Visceral Leishmaniasis With Associated Immune Dysregulation Leading to Lymphoma

Nwamaka M. Osakwe, MBBS; Capt Andrew Paulus, USAF MC*; Capt Paul F. Haggerty, USAF MC†; Lt Col Roger A. Wood, USAF MC‡; Maj Sara J. Becker, USAF MC§; COL Peter J. Weina, MC USA‖; Col Matthew J. Dolan, USAF MC (Ret.)¶; Maj Vidhya Prakash, USAF MC§*

ABSTRACT Objective: We describe an atypical presentation of visceral leishmaniasis (VL) complicated by Epstein–Barr virus (EBV)-lymphoproliferative disorder and angioimmunoblastic T-cell lymphoma in a U.S. Government contractor recently deployed to Iraq and Afghanistan. Methods: We performed a search of PubMed (1966–2012) using the terms visceral, leishmaniasis, operation, iraqi, freedom, desert, storm, EBV, lymphoproliferative, angioimmunoblastic, and lymphoma. The purpose of the search was two-fold: to find reported cases of VL during U.S. military operations and to ascertain if lymphoproliferative disorder (specifically, because of EBV) was ever described as a sequelae of VL. Results: Case series of VL acquired in the Middle East between 1990 and 2012 showed that while fever, abdominal pain, and hepatosplenomegaly were common signs and symptoms of VL, diffuse lymphadenopathy (our patient's presentation) was rare. Moreover, VL in and of itself lends to profound immune dysregulation, leading to a myriad of complications to include EBV-lymphoproliferative diseases. Conclusions: Diffuse lymphadenopathy because of VL is a very atypical presentation for infection acquired in the Middle East. Clinicians must be mindful of the extreme immune dysfunction that occurs as a result of this potentially fatal infection and the associated complications to include EBV-related lymphoproliferative disorders and lymphoma.

INTRODUCTION

Visceral leishmaniasis (VL), also referred to as kala-azar, is a disseminated protozoan infection occurring primarily in the tropics and subtropics. The causative agents include *Leishmania donovani* and *Leishmania infantum* with infection transmitted by sand flies.[1,2] Clinical presentation ranges from asymptomatic, self-resolving infections to insidious onset of fever, weight loss, weakness, fatigue, and hepatomegaly.[1,3] Although lymphadenopathy is common in patients in Sudan, it is less common in other areas.[1,4] The majority of cases of VL occur in India, Brazil, Sudan, and Bangladesh,[1] though there have been scattered reports of VL and viscerotropic leishmaniasis in soldiers deployed to Afghanistan and Iraq.[2,5] Delay in diagnosis and initiation of effective therapy is problematic as untreated infection can be fatal.[6]

Immunologic dysfunction is a key component of disease because of VL. VL in and of itself can lead to immunosuppressant, specifically because of ensuing deficits in cell-mediated immunity.[7] Patients with primary and secondary immunodeficiencies are prone to Epstein–Barr virus-related lymphoproliferative disease (EBV-LPD) and lymphoma.[8,9] EBV can manifest in either a latent or replicative life cycle.[9] Active viral replication may be because of deficits in immunosurveillance, which then lead to lymphoproliferation.[9] We hypothesize that progression of EBV-LPD led to development of angioimmunoblastic T-cell lymphoma.

Since World War II, U.S. military operations have had exposure to cutaneous and VL in the Middle East. During the first Gulf war, an unusually high rate of VL was reported among hospitalized soliders.[10] According to a report by the Army Medical Surveillance Activity Office in 2007, the U.S. Army received fewer reports of leishmaniasis in Iraq and Afghanistan. However, this may have been because of inadequate case reporting as opposed to fewer infections.[11] This case is intended to raise awareness of continued exposure to VL in servicemen and the complications associated with resultant immune dysregulation from the infection itself.

