Case Report: Visceral Leishmaniasis Falsely Diagnosed as Q Fever

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Abstract. Visceral leishmaniasis (VL) is a systemic infection caused by the protozoal parasite *Leishmania*, spread via the bloodstream to the reticuloendothelial system, through the bite of the sand fly. It is endemic in parts of Africa, South America, Asia, and Europe, including the Mediterranean. Here, we describe a case of VL that was initially diagnosed as Q fever based on positive *Coxiella burnetii* serology and showed a partial response to doxycycline treatment.

CASE PRESENTATION

A 21-year-old man presented to a specialist infectious diseases service at a London hospital with fever, weight loss, and night sweats of 2-week duration, accompanied by abdominal discomfort. He was born in the United Kingdom and had lived his life between the United Kingdom and Spain, predominantly Barcelona and Valencia. His only other travel was a holiday to Morocco 2 years before presentation. He worked in a pastry factory and had a healthy pet dog. He had never worked with animals or consumed unpasteurized dairy or raw meat. On systems review, he denied rashes, arthralgia, or respiratory symptoms.

His medical history was notable for a similar presentation 6 months ago in Spain, with fever, pancytopenia, and splenomegaly. Among numerous investigations, *Coxiella burnetii* serology (immunofluorescence assay [IFA], Vircell) was positive (phase 1 IgG 1:180; phase 2 IgG 1:640), and he was treated for Q fever with 2 weeks of doxycycline and his fever resolved completely.

On examination, he was febrile at 38.7°C and looked generally unwell. He had no rashes, and cardiorespiratory examination was unremarkable. His liver was palpable at 3 cm below the costal margin, and he had splenomegaly extending across the midline, with palpable subcentimeter cervical and inguinal lymph nodes.

Baseline investigations demonstrated pancytopenia (hemoglobin 86 g/L, platelets 88×10^6 /L, white cell count 0.9×10^6 /L, and neutrophils 0.3×10^6 /L). Liver and renal function tests were normal, and C-reactive protein was raised at 137 mg/L. A blood film showed rouleaux formation in keeping with an inflammatory state, and no abnormal cells were seen. Thick and thin films for malaria, HIV serology, and four sets of blood cultures were all negative.

Computed tomography of his abdomen and pelvis demonstrated hepatomegaly and massive splenomegaly of 28 cm, with no other abnormal findings (Figure 1). He continued to spike temperatures over 38°C, with no response to piperacillin-tazobactam (given as empirical treatment of neutropenic fever).

In the context of pancytopenia, hepatosplenomegaly, and B symptoms (fever, weight loss, and night sweats), the differential diagnosis included infection or hematological malignancy. Two bone marrow aspirates from day 10 and day 11 of

admission demonstrated only reactive changes, and no parasites were seen.

Serology for *Bartonella*, *Brucella*, and *Rickettsiae* was all negative. Q fever serology showed negative *C. burnetii* phase 1 IgG and positive phase 2 IgG (titer 1:160).

Leishmania IFA sent on day 12 with result obtained on day 17 of admission was strongly positive at 1:256. Bone marrow PCR sent on day 11 and reported on day 33 was positive for *Leishmania donovani* complex DNA, confirming a diagnosis of visceral leishmaniasis (VL). He was commenced on liposomal amphotericin B (AmBisome, Gilead Sciences International Ltd., Cambridge, UK) at 3 mg/kg, given on days 1–5, day 14, and day 21. His fever resolved after 48 hours of treatment, and he was discharged to complete his treatment as an outpatient. He remained well on follow-up at 6 months.

DISCUSSION

Our case demonstrates two aspects of interest—the potential pitfalls in diagnosing VL and the marked but temporary clinical response our patient demonstrated following initial doxycycline treatment.

