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Amebiasis as the Cause of Pediatric Fever of Unknown Origin

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Abstract

Amebiasis is a parasitic infection caused by the protozoa *Entamoeba histolytica*. It is capable of causing a spectrum of illnesses from asymptomatic infection, to dysentery and invasive extra-intestinal conditions, the most common of which is liver abscess. Here is presented the case of a 14-month old boy presented with Fever of Unknown Origin, which after work-up was diagnosed as amebic liver abscess. Although amebiasis is more prevalent in developing countries the increasing phenomena of migration and tourism has transformed it into a global health issue. It is recommended to maintain a high index of suspicion while valuating a child with Fever of Unknown Origin.

Keywords

Amebiasis, Abscess, Liver, Fever, Child

1. Introduction

Amebiasis is a parasitic infection caused by the protozoa *Entamoeba histolytica*, which can inflict both intestinal and extra-intestinal disease, the most common of those is liver abscess. *E. histolytica* is a pseudopod-forming, non-fllagelated protozoal parasite that causes proteolysis and tissue lysis, and can induce host-cell apoptosis (**Figure 1**) [1]. It is transmitted through the fecal-oral route. Infective cysts are found in fecally contaminated soil, fertilizer, food, water supplies and hands of food handlers. The National Institute of Allergy and Infectious Diseases (NIAD) has classified *E. histolytica* as a category B biodefense pathogen because of its low infectious dose, environmental stability, resistance to chlorine, and easy dissemination through contamination of food and water supplies [2].

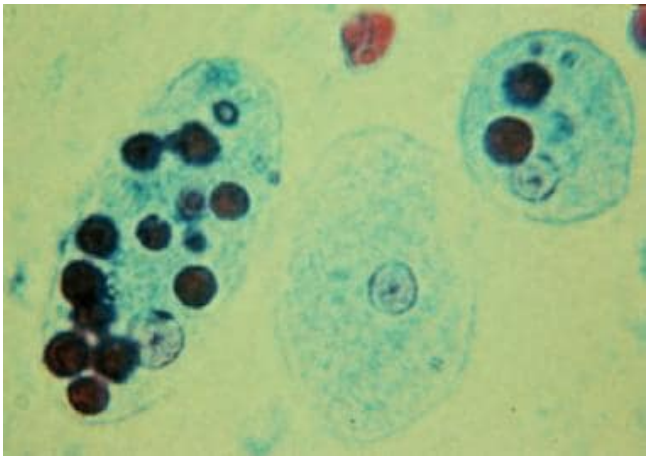

Figure 1. Trichrome stain of *Entamoeba histolytica* trophozoites in amebiasis. Two diagnostic characteristics are observed. Two trophozoites have ingested erythrocytes, and all 3 have nuclei with small, centrally located karyosomes.

Ingestion of *E. histolytica* cysts from the environment is followed by encystation in the terminal ileum or colon to form highly motile trophozoites which may encyst and excrete in the feces or may invade the intestinal mucosal barrier, this way gaining access to the bloodstream and disseminating to the liver, lung and other sites. The incubating period for *E. histolytica* infection is commonly 2 - 4 weeks but may range from a few days to years. The clinical spectrum of amebiasis ranges from asymptomatic infection to fulminant colitis and peritonitis to extra-intestinal amebiasis, the most common form of which is amebic liver abscess. Amebiasis is more severe in very young patients, in elderly and in patients receiving corticosteroids. As many as 90% of *E. histolytica* infections are asymptomatic. Amebic colitis is gradual in onset, with symptoms presenting over 1 - 2 weeks, the most common symptom is diarrhea and fever is noted in 10% - 30% of patients. Amebic liver abscess is the most common form of extras-intestinal amebiasis. Laboratory diagnosis of amebiasis is made by demonstrating the organism or by performing immunologic techniques [3].

Treatment of amebiasis includes pharmacologic therapy, surgical intervention and preventive measures. In endemic areas, asymptomatic infections are not treated. In non-endemic areas, asymptomatic infection should be treated because invasive disease may develop and shedding of *E. histolytica* cysts in the environment is a public health concern [4]. Luminal agents (eg. Paramomycin, Iodoquinol, Diloxanide furoate) that are minimally absorbed by the gastro-intestinal tract are the best choice for intestinal amebiasis [5]. Metronidazole is the mainstay of therapy for invasive amebiasis [6]. Amebic liver abscess of up to 10 cm can be cured with metronidazole without drainage [7].

