Case Report: Visceral Leishmaniasis with *Salmonella* Paratyphi and *Brucella melitensis* Coinfection as a Cause of Persistent Fever in a Patient from Sudan

Sayda El Safi,1* Hussam Elshikh,1 Enaam El Sanousy,2 Nagwa El Amin,1 Alfarazdag Mohammed,1 Kristien Verdonck,3 Jan Jacobs,3,4 Marleen Boelaert,3 and François Chappuis5

1Faculty of Medicine, University of Khartoum, Khartoum, Sudan; 2Brucella Department, Veterinary Research Institute, Khartoum, Sudan; 3Institute of Tropical Medicine, Antwerp, Belgium; 4Department of Microbiology and Immunology, KU Leuven, University of Leuven, Leuven, Belgium; 5Division of Tropical and Humanitarian Medicine, Geneva University Hospitals, Geneva, Switzerland

Abstract. We describe the case of a 12-year-old boy from Sudan who presented with fever of 1-week duration, headache, cough, and vomiting. A set of diagnostic tests led to the diagnosis of three infectious diseases: visceral leishmaniasis (probable diagnosis based on positive direct agglutination test), enteric fever (blood culture grown with *Salmonella* Paratyphi), and brucellosis (blood culture grown with *Brucella melitensis*). The patient received specific treatment of the three infections and recovered. This case illustrates the occurrence and possible implications of coinfections in patients with persistent fever, including conditions that are hard to diagnose in field settings, such as brucellosis and enteric fever.

CASE REPORT

A 12-year-old boy presented to the outpatient clinic of Tabarak Allah Rural Hospital in Gedaref State in October 2013, with complaints of fever, chills, headache, dry cough, and vomiting for 1 week, and with anorexia for the last 2 days. The patient had no history of visceral leishmaniasis, but he came from Barbar El Fugara village in the Atbara River area (lat. 13°34' 47.7" N, long. 36°18' 30.6" E), the most endemic area for visceral leishmaniasis in Sudan. He was enrolled in a clinical study called “Neglected Infectious Diseases Diagnosis” (NIDIAG)1 and underwent standard history taking, physical examination, and a set of diagnostic tests targeting severe and treatable infectious causes of persistent fever, that is, visceral leishmaniasis, malaria, tuberculosis, enteric fever, brucellosis, amebic liver abscess, relapsing fever, rickettsial diseases, leptospirosis, and human immunodeficiency virus (HIV) infection. The NIDIAG project did not interfere with the choice of treatment of the included patients, but made sure that essential medicines for the target conditions were present at the study site.

The initial physical examination (day 0) revealed that his weight was 21 kg, height 118 cm, axillary temperature 40.7°C, respiratory rate 30/minute, heart rate 108/minute, and blood pressure 90/70 mm Hg. He presented with a normal level of consciousness, moderate cachexia, pallor, cervical and inguinal lymphadenopathy (size 1 cm), and bilateral tonsil inflammation. Chest examination revealed crackles and decreased air entry in the right lung. No abnormalities were found on abdominal examination. The rest of the physical examination was unremarkable.

On laboratory testing, the hemoglobin level was 11.2 g/dL and the white blood cell count 12.6 × 10⁹/L. Urine analysis revealed 10–25 leukocytes/µL. Both Giemsa-stained blood microscopy and rapid diagnostic tests for malaria (PF-HRP2 and pan-pLDH) were negative. A rapid diagnostic test for HIV (Determine™, Inverness Medical, Shinjuku-ku, Japan) was negative. Direct microscopic search for *Leishmania* amastigotes on lymph node aspirate was negative, and as the patient did not have clinical splenomegaly, spleen aspiration was not carried out. Blood samples were collected for the direct agglutination test for visceral leishmaniasis and for blood culture (using two HiMedia™ (HiMedia Laboratories, Mumbai, India) culture bottles and searching for *Salmonella* and *Brucella*).

