showed a 5.8 X 5.7 cm mass with central necrosis and adjacent edema (figure 1).



**Figure 1.** Coronal image of a triple-phase MRI with contrast of the abdomen. Arrow points to a large, walled mass with a central hypodensity in the liver that was subsequently identified as an amoebic abscess.

The patient initially received piperacillin-tazobactam for a possible bacterial hepatic abscess. However, given his recent travel history, the possibility of a parasitic abscess could not be excluded. The patient's abdominal pain did not improve with piperacillin-tazobactam, and on the second hospital day the abscess was drained percutaneously. The abscess drained a purulent, dark-brown material, and the Gram stain was negative for any organisms. Following the Gram stain, the patient was started on metronidazole for a presumed amoebic abscess. Within a day of draining the abscess and initiating metronidazole, the patient's abdominal pain began to resolve. The patient was

discharged on a ten-day course of metronidazole and a seven-day course of paromomycin. Prior to discharge, a serum sample was sent to a reference lab for amoebic serology studies. Several weeks later, serologic testing came back positive for anti-amoebic antibodies.

## DISCUSSION

### *Epidemiology, Pathophysiology, and Clinical Presentation*

The genus *Entamoeba* contains numerous species, three of which, *E. histolytica*, *E. dispar*, and *E. moshkovskii*, can be pathogenic in the human colon.<sup>1</sup> It is estimated that 40-50 million people are infected annually with *Entamoeba* species, and that there are 40,000-100,000 deaths annually due to these infections.<sup>2</sup> Most *Entamoeba* infections are due to *E. dispar*, followed by *E. histolytica* and *E. moshkovskii*. *E. dispar* infection was believed to be non-pathogenic; however, it is now known to be pathogenic, albeit less frequently than *E. moshkovskii* and *E. histolytica*.<sup>3-6</sup> Both *E. moshkovskii* and *E. histolytica* are capable of invading the colonic mucosa and extra-colonic organs, particularly the liver. Until recently, *E. dispar* was believed to only colonize the colon, however, extra-colonic organ involvement, including the liver, has been reported.<sup>3,7</sup>

*Entamoeba* species are endemic in most parts of the developing world. In industrialized countries, most cases occur in immigrants or in individuals who have traveled to endemic areas, although men who have sex with men and institutionalized individuals are also at an increased risk of infection. Infected individuals will pass *E. histolytica* cysts in their feces, which, if ingested in contaminated food or water, can cause infection in other hosts.<sup>2,7</sup> Once ingested, trophocytes will undergo excystation in the ileum and will migrate into and attach to the colonic mucosa.<sup>2</sup> The excystation and migration process can take days to years to occur.<sup>7</sup> Approximately 90% of individuals with *E. histolytica* will have asymptomatic infections, while 10% will develop amoebic colitis. The colitis, due to penetration of the colonic mucosa by trophocytes, may be self-limited and manifest as abdominal pain, fever, and diarrhea with possible hematochezia.<sup>7</sup> Although uncommon, patients with amoebic colitis can also develop more severe complications, such as fulminant colitis or bowel perforations. Bowel strictures are also an uncommon long-term complication.<sup>6,7</sup> Given the high rates of asymptomatic infection, there is ongoing research to identify the genetic hallmarks associated with virulent strains of *E. histolytica*.<sup>8</sup>

Patients with amoebic colitis may also develop disseminated amoebic infections; the most common extra-colonic site is the liver, although the lungs, brain, and skin can also be infected.<sup>7,9-12</sup> It is estimated that less than 1% of individuals infected with *E. histolytica* infection will develop liver involvement. Typically amoebic colitis occurs in the ascending colon, and since the superior mesenteric vein drains into the right hepatic lobe, most cases of invasive *E. histolytica* will involve this region of the liver.<sup>13</sup> Due to inflammation and ultimately destruction of hepatocytes, the invasive amoebas will cause small cysts that amalgamate

into a larger cyst.<sup>2,7</sup> Symptoms of an amoebic liver abscess (ALA) include right upper quadrant tenderness, generalized abdominal pain, fever, and weakness.<sup>14</sup> The time from the development of an ALA to clinical presentation can vary from as soon as a week to more than a month. Similar to our patient, individuals with an ALA will frequently admit to a distant history of abdominal pain and diarrhea that later resolved.<sup>13</sup>