2. Aim

The aim of this case report is to highlight the role of amebic liver abscess in pediatric Fever of Unknown Origin.

3. Case Report

A 14-month old boy L.E. admitted at the University Hospital Center "Mother Teresa" of Tirana, Albania with a history of 9 days moderate grade fever 38˚C - 39˚C, sporadic vomiting and loose stool 3 - 4 times a day. He was treated with oral antibiotics by a local clinic but fever persisted. The child lived in a rural area with his parents and grandparents. All the family members were healthy and he had been healthy too till then. Vaccination was performed according to the age of the child. The family did not keep domestic animals at home and consumed safe food.

On physical examination the child appeared moderately ill. Neurologic examination was normal. Sclera was normal, no pharyngeal injection or cervical lymphadenopathy was observed. No abnormalities were found on respiratory and cardio-vascular systems. The abdomen was soft, not distended, bowl sounds were present, liver and spleen were not palpable. No rash was observed on the skin.

Laboratory examination revealed: Leukocytosis WBC 17,300 cells/mm^3 (41% neutrophils, 52% lymphocytes), RBC 3,280,000 cells/mm^3, mild anemia Hemoglobin level 9.5 g/dl, Hematocrit value 30%, Platelet count (PLT) 324,000 cells/mm^3, Erythrocyte sedimentation rate 13 mm/h (<15 mm/h), elevated Aspartate aminotransferase 96 U/L (21 - 44 U/L), elevated Alanine aminotransferase 133 U/L (9 - 25 U/L), blood Urea Nitrogen (BUN) 27.2 mg/dL (10.9 - 36 mg/dL), Creatinine 0.43 mg/dL (0.38 - 0.54 mg/dL), Total bilirubin 0.19 mg/dL (<0.4 mg/dL), serum Total protein level 6.6 g/dL (5.6 - 7.5 g/dL), Albumin 4.3 g/dL (3.8 - 5.4 g/dL), normal C reactive protein 0.27 mg/dL (<0.5 mg/dL), normal Fibrinogen activity 365 mg/dL (160 - 390 mg/dL), normal Ferritin value 69 ng/mL (13.7 - 79.8 ng/mL) (Table 1).

Table 1. Laboratory examinations values.

WBC	17,300 cells/mm^3
RBC	3,280,000 cells/mm^3
Hemoglobin	9.5 g/dl
Hematocrit	30%
PLT	324,000 cells/mm^3
ESR	13 mm/h (<15 mm/h)
ALT	133 U/L (9 - 25 U/L)
AST	96 U/L (21 - 44 U/L)
BUN	27.2 mg/dL (10.9 - 36 mg/dL)
Creatinine	0.43 mg/dL (0.38 - 0.54 mg/dL)
Total protein	6.6 g/dL (5.6 - 7.5 g/dL)
Albumin	4.3 g/dL (3.8 - 5.4 g/dL)
Total bilirubin	0.19 mg/dL (<0.4 mg/dL)
CRP	0.27 mg/dL (<0.5 mg/dL)
Fibrinogen	365 mg/dL (160 - 390 mg/dL)
Ferritin	69 ng/mL (13.7 - 79.8 ng/mL)

Radiologic examination of thorax and abdomen revealed no abnormalities. Serologic examination for Salmonellosis, Brucellosis and Rickettsiosis were negative. Cultures of blood, urine and feces resulted in no bacterial growth. Also negative were the tests for HIV, EBV, CMV, Hepatitis A, COVID-19. MANTHOUX test for Tuberculosis was within normal range. After one week of hospitalization no diagnosis was done and fever persisted. So a second radiologic examination was decided to be performed. Ultimately a total body computed tomography discovered a liver abscess (1.7 cm & 1.3 cm). Serologic examination for *E. histolytica* resulted positive. Treatment with metronidazole was initiated. Fever subsided on the third day. Treatment with metronidazole was continued for 2 weeks and the child recovered completely.

4. Discussion

Fever is one of oldest and most prominent feature of disease and also the most common reason for pediatric medical consultations worldwide. It represents a complex adaptive response of the host to various immune challenges whether infectious or non-infectious and commonly occurs in response to infection, inflammation and trauma. Fever is considered a defense mechanism leading to immune activation, decrease in bacterial and viral growth rate and improve host survival in response to invasion by foreign agents [8]. However whet it reaches high degrees and is prolonged in duration causes deleterious effects such as direct cellular damage, local and systemic effects [9] [10].