On day 0, the clinical picture was consistent with bacterial pneumonia, and oral erythromycin and amoxicillin treatment was initiated. On day 2, as the high fever persisted, treatment was switched to intravenous ceftriaxone. The next day, the direct agglutination test was found to be positive (titer 1/12,800) and, accordingly, a diagnosis of probable visceral leishmaniasis was made. The patient was admitted to the hospital and received intramuscular sodium sibogluconate (20 mg/kg) combined with paromomycin (15 mg/kg) daily for 17 days, and ceftriaxone was stopped. The fever subsided in the following days and the patient was discharged on day 19 with no remaining symptoms and signs.

On day 12, the reference laboratory in Khartoum identified *Salmonella* Paratyphi in the blood culture taken on admission, but the result could only be communicated to the medical team in the field and subsequently to the patient on day 25. The paromomycin component of the treatment of visceral leishmaniasis could have had a partial effect on the patient’s salmonellosis, as paromomycin is an aminoglycoside with poor activity against intracellular bacteria. The attending physician decided to treat the patient with trimethoprim/sulfamethoxazole for 2 weeks. On day 43, *Brucella melitensis* biovar 1 was identified in the admission blood cultures and, despite the absence of symptoms, the patient was treated with oral doxycycline for 6 weeks and intramuscular gentamicin for 2 weeks. The patient remained well during treatment and follow-up.

DISCUSSION

To our knowledge, this is the first report in the English literature of isolation of *Salmonella* and *Brucella* in blood cultures of a febrile patient with probable visceral leishmaniasis. The identification of *Salmonella* sp. and *Brucella* sp. at reference laboratories of the University of Khartoum was confirmed and further characterized as *Salmonella* Paratyphi. Microbiology Laboratory, Institute of Tropical Medicine, Antwerp,
Latin America, with an estimated worldwide 21.6 million cases (types: A, B, and C) and widely distributed in Asia, Africa, and Europe. In Sudan, several visceral leishmaniasis epidemics were reported, claiming a huge death toll. In Gedaref State in the eastern part of the country is prone to leishmaniasis. Prolonged fever with lymphadenopathy should raise the suspicion of visceral leishmaniasis in Sudan.3

Half of the 30,000–50,000 annual visceral leishmaniasis cases estimated in East Africa, the second largest visceral leishmaniasis focus in the world after South Asia, are thought to occur in Sudan.4 In this country, several visceral leishmaniasis epidemics were reported, claiming a huge death toll.5 Gedaref State in the eastern part of the country is prone to epidemics and presently accounts for the vast majority of visceral leishmaniasis cases in Sudan, particularly in the Atbara River area.6

Although visceral leishmaniasis is a well-recognized and quantified health problem in Sudan, there are no such national data for enteric fever and brucellosis, and the exact contribution of these conditions to febrile illness in the country is not known. Enteric fever is a systemic illness caused by Salmonella Typhi and Salmonella Paratyphi (divided into three subtypes: A, B, and C) and widely distributed in Asia, Africa, and Latin America, with an estimated worldwide 21.6 million cases and 200,000 deaths in 2004.7 Transmission occurs through consumption of contaminated food and drinks handled by people who shed the organism from stool or, less commonly, urine. Classic presentation includes acute or persistent fever, abdominal pain, diarrhea or constipation, dry cough, and hepatosplenomegaly. Reports from Gedaref state indicated that 4% of visceral leishmaniasis patients did not present with splenomegaly;8 the absence of splenomegaly, especially in a patient with only 1 week of fever, should therefore not be regarded as evidence that rules out a diagnosis of visceral leishmaniasis. Prolonged fever with lymphadenopathy should raise the suspicion of visceral leishmaniasis in Sudan.3

Enteric fever was found to be the second most common laboratory-confirmed diagnosis for acute fever patients in a study conducted in Port Sudan in eastern Sudan.9