CASE SUMMARY

The patient was a 50-year-old Caucasian male government contractor who presented with progressive, nontender lymphadenopathy involving his cervical, axillary, and inguinal lymph nodes, 6 months after returning from deployments to Iraq and Afghanistan. He had been in each country for 1 year

*Department of Internal Medicine, Wright State University Boonshoft School of Medicine, Miami Valley Hospital, Weber CHE Building, 2nd Floor, 128 East Apple Street, Dayton, OH 45409.

†Department of Internal Medicine, Wright-Patterson Medical Center, 88th MDOS/SGOM, 4881 Sugar Maple Drive, Wright-Patterson AFB, OH 45433.

‡Division of Hematology/Oncology, Department of Internal Medicine, Wright-Patterson Medical Center, 88th MDOS/SGOM, 4881 Sugar Maple Drive, Wright-Patterson AFB, OH 45433.

§Division of Infectious Disease, Department of Internal Medicine, Wright-Patterson Medical Center, 88th MDOS/SGOM, 4881 Sugar Maple Drive, Wright-Patterson AFB, OH 45433.

‖Division of Infectious Diseases, Department of Internal Medicine, Walter Reed Army Institute of Research, Silver Spring, MD.

¶Defense Institute for Medical Operations (DIMO), Building 3550, Room 301, 2201 Pepperrell Street, Lackland AFB, TX 78236.

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starting with 6 months in Iraq immediately followed by 6 months in Afghanistan. He also endorsed fever, drenching night sweats, fatigue, and abdominal distension.

On examination, his temperature was 97.7°F (36.5°C), heart rate was 120 bpm, and respiratory rate was 17. Pertinent findings on examination included nontender cervical, axillary, and inguinal lymphadenopathy, a maculopapular rash on the chest and splenomegaly. Laboratory evaluation revealed a WBC count of 5.4×10^3/mcL, Hb count of 14.7 g/dL, platelet count of 146,000/mcL, AST 21 U/L, and ALT 83 U/L. A computed tomography (CT) of the neck, chest, abdomen, and pelvis confirmed generalized lymphadenopathy and splenomegaly. He was admitted to the inpatient internal medicine service for expedited workup for suspected malignancy.

Workup including an inguinal lymph node and bone marrow biopsy revealed a reactive process, noncaseating granulomas and no malignant cells with negative stains for acid fast baceria and fungal organisms. A recombinant antigen (rK39) assay for VL was positive. The patient was started on intravenous liposomal amphotericin B (AmBisome) 3 mg/kg daily and within 24 hours experienced resolution of fever. He completed a full course of therapy for VL, which entailed AmBisome 3 mg/kg/day on days 1 to 5 followed by 3 mg/kg/day on days 14 and 21 and experienced gradual resolution of splenomegaly and lymphadenopathy.

On the last day of AmBisome therapy, he underwent a CT of the neck to evaluate a postoperative seroma at his biopsy site. He was sent to the Emergency Department because of a diffuse rash that developed within minutes of receiving intravenous contrast for the CT. Within 24 hours of receiving corticosteroid therapy for possible allergic reaction to contrast dye, he experienced relapse of lymphadenopathy, splenomegaly, and rash. Despite a second course of AmBisome for presumed relapse of VL, his lymphadenopathy persisted. Repeat rK39 assay results returned as negative, however. At this juncture, a definitive diagnosis of EBV-positive B-cell LPD resembling polymorphic B-cell lymphoma was made based on multiple expert rereviews of previous biopsies. The patient was reevaluated in Medical Oncology and started on rituximab but experienced no relief in his symptoms. He was admitted to an outside institution because of ongoing fever and lymphadenopathy, where he underwent repeat lymph node and bone marrow biopsies. The lymph node pathology showed angioimmunoblastic T-cell lymphoma and EBV-positive polyclonal B-cell LPD. Bone marrow pathology showed positive marrow involvement of T-cell lymphoma with lymphoma cells representing less than 20% of the marrow. He is currently undergoing chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone.