Fever of Unknown Origin (FUO) in adults was defined by Petersdorf and Besson in 1961 as a state of febrile illness for more than three weeks with a body temperature greater than 38.3˚C on several occasions and uncertain diagnosis after one week of study in hospital [11]. The definition of FUO in children varies from 1 - 3 weeks. FUO remains a challenge even with modern advances in medicine and it may be a symptom of approximately 200 described diseases. The leading cause of FUO in children is infections followed by collagen vascular diseases, whereas malignancy is typically not heralded by fever alone in childhood [12].

Considering the duration of fever in the presenting case (9 days), it was classified as sub-acute fever (1 - 2 weeks in duration). Sub-acute fever may be found in typhoid fever and inta-abdominal abscesses as the most common among other causes. At first sight typhoid fever seemed the most probable diagnosis as the child had also vomiting, diarrhea, and an increase in liver aminotransferases, but the negative result of the serologic test for Salmonellosis did not confirm the suspected diagnosis. On the other hand radiologic examination of the abdomen and thorax showed no lesions, so no suspicion was raised upon the presence of abdominal abscesses as the potential cause of fever. Meantime negative results of blood, urine and feces indicated no presence of bacteria, and also negative tests for HIV, EBV, CMV, Hepatitis A, COVID-19 excluded viral infections as the cause of fever. Serologic tests excluded Brucellosis and Rickettsiosis too.

After one week of hospitalization no diagnosis was performed whereas fever

entered in the chronic or persistent phase (>2 weeks in duration). So it was reasonable to rule out Tuberculosis (negative MANTHOUX test) as a chronic bacterial infection. The absence of changes on blood count (except mild anemia), and no detection of abnormal pathologic cells on peripheral blood smear indicated no malignant cause of the fever. The fact that inflammatory parameters (ferritin, fibrinogen, C-reactive protein) were within normal range did not pointed towards connective tissue disease.

That confusing scenario made necessary the performing of a second radiologic examination (total body computed tomography), which resulted a benefit as it discovered small liver abscess (1.7 cm & 1.3 cm). Serologic test for *E. hitolytica* confirmed the diagnosis of amebic liver abscess, which probably was too small to be detected in the previous examination. As it was expected, fever subsided after 2 days of metronidazole treatment.

Amebiasis is a major global health worldwide, but developing countries suffer the great burden of the disease. Approximately 50 million cases of invasive *E. histolytica* disease occur globally each year, resulting in as many as 100,000 deaths [13]. Amebiasis is the second leading cause of death due to parasitic disease, following malaria at the first place. The burden of the disease is much greater because 10% - 20% of infected individuals become symptomatic [14]. The prevalence of *Entamoeba* infection is as high as 50% in areas of Central and South America, Africa and Asia [15]. Amoebiasis cases in Albania were estimated to be 45 cases per 100,000 inhabitants during 1997-2000, afterwards with improvement of sanity and public health control it dropped to 5 - 8 cases per 100,000 inhabitants.

Although most cases of amebiasis are asymptomatic, invasive extraintestinal disease can occur. Spread of amebiasis to the liver occurs via the portal blood. The pathogenic strains evade the complement-mediated lysis in the bloodstream. Trophozoites that reach the liver create unique abscesses [1]. Serum antibodies in patients with amebic liver abscess develop in 7 days and persist for as long as 10 years. Cell-mediated immunity is important in limiting disease and preventing recurrences. Amebic liver abscess is the most common form of extras-intestinal amebiasis and occurs in as many as 5% of patients with symptomatic intestinal amebiasis [16]. Approximately 80% of patients with amebic liver abscess present within 2 - 4 weeks of infection with fever the most typical presentation (90% of cases), accompanied by right upper quadrant pain. Associated gastrointestinal symptoms occur in 10% - 35% of patients and include nausea, vomiting, abdominal distention, diarrhea and constipation. More than one-third of patients who present with amebic liver abscess do not have history of prior gastro-intestinal symptoms. Although the disease is more prevalent in developing countries, with the increasing phenomena of migration and international tourism it is becoming a global health issue.

5. Conclusion

Amebiasis in children is mostly asymptomatic, but it can evolve in invasive

forms such as liver abscess, which is characterized by prolonged and persistent fever. It is more prevalent in developing countries, but with the increasing phenomena of migration and international tourism, it is becoming a global health issue. So a high index of suspicion should be kept while valuating a child with Fever of Unknown Origin.