Our patient's initial positive *C. burnetii* serology results were more likely to be false positives, for the following reasons, although it is not possible to definitively exclude the possibility of Q fever and VL coinfection in retrospect. His clinical syndrome on first presentation was not in keeping with Q fever. Acute Q fever typically presents with acute pneumonia and hepatitis (although he did have hepatomegaly, he did not have a transaminitis) and does not present with massive splenomegaly or pancytopenia. His repeat serology was not in keeping with chronic Q fever, as phase 1 *C. burnetii* antibodies are a key feature of chronic Q fever, which were not detected subsequently. On detailed questioning, he had no epidemiological risk factors for acquiring this zoonotic disease, including exposure to farm animals, work in an abattoir, or residence in/travel to a Q fever-endemic area. Finally, his symptoms on both presentations could all be explained by VL.

False-positive *C. burnetii* serology due to other bacterial infections, including *Legionella* and *Bartonella*, has been described.^{1,2} To our knowledge, false-positive *C. burnetii* serology due to VL has not been reported, although false-positive serology for other infections in patients with VL has been described, including leptospirosis³ and trypanosomiasis.⁴ Clinicians ought to be aware of this possibility, as patients with unexplained fevers may be investigated with serological tests for atypical bacterial infections, and a positive result may not represent a true positive, especially when the exposure history and clinical syndrome are inconsistent.

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FIGURE 1. Coronal computed tomography scan of chest and abdomen, demonstrating hepatomegaly and massive splenomegaly.

This also highlights the importance of appropriate history-taking before sending specific investigations. Our patient's pancytopenia, fever, and splenomegaly were all in keeping with VL. Symptoms occur because of infection with *Leishmania* parasites which enter the host when an infected female phlebotomine sand fly takes a blood meal and subsequently infect mononuclear phagocytic cells within the reticuloendothelial system. *Leishmania infantum* is known to be hypoendemic in Spain (0.41 cases per 100,000 people)⁵ and is one of three species within the *L. donovani* complex, the others being *L. donovani* and *Leishmania chagasi*.⁶

The diagnosis of our patient was delayed by a week as no parasites were seen on two bone marrow aspirates. This serves as a reminder that bone marrow aspirate morphology is not 100% sensitive for the diagnosis. Reported sensitivity is variable and time dependent, ranging from 55% to 90%,^{7,8} and rising proportionally with time spent looking at the slide.⁹ Thus, when the clinical syndrome and epidemiology is in keeping with VL, negative bone marrow aspirate morphology should not be used to exclude the diagnosis, and bone marrow aspirate PCR should be considered.

Our patient described clear clinical improvement in VL symptoms and signs, sustained for a 6-month period, following 2-week doxycycline treatment given for suspected Q fever. The sustained response to doxycycline suggests direct antiparasitic activity against *Leishmania*, rather than an anti-inflammatory or immunomodulatory effect. Doxycycline is an effective antimalarial drug. Although the mechanism of action of doxycycline against malaria is not fully understood, it is hypothesized that it may interfere with the synthesis of mitochondrial proteins.¹⁰

Doxycycline monotherapy has been shown to be effective in cases of cutaneous leishmaniasis (CL). Masmoudi et al.¹¹ prospectively treated 14 patients with CL with 15–30 days of doxycycline 200 mg daily and demonstrated “complete desinfiltration” of the lesions in 10 patients (71%). Malik et al.¹²

compared oral doxycycline 200 mg daily to oral chloroquine 250 mg twice daily in 50 patients with CL and found that 23 of 25 patients (92%) who took doxycycline (for up to 12 weeks) had either complete re-epithelialization or healing of the lesions without induration.

A hamster experimental model of VL demonstrated a reduction in mortality at 3–5 weeks from 15% to 0% using doxycycline treatment, although the mechanism of action was unclear.¹³ Published human data of doxycycline use in VL are limited to a single case report. An immunocompetent Kosovan patient with a fever and dry cough was treated with 3 weeks of doxycycline 100 mg twice daily because of positive leptospirosis serology, with complete resolution of symptoms. His symptoms recurred a month later, he was treated with a further 16 days of doxycycline, and they were attenuated but did not resolve. Amastigotes were found in the bone marrow, and serology confirmed a diagnosis of *L. infantum*.³

Our case and other published cases highlight a potential role for doxycycline as adjunctive treatment for VL. Liposomal amphotericin B is the gold standard treatment for treating VL, but its use in endemic areas is limited by its price, as well as logistic issues relating to its storage (below 25°C/77°F) and administration (requires filtration, dilution, and slow intravenous infusion),¹⁴ and therefore exploration of alternative oral options is warranted. Given the relative low cost of doxycycline and its good safety profile, even when taken long term, it may be an appealing option, particularly in lower resource settings. The role of doxycycline as an adjunctive agent for treating VL merits further study.