Brucellosis is one of the world’s most common zoonotic infections, with greater than half a million new cases annually and highly variable incidence rates ranging from 0.02 (France) to 269 per 100,000 per year (Iraq). It is caused by several species of Brucella, which are fastidious Gram-negative aerobic coccobacilli. Transmission to humans occurs mainly through contact with fluids from infected domestic animals such as cattle, goats, and sheep, or by ingestion of their unpasteurized milk and other dairy products.10 Brucellosis is a bacteremic systemic infection that may involve any organ of the body. The disease in humans presents as an acute or persistent febrile illness, with or without focal clinical symptoms and signs.11 Brucellosis is one of the important zoonotic diseases among livestock in Sudan, where several studies were conducted to investigate the prevalence of the infection among animals and the proportion of human contacts with positive serology.12–14 In addition, 29 patients with long-standing fever from Central Sudan were diagnosed with probable brucellosis on the basis of one serological test.15

COINFECTION LEISHMANIA, SALMONELLA, AND BRUCELLA IN SUDAN

Comorbidity of visceral leishmaniasis with other nonspecific (e.g., pneumonia and meningitis) or specific infectious diseases including HIV/AIDS, tuberculosis, and malaria has been reported from different parts of the world including Sudan.17–19 Comorbidity of visceral leishmaniasis and salmonellosis was described in a 16-month-old baby with prolonged fever in Turkey.20 In that report, however, the diagnosis of enteric fever was based on serology (Widal test), and a false-positive result could not be ruled out. The occurrence of concurrent infections with Salmonella and Brucella in febrile illness has been reported in two patients with acute fever in Egypt, but the diagnosis of brucellosis was based on serology in both cases.21

Coinfections cause diagnostic and therapeutic challenges. This was well illustrated in the patient presented here. The relative contribution of the different conditions to the clinical symptoms and signs at admission, and the relative contribution of the different treatments to the patient’s recovery are impossible to disentangle. Although visceral leishmaniasis could be diagnosed on site because of the availability of serology (direct agglutination test), the results of Salmonella sp. and Brucella sp. could only be obtained and communicated to the caregivers, and ultimately to the patient, on days 25 and 43, respectively. In fact, these conditions would have been simply missed if blood cultures had not been implemented for the purpose of the NIDIAG study. We, therefore, highlight the need 1) to develop diagnostic guidance tools for persistent fever that consider that several conditions may coexist and 2) to develop and/or deploy field-based accurate diagnostic tests for both enteric fever and brucellosis.

Received June 1, 2018. Accepted for publication August 5, 2018.

Published online September 24, 2018.

Acknowledgments: We would like to thank the staff from the Ministry of Health and from Médecins sans Frontières at Tabarak Allah Hospital, Gedaref State for their help. Our thanks are also due to Abdallah El Basheer, Salah Abdallah Mohamed, Awad Hammad, and Ahmed El Mustafa for their technical assistance.

Financial support: This work is part of the NIDIAG European research network (Collaborative Project) supported by the European Union’s Seventh Framework Programme for research, technological development, and demonstration under grant agreement no 260260.

Authors’ addresses: Sayda El Safi, Hussam Elshikh, Nagwa El Amin, and Alfarazdag Mohammed, Faculty of Medicine, University of Khartoum, Khartoum, Sudan, E-mails: shelsahi@yahoo.com, nosamelesikhi@yahoo.com, nagwaemalin@yahoo.com, and elfarazdag@yahoo.com. Ensaam El Sanoussi, Brucella Department, Veterinary Research Institute, Khartoum, Sudan, E-mail: ensaamis@hotmail.com. Kristien Verdonck, Jan Jacobs, and Marleen Boelaert, Institute of
REFERENCES

1. Alirol E et al., 2016. Diagnosis of persistent fever in the tropics: set of standard operating procedures used in the NIDIAG febrile syndrome study. PLoS Negl Trop Dis 10: e0004749.

2. Zijlstra EE, el-Hassan AM, 2001. Leishmaniasis in Sudan. Visceral leishmaniasis. Trans R Soc Trop Med Hyg 95 (Suppl 1): S27–S58.