DISCUSSION

VL is a vector-borne disease that is transmitted by the female phlebotomine sand fly. The sand fly is typically most active at night and its bites may go unnoticed.[12] The incubation period for VL is generally 2 to 6 months, though it can range from a few weeks to over 2 years.[1,12] Onset is usually insidious and almost always starts with persistent fever followed by fatigue, anorexia, weight loss, and abdominal enlargement because of hepatosplenomegaly.[1,4,12] Lymphadenopathy is frequently seen in Sudanese VL but is uncommon in other areas. When present, lymphadenopathy is generalized and can include epitrochlear, cervical, axillary, and inguinal lymph nodes.[4] There have been cases of localized lymphadenopathy as the presenting finding in patients in Southern Europe and Latin America, though these cases lacked other systemic signs and symptoms.[13,14] Extensive lymphadenopathy has also been reported in cases of cutaneous leishmaniasis in Northeast Brazil.[14]

Laboratory studies are often significant for pancytopenia (anemia is typically present) and hypergammaglobulinemia.[1] Leukopenia is prominent in these patients; however, this was not the case in our patient who had leukocytosis (the etiology remains unclear). Although mild glomerulonephritis has been described, renal failure is rare.[1] Our patient had acute kidney injury, and this was thought to be secondary to hypoalbuminemia-induced third spacing of intracellular fluids. His kidney function returned to baseline with treatment.

The mainstay in diagnosis of VL is demonstration of parasites in tissue by direct visualization or culture. In specialized parasitology laboratories, a polymerase chain reaction test can be performed on these samples to detect Leishmania DNA.[15] Several serological techniques that measure antibody levels have also been developed for the diagnosis of VL. These include a direct agglutination test, enzyme linked immunosorbent assay using antibody to native gp63, rK39 of *Leishmania chagasi* (that cross-reacts with *L. donovani* and *L. infantum*), and indirect immunofluorescence antibody test. Optimal results have been shown by antigen rK39 with sensitivity of 100% and specificity of 96%.[15] In addition, antibody titers to rK39 correlate with parasite burden and may be used to monitor the response to treatment and assist in predicting clinical relapse.[4,5] This finding is consistent with what was observed in our patient as VL was diagnosed using the rK39 assay and repeat testing following treatment with AmBisome was negative.

VL is of significant concern to the U.S. military since hundreds of thousands of troops have been stationed in endemic areas since the start of Operation Enduring Freedom and Operation Iraqi Freedom. Afghanistan has one of the highest incidences of cutaneous leishmaniasis in the world, but there had only been 23 reported cases of VL in the literature before the start of Operation Enduring Freedom.[16] Since then, there have been an increasing number of reported cases of VL in U.S. military personnel. In fact, after Operation Desert Storm in 1991, a case series detailed eight soldiers who were found to have viscerotropic leishmaniasis in the setting of exposure in Saudi Arabia.[5] Even though most of their symptoms paralleled the reported spectrum of VL, these eight patients had a myriad of nonspecific clinical signs and symptoms. Two patients had evidence of lymphadenopathy,

one of whom had localized axillary lymphadenopathy. A more recent case series detailed VL in four soldiers with deployments to Iraq and Afghanistan.[2] All these patients presented with fever and splenomegaly along with various other nonspecific signs and symptoms. However, none was found to have diffuse lymphadenopathy (Table I).

Our patient had a very atypical presentation of VL. Although diffuse lymphadenopathy is common in infections acquired in the Sudan, it is unusual elsewhere. There was a high index of suspicion for lymphoma initially, in addition to infectious diseases such as infectious mononucleosis and resultant hemophagocytic lymphohistiocytosis, toxoplasmosis, acute retroviral syndrome because of HIV as well as rheumatologic etiologies such as rheumatoid arthritis, systemic lupus erythematosus, and Sjogrens syndrome. An extensive workup to include multiple serologies and lymph node biopsies and cultures were unrevealing for any of these etiologies. Inguinal lymph node and cervical lymph node biopsies along with bone marrow biopsy, while negative for malignancy, did not show intracellular amastigotes of Leishmania as expected, further complicating diagnosis. However, as previously noted, superior sensitivity and specificity of the rK39 assay helped to solidify his diagnosis and prompt immediate treatment.