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### *Diagnosis and treatment*

Patients with an ALA will classically present with right upper quadrant pain, and will have a history of living or traveling to a developing country. Additionally, if large enough, ALA can cause jaundice due to biliary obstruction, as well as inferior vena cava obstruction secondary to external compression by an abscess.<sup>13</sup> On laboratory testing, patients will often have mild leukocytosis without eosinophilia, as well as elevated c-reactive protein and/or erythrocyte sedimentation rates.<sup>13,14</sup>

Broadly, there are two types of ALA: acute (patients who present with less than ten days of symptoms) or chronic (patients who present with greater than two weeks of symptoms). Patients with acute abscesses tend to present with fevers, chills, and a severely tender liver and abdomen, whereas patients with chronic ALA tend to have a protracted course of less severe abdominal pain. Patients with acute ALA will often have a normal alkaline phosphatase with an elevated AST, while patients with chronic ALA will have an abnormal alkaline phosphatase with a normal AST level. Both acute and chronic abscesses respond well to treatment, but acute abscesses are more prone to complications, such as cyst rupture or suprainfection.<sup>13</sup>

Although imaging modalities can identify hepatic abscesses, they are often unable to distinguish ALA from other infections, such as *Mycobacterium tuberculosis*, a hydatid cyst, or bacterial cysts secondary to ascending cholangitis.<sup>13</sup> Most hepatic abscesses can be identified by ultrasound, which, for an ALA, will show a homogeneous hypoechoic oval lesion. If further imaging is needed, a computerized tomography (CT) scan or magnetic resonance imaging (MRI) can be used.<sup>6,13</sup> Since ALA, unlike pyogenic abscesses, contain few leukocytes, a 99mTc scan can be used to distinguish the two. Using this modality, an ALA will appear as a "cold" lesion with a "hot" rim, while an entire pyogenic abscess will be "hot."<sup>13</sup>

There are several laboratory tests available to confirm the diagnosis of amebiasis. Stool ova and parasites studies, which are commonly used in resource poor areas, only have a sensitivity of 25-60% in amoebic colitis and a sensitivity <10% in patients with ALA.<sup>1,6</sup> In patients not from endemic areas, anti-amoebic serum serology tests are often the preferred method of diagnosis. There are numerous commercially available antibody assays which have sensitivities of 93.3-100% and specificities of 90.9-100%. There are also commercially available stool, serum, and ALA purulence antigen testing kits which have sensitivities of 54.5-100% and specificities of 93-100%.<sup>1</sup> Entamoeba PCR primers are also available which, unlike most antibody and antigen assays, can distinguish Entamoeba species in stool and ALA purulence samples.<sup>1,3</sup>

In non-endemic areas, patients with asymptomatic colonic amebiasis should be treated with a luminal agent that will kill amoebic cysts and trophocytes. The preferred luminal agents in the United States are paramomycin or iodoquinol, although a third agent, diloxanide furorate, can be used, but it has limited availability.<sup>13</sup> If a patient has symptomatic amoebic colitis or disseminated amebiasis, such as an ALA, a nitroimidazole agent is given in addition to a luminal agent. The first line nitroimidazole agent is metronidazole. Alternatives to metronidazole include secnidazole, which is not available in the United States, and tinidazole. If a patient cannot tolerate or fails treatment with a nitroimidazole, chloroquine can be used instead. By the time an ALA is diagnosed, most patients will no longer have amoebic trophocytes or cysts in their colon. Failure to give ALA patients a luminal agent concomitantly with a nitroimidazole can result in hepatic reinfection in up to 10% of cases.<sup>13,15</sup>

