BRIEF COMMUNICATION

Visceral Leishmaniasis-Associated Hemophagocytic Lymphohistiocytosis in a Traveler Returning From a Pilgrimage to the Camino de Santiago

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We report the case of a 73-year-old American traveler who presented with 3 weeks of fatigue, fevers, chills, and pancytopenia. Clinical and laboratory findings were consistent with hemophagocytic lymphohistiocytosis (HLH) and bone marrow biopsy revealed amastigotes consistent with visceral leishmaniasis. The range of endemic visceral leishmaniasis transmission now extends into northern Spain and travelers to this region should use personal protective measures against sand fly exposure.

The number of travelers to the Camino de Santiago has more than doubled over the last 10 years, from 74,614 in 2003 to 192,488 in 2012. Most travel on foot. Of those who made the pilgrimage in 2012, 7,071 (7.27%) were American tourists.1 There are limited publications on adverse events associated with travel to this region and to date there have been no reports of visceral leishmaniasis in a traveler returning from this region. Travel along the Camino de Santiago peaks between May and October, coinciding with seasonal peaks in the population of Phlebotomus perniciosus and Phlebotomus ariasi, the two primary phlebotomine sand fly vectors of Leishmania infantum in Spain.2 In this case report, we present a case of fever in a returning pilgrim and discuss the expanding range of visceral leishmaniasis within Spain, the association of this condition with hemophagocytic lymphohistiocytosis (HLH), and the need for pre-travel precautions and increased diagnostic suspicion for this potentially devastating zoonosis.

Case Report

A 73-year-old man presented to the emergency room of a community hospital in Northern California with 3 weeks of progressive fatigue, fever, and chills. The fatigue had developed during a vacation to British Columbia, and had worsened such that the patient, who previously walked 5 miles a day, was confined to bed. He described diurnal fever and chills, as well as drenching sweats, progressive abdominal distention, and anorexia. He denied dyspnea, arthritis or arthralgias, abdominal pain, and weight loss. The patient had no sick contacts and no contacts with animals. He had a remote history of prostate cancer treated with brachytherapy, and took hydrochlorothiazide and lisinopril for hypertension. He lived in suburban Northern California, and his only travel besides his recent trip to British Columbia was a pilgrimage along the Camino de Santiago in Northern Spain through the autonomous communities of Catalonia, Aragon, Navarre, La Rioja, Castile-León, and Galicia (Figure 1), which he undertook 11 months prior to presentation.

The patient was noted to have modest hepatosplenomegaly (spleen size 13 cm by computerized tomography) and abdominal distention at tests taken outside the hospital. He was pancytopenic (hemoglobin 8.0 g/dL, white blood cell count 2,000 cells/μL, and platelets 51,000/μL), had elevated transaminases

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Figure 1 The patient’s path across Spain (black line) with the distribution of Phlebotomus perniciosus (diagonal lines) and Phlebotomus ariasi (dots), the sand fly vectors of Leishmania infantum, adapted from reference (12).

(aspartate aminotransferase and alanine transaminase of 294 and 212 U/L, respectively), and markedly elevated ferritin of 23,517 μg/L with a fibrinogen of 83 mg/dL and triglycerides of 186 mg/dL. Multiple blood cultures were drawn over the course of his hospitalization, all of which were negative. Serological testing for human immunodeficiency virus (HIV), hepatitis A, B, and C, coccidioides, blastomyces, parvovirus, and echinococcus was negative. Serum angiotensin-converting enzyme and ceruloplasmin levels were also within normal limits. Urinary histoplasma antigen showed a borderline positive result of 0.9 ng/mL (reference range <0.7, borderline 0.7–2.9). Biopsies of the bone marrow, liver, and a retroperitoneal lymph node were performed and the patient was then transferred to the University of California, San Francisco Medical Center, for further evaluation with a preliminary diagnosis of HLH of unknown etiology.

The next day, review of the bone marrow biopsy slides revealed granulomas filled with apoptotic debris, intracellular and extracellular microorganisms consistent with amastigotes, and rare red blood cells phagocytized by macrophages (Figure 2). There was no evidence of histoplasmosis or hematologic malignancy. The immunofluorescent antibody test for Leishmania donovani performed at the Centers for Disease Control and Prevention (Atlanta, GA) was positive at a dilution of 1:512. Soluble interleukin-2 (IL-2) receptor returned at 50,591 μg/mL (reference range 406–1100 μg/mL) confirming the diagnosis of HLH.

The patient was treated with liposomal amphotericin B (Ambisome Astellas, Northbrook, IL, USA) 3 mg/kg/day for 5 days followed by two subsequent outpatient infusions of 3 mg/kg to total 21 mg/kg. In outpatient follow-up 9 days after the initiation of
amphotericin treatment, the patient reported modest improvement in his fatigue and anorexia as well as remission of his fevers and chills. His pancytopenia, transaminases, and ferritin normalized. There has been no evidence of relapse 6 months after completion of therapy.

Discussion

Leishmaniasis is endemic in Spain, with the highest transmission rates in the southern and eastern regions of the country, but recent years have seen northward extension of sand fly vectors and infected domestic dogs (the primary reservoir of L. infantum), and a large outbreak in central Spain attributed to an unusual zoonotic reservoir host. Between 1997 and 2008, the nationwide incidence of first-time hospitalizations for leishmaniasis remained stable at 0.41 cases per 100,000 citizens. However, between 2010 and 2012 there was a fivefold increase in the number of cases reported in the province of Madrid, due to an outbreak in a suburban area south of the city. This outbreak, which featured the emergence of hares as a new reservoir, was ascribed to several factors, including increasing population density and new suburban housing developments in a previously rural landscape. Similar factors, as well as increased sand fly density and range due to climate change, may contribute to the recently observed northward spread of canine leishmaniasis. An increase in canine L. infantum incidence in a community often precedes an increase in human cases and is consistent with the extension of L. infantum transmission into previously nonendemic regions along the Camino de Santiago.

Providers who care for travelers to northern Spain and the Camino de Santiago should counsel patients regarding the risk of leishmaniasis. Travelers should minimize the amount of exposed skin and treat uncovered skin with DEET-based insect repellents. The pyloric flap is an effective method to treat unclothed stomach regions. Travelers should use personal protective measures against sand fly exposure. In addition, providers should include visceral leishmaniasis on the differential diagnosis of ill, returning travelers from northern Spain. HLH is a rare complication of visceral leishmaniasis usually curable with appropriate antileishmanial treatment.

Conclusion

Travelers who plan to walk the Camino de Santiago should use personal protective measures against sand fly exposure. In addition, providers should include visceral leishmaniasis on the differential diagnosis of ill, returning travelers from northern Spain. HLH is a rare complication of visceral leishmaniasis usually curable with appropriate antileishmanial treatment.

Declarations of Interests

The authors state they have no conflicts of interest to declare.

References