This patient's case was further complicated by what was initially thought to be relapse of VL. Relapse following adequate treatment for VL is not infrequent. A U.S. Food and Drug Administration review of clinical trials to support approval of AmBisome for treatment of VL revealed a higher rate of relapse in immunosuppressed patients when compared to immunocompetent patients.[17] VL is recognized as an opportunistic infection in patients who experience functional T-cell deficiency following treatment with corticosteroids, other immunosuppressive agents or because of advanced AIDS.[18] Interestingly, it has been documented that immunologic dysfunction and depressed cell-mediated immunity are hallmarks of VL infection.[19] Specifically, there is a decline in lymphocyte ability to proliferate in response to Leishmania antigen.[7] One study that examined postmortem spleens and lymph nodes of cases of VL showed small lymphocyte depletion in thymus-dependent regions.[20] Furthermore, another study by Carvalho et al showed that patients with active VL had significantly lower interleukin-2 and γ interferon levels that are important in mediating several lymphocyte functions.[19] This inability to generate interleukin-2 and γ interferon to Leishmania antigens during VL infection lends itself to profound immune dysregulation.[19]

Some of the major pathogenic etiologies important in the development of EBV-LPD/lymphoma in patients with immunodeficiency include the use of immunosuppressants in patients with transplantation or rheumatic disease and AIDS associated with HIV infection.[21] Among transplant patients, EBV-LPD/lymphoma was described in patients who had been treated with corticosteroids and azathioprine.[21] In addition, an increase in the incidence of EBV-LPD/lymphoma was documented with the introduction of calcineurin inhibitors.[21] It is, therefore, not surprising that patients with secondary immunodeficiencies because of VL are prone to EBV-LPD/lymphoma. Decrease in immunosuppressive therapy sometimes led to regression of EBV-LPD, underscoring the possibility that reduction in immunosurveillance is associated with risk of EBV-LPD.[8] Other treatment options for LPD include anti-B-cell monoclonal antibodies such as rituximab and chemotherapy. We hypothesize that EBV-LPD in our patient occurred because of reactivation of latent EBV due to profound immune dysregulation from VL. His profound immunosuppression because of VL coupled with added insult from corticosteroid therapy likely facilitated the development of progressive EBV-LPD to non-B-cell NHL. The fact that he responded dramatically to VL treatment initially argues against non-B-cell NHL as the primary process, although this remains possible.

In conclusion, VL is a disseminated infection associated with high mortality left untreated. It holds particular relevance to health care workers caring for returning military and other Defense Department employees given recent reports of infection acquired during deployments to Iraq and Afghanistan. Many of these potential cases would be predicted to occur outside the military or Veterans Administration health care setting, raising the need to consider specific diagnostic testing for this potentially fatal infection in the context of a history of service in Iraq or Afghanistan. Although lymphadenopathy is an atypical presentation of infection acquired in the Middle East, VL should certainly remain in the differential in any patient with associated fever and splenomegaly. Furthermore,

TABLE I. Reported Cases of VL in the U.S. Military Since 1990

Time Period	Number of Cases	Location	Incubation Period (Months)	Symptoms at Presentation	Physical Findings
1990–1991	8	Saudi Arabia	1–14	Fever 5/8 Fatigue 7/8 Abdominal Pain 7/8 Malaise 7/8	Hepatomegaly4/8 Splenomegaly 4/8 Lymphadenopathy 2/8 Normal 2/8
2002–2004	4	Iraq 2/4, Afghanistan 2/4	6	Fever 4/4 Weight Loss 4/4 Night Sweats 4/4	Hepatomegaly 2/4 Splenomegaly 4/4 Lymphadenopathy 0/4
2011 (Index Case)	1	Iraq and Afghanistan	6	Fever Generalized Lymphadenopathy Night Sweats	Splenomegaly Lymphadenopathy Maculopapular Rash

clinicians should not discount the profound immune dysregulation associated with widely disseminated infection and be vigilant in entertaining complications to include EBV-related lymphoproliferative disorders and lymphomas as a complication of infection.

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