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REFERENCES

1. Rahimian J, Raoult D, Tang YW, Hanna BA, 2006. *Bartonella quintana* endocarditis with positive serology for *Coxiella burnetii*. *J Infect* 53: e151–e153.
2. Edouard S, Million M, Casalta JP, Collart F, Amphoux B, Raoult D, 2017. Low antibodies titer and serological cross-reaction between *Coxiella burnetii* and *Legionella pneumophila* challenge the diagnosis of mediastinitis, an emerging Q fever clinical entity. *Infection* 45: 911–915.
3. Heer K, Pfister D, Briner V, 1999. Revival of tetracyclines--in the treatment of visceral leishmaniasis? *Schweiz Med Wochenschr* 129: 810–812.
4. Caballero ZC, Sousa OE, Marques WP, Saez-Alquezar A, Umezawa ES, 2007. Evaluation of serological tests to identify *Trypanosoma cruzi* infection in humans and determine cross-reactivity with *Trypanosoma rangeli* and *Leishmania* spp. *Clin Vaccine Immunol* 14: 1045–1049.
5. World Health Organization, 2019. *Leishmaniasis Country Profiles—Spain*. Geneva, Switzerland: WHO. Available at: https://www.who.int/leishmaniasis/burden/Leishmaniasis_Spain/en/. Accessed December 17, 2019.
6. Centers for Disease Control and Prevention, 2017. *Leishmaniasis Parasite Biology*. Available at: <https://www.cdc.gov/dpdx/leishmaniasis/index.html>. Accessed December 17, 2019.
7. Zijlstra EE, Siddig Ali M, El-Hassan AM, El-Toum IA, Satti M, Ghalib HW, Kager PA, 1992. Kala-azar: a comparative study of parasitological methods and the direct agglutination test in diagnosis. *Trans R Soc Trop Med Hyg* 86: 505–507.

8. Piarroux R, Gambarelli F, Dumon H, Fontes M, Dunan S, Mary C, Toga B, Quilici M, 1994. Comparison of PCR with direct examination of bone marrow aspiration, myeloculture, and serology for diagnosis of visceral leishmaniasis in immunocompromised patients. *J Clin Microbiol* 32: 746–749.
9. da Silva MR, Stewart JM, Costa CH, 2005. Sensitivity of bone marrow aspirates in the diagnosis of visceral leishmaniasis. *Am J Trop Med Hyg* 72: 811–814.
10. Gaillard T, Madamet M, Pradines B, 2015. Tetracyclines in malaria. *Malar J* 14: 455.
11. Masmoudi A, Dammak A, Chaaben H, Maalej N, Akrouf F, Turki H, 2008. Doxycycline for the treatment of cutaneous leishmaniasis. *Dermatol Online J* 14: 22.
12. Malik F, Hanif MM, Mustafa G, 2019. Comparing the efficacy of oral chloroquine versus oral tetracycline in the treatment of cutaneous leishmaniasis. *J Coll Physicians Surg Pak* 29: 403–405.
13. Alving CR, Steck EA, Chapman WL, Jr., Waits VB, Hendricks LD, Swartz GM, Jr., Hanson WL, 1980. Liposomes in leishmaniasis: therapeutic effects of antimonial drugs, 8-aminoquinolines, and tetracycline. *Life Sci* 26: 2231–2238.
14. Salih NA et al., 2014. Liposomal amphotericin B for complicated visceral leishmaniasis (kala-azar) in eastern Sudan: how effective is treatment for this neglected disease? *Trop Med Int Health* 19: 146–152.