3. Kirk R, Sati MH, 1940. Studies in leishmaniasis in the Anglo-Egyptian Sudan. 11. Skin and lymph glands in kala-azar. Trans R Soc Trop Med Hyg 33: 501–506.

4. Alvar J, Vélez ID, Bern C, Herrero M, Desjeux P, Cano J, Jannin J, den Boer M; the WHO Leishmaniasis Control Team, 2012. Leishmaniasis worldwide and global estimates of its incidence. PLoS One 7: e35671.

5. Seaman J, Mercer AJ, Sondorp E, 1996. The epidemic of visceral leishmaniasis in western Upper Nile, southern Sudan: course and impact from 1984 to 1994, 1996. Int J Epidemiol 25: 862–971.

6. EL-Safi SH, Bucheton B, Kheir MM, Musa HA, EL-Obaid M, Hammad A, Dessein A, 2002. Epidemiology of visceral leishmaniasis in Atbara River area, eastern Sudan: the outbreak of Barbar El Fugara village (1996–1997). Microbes Infect 4: 1439–1447.

7. Crump JA, Luby SP, Mintz ED, 2004. The global burden of typhoid fever. Bull World Health Organ 82: 346–353.

8. Ministry of Health, Gedaref State, 2010. Enteric Fever Annual Records.

9. Hyams KC, Oldfield EC, Scott RM, Bourgeois AL, Gardiner H, Pazzaglia G, Moussa M, Saleh AS, Dawi CE, Daniell FD, 1986. Evaluation of febrile patients in Port Sudan, Sudan: isolation of dengue virus. Am J Trop Med Hyg 35: 860–865.

10. Franco MP, Mulder M, Gilman RH, Smits HL, 2007. Human brucellosis. Lancet Infect Dis 7: 775–786.

11. Young EJ, 1995. An overview of human brucellosis. Clin Infect Dis 21: 283–289.

12. Gumaa MM, Osman HM, Omer MM, El Sanousi EM, Godfroid J, Ahmed AM, 2014. Seroprevalence of brucellosis in sheep and isolation of Brucella abortus biovar 6 in Kassala state, eastern Sudan. Rev Sci Tech 33: 957–965.

13. Omer MM, Musa MT, Bakhiet MR, Perrett L, 2010. Brucellosis in camels, cattle and humans: associations and evaluation of serological tests used for diagnosis of the disease in certain nomadic localities in Sudan. Rev Sci Tech 29: 663–669.

14. EL-Safi SH, Bucheton B, Kheir MM, Musa HA, EL-Obaid M, Hammad A, Dessein A, 2002. Epidemiology of visceral leishmaniasis in Atbara River area, eastern Sudan: the outbreak of Barbar El Fugara village (1996–1997). Microbes Infect 4: 1439–1447.

15. World Health Organization, 2018. Leishmaniasis and HIV Coinfection. Available at: http://www.who.int/leishmaniasis/burden/hiv_coinfection/burden_hiv_coinfection/en/. Accessed August 30, 2018.

16. Hasnain MG, Ghosh P, Sharafat Sonin MS, Baker J, Mondal D, 2014. First case of pulmonary tuberculosis and visceral leishmaniasis coinfection successfully treated with antituberculosis drug and liposomal amphotericin. Clin Case Rep 2: 331–332.

17. Van den Bogaart E et al., 2013. Concomitant malaria among visceral leishmaniasis in-patients from Gedarif and Sennar states, Sudan: a retrospective case-control study. BMC Public Health 13: 332.

18. Kayseri E, Hizarcioğu M, Güleş P, Apa H, Keskin S, 2005. Coexistence of kala-azar and salmonellosis in a 16 month-old baby? Or a false positive Widal reaction in kala-azar? [article in Turkish]. Türkiye Parazitol Derg 29: 141–144.

19. Parker TM, Murray CK, Richards AL, Samir A, Ismail T, Fadeel MA, Jiang J, Wasty MO, Pimentel G, 2007. Concurrent infections in acute febrile illness patients in Egypt. Am J Trop Med Hyg 77: 390–392.