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The publication was performed on consent of the child's parent providing the anonymity.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Stanley Jr., S.L. (2003) Amoebiasis. *Lancet*, **361**, 1025-1034. https://doi.org/10.1016/S0140-6736(03)12830-9

[2] Shirley, D.T., Farr, L., Watanabe, K. and Moonah, S. (2018) A Review of the Global Burden, New Diagnostics, and Current Therapeutics for Amebiasis. *Open Forum Infectious Diseases*, **5**, ofy161. https://doi.org/10.1093/ofid/ofy161

[3] Tanyuksel, M. and Petri Jr., W.A. (2003) Laboratory Diagnosis of Amebiasis. *Clinical Microbiology Reviews*, **16**, 713-729. https://doi.org/10.1128/CMR.16.4.713-729.2003

[4] Gonzales, M.L., Dans, L.F. and Martinez, E.G. (2009) Antiamoebic Drugs for Treating Amoebic Colitis. *Cochrane Database of Systematic Reviews*, Article ID: CD006085. https://doi.org/10.1002/14651858.CD006085.pub2

[5] Salles, J.M., Salles, M.J., Moraes, L.A. and Silva, M.C. (2007) Invasive Amebiasis: An Update on Diagnosis and Management. *Expert Review of Anti-infective Therapy*, **5**, 893-901. https://doi.org/10.1586/14787210.5.5.893

[6] Moon, T.D. and Oberhelman, R.A. (2005) Antiparasitic Therapy in Children. *Pediatric Clinics of North America*, **52**, 917-948. https://doi.org/10.1016/j.pcl.2005.02.012

[7] Bammigatti, C., Ramasubramanian, N.S., Kadhiravan, T. and Das, A.K. (2013) Percutaneous Needle Aspiration in Uncomplicated Amebic Liver Abscess: A Randomized Trial. *Tropical Doctor*, **43**, 19-22. https://doi.org/10.1177/0049475513481767

[8] Mackowiak, P.A. (1994) Fever: Blessing or Curse? A Unifying Hypothesis. *Annals of Internal Medicine*, **120**, 1037-1040. https://doi.org/10.7326/0003-4819-120-12-199406150-00010

[9] Hildebrandt, B., Wust, P., Ahlers, O., Dieing, A., Sreenivasa, G., Kerner, T., *et al.* (2002) The Cellular and Molecular Basis of Hyperthermia. *Critical Reviews in Oncology/Hematology*, **43**, 33-56. https://doi.org/10.1016/S1040-8428(01)00179-2

[10] Roti, J.L. (2008) Cellular Responses to Hyperthermia (40-46 °C): Cell Killing and Molecular Events. *International Journal of Hyperthermia*, **24**, 3-15. https://doi.org/10.1080/02656730701769841

[11] Fusco, F.M., Pisapia, R., Nardiello, S., Cicala, S.D., Gaeta, G.B. and Brancaccio, G. (2019) Fever of Unknown Origin (FUO): Which Are the Factors Influencing the Final Diagnosis? A 2005-2015 Systematic Review. *BMC Infectious Diseases*, **19**, Article No. 653. https://doi.org/10.1186/s12879-019-4285-8

[12] Finkelstein, J.A., Christiansen, C.L. and Platt, R. (2000) Fever in Pediatric Primary Care: Occurrence, Management, and Outcomes. *Pediatrics*, **105**, 260-266. https://doi.org/10.1542/peds.105.S2.260

[13] Stauffer, W., Abd-Alla, M. and Ravdin, J.I. (2006) Prevalence and Incidence of Entamoeba Histolytica Infection in South Africa and Egypt. *Archives of Medical Research*, **37**, 266-268. https://doi.org/10.1016/j.arcmed.2005.10.006

[14] Ximénez, C., Morán, P., Rojas, L., Valadez, A. and Gómez, A. (2009) Reassessment of the Epidemiology of Amebiasis: State of the Art. *Infection, Genetics and Evolution*, **9**, 1023-1032. https://doi.org/10.1016/j.meegid.2009.06.008

[15] Tengku, S.A. and Norhayati, M. (2011) Public Health and Clinical Importance of Amoebiasis in Malaysia: A Review. *Tropical Biomedicine*, **28**, 194-222.

[16] Rao, S., Solaymani-Mohammadi, S., Petri Jr., W.A. and Parker, S.K. (2009) Hepatic Amebiasis: A Reminder of the Complications. *Current Opinion in Pediatrics*, **21**, 145-149. https://doi.org/10.1097/MOP.0b013e32831ef249