Symptoms in patients with a liver abscess frequently improve within 72 hours of initiating metronidazole.<sup>14</sup> If not treated, there is a risk of spontaneous abscess rupture which, depending on the location, can drain into the peritoneum, pleural cavity, pericardium, or biliary tree. Such spontaneous ruptures can be fatal.<sup>16</sup> Although anti-amoebic agents are the primary treatment of ALA, percutaneous drainage is indicated if a patient does not improve within 3-7 days of initiating anti-amoebic therapy, if the abscess has a wall thicker than 10 mm, if the abscess is larger than 5 cm, or if the abscess is in the left hepatic lobe.<sup>13,16</sup>

After initiating treatment, some ALA may resolve in as little as three months, but most will take six-nine months to fully resolve. Due to the gradual resolution of the cysts, as long as the patient remains asymptomatic, serial ultrasounds of the liver are not indicated.<sup>16</sup> Patients who undergo percutaneous drainage of their abscess are more likely to have resolution of the abscess sooner than those who only receive medical management. Ultimately, long-term sequelae of properly treated ALA are rare.<sup>13</sup>

## REFERENCES

1. Fotedar R, Stark D, Beebe N, et al. Laboratory diagnostic techniques for Entamoeba species. *Clin Microbiol Rev.* 2007;20:511-32.
2. Wuerz T, Kane JB, Boggild AK, et al. A review of amoebic liver abscess for clinicians in a nonendemic setting. *Can J Gastroenterol.* 2012;26:729-33.
3. Ximenez C, Cerritos R, Rojas L, et al. Human amebiasis: breaking the paradigm? *Int J Environ Res Public Health.* 2010;7:1105-20.
4. Oliveira FM, Neumann E, Gomes MA, Caliri MV. Entamoeba dispar: could it be pathogenic. *Trop Parasitol.* 2015;5:9-14.
5. Nanda R, Baveja U, Anand BS. Entamoeba histolytica cyst passers: clinical features and outcome in untreated subjects. *Lancet.* 1984;11:301-3.
6. Petri WA, Singh U. Diagnosis and management of amebiasis. *Clin Infect Dis.* 1999;29:1117-25.
7. Ross AGP, Olds GR, Cripps AW, Farrar JJ, McManus DP. Enteropathogens and chronic illness in returning travelers. *N Engl J Med.* 2013;368:1817-25.
8. Wilson IW, Weedall GD, Hall N. Host-parasite interactions in Entamoeba histolytica and Entamoeba dispar: what have we learned from their genomes? *Parasite Immunol.* 2012;34:90-9.
9. Fernandez-Diez, Magana M, Magana ML. Cutaneous amebiasis: 50 years of experience. *Cutis.* 2012;90:310-4.
10. Maldonado-Barrera CA, Campos-Esparza MR, Munoz-Fernandez L, et al. Clinical case of cerebral amebiasis cause by E. histolytica. *Parasitol Res.* 2012;110:1291-6.
11. Abdel Razeq AA, Watcharakorn A, Castillo M. Parasitic diseases of the central nervous system. *Neuroimaging Clin N Am.* 2011;21:815-41.
12. Shamsuzzaman SM, Hashiguchi Y. Thoracic amebiasis. *Clin Chest Med.* 2002;23:479-92.
13. Hughes MA, Petri WA. Amebic liver abscess. *Infect Dis Clin North Am.* 2000;12:565-82.
14. Blessmann J, Binh HD, Hung DM, Tannich E, Burschard G. Treatment of amoebic liver abscess with metronidazole alone or in combination with ultrasound-guided needle aspiration: a comparative, prospective and randomized study. *Trop Med Int Health.* 2003;8:1030-4.
15. Irusen EM, Jackson TF, Simjee AE. Asymptomatic intestinal colonization by pathogenic Entamoeba histolytica in amoebic liver abscess: prevalence, response to therapy and pathogenic potential. *Clin Infect Dis.* 1992;14:889-93.
16. Sharma MP, Ahuja V. Amebiasis. *N Engl J Med.* 2003;349:307-8.

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