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ID TEACHING CASES

A Wandering Missionary's Burden: Persistent Fever and Progressive Somnolence in a Returning Traveler

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Human African trypanosomiasis incidence has declined, but diagnosis remains difficult, especially in nonendemic areas. Our patient presented with fever, progressive lethargy, and weight loss for 5 months and had previously traveled to Ghana and Cameroon but had not been to areas with recently reported African trypanosomiasis. Extensive workup was negative, except for lymphocytic pleocytosis in cerebrospinal fluid; ultimately, a bone marrow aspiration revealed necrotizing granulomatous inflammation with 2 trypanosomes discovered on the aspirate smear, consistent with *Trypanosoma brucei*. The patient was treated with combination nifurtimox and eflornithine with full recovery.

Keywords. African sleeping sickness; fever in a returning traveler; human African trypanosomiasis; *Trypanosoma brucei*.

Tremendous progress has been made toward elimination of *gambiense* human African trypanosomiasis (HAT), with only a single case reported among 42 173 ill returning travelers in the GeoSentinel Surveillance network, between 2007 and 2011. In 2019 there were 874 cases of *gambiense* HAT reported worldwide; no cases were reported from Ghana and 20 cases were reported from Cameroon. This case highlights the challenges in diagnosing an increasingly rare infectious disease. Despite progress toward interruption of transmission, clinicians should remain vigilant for HAT and consider the diagnosis in patients with compatible clinical manifestations and exposure history, given the limitations of surveillance and likely changing disease presence throughout sub-Saharan Africa.

CASE PRESENTATION

A 51-year-old man presented to our hospital in Dallas, Texas, in September 2019, for evaluation of fevers, confusion, lethargy, and a 35-pound (~15.8 kg) weight loss. He was confused and had difficulty finding words, though his sister reported he had been completely well until 5 months prior to presentation.

The patient's medical history included hypertension, controlled with nifedipine. His family history was significant for hypertension and kidney disease. He worked as a theological professor and did not use tobacco products, alcohol, herbal supplements, or illicit drugs. The patient denied headache, cough, dyspnea, rash, joint pain, or diarrhea, though his family noticed generalized weakness, confusion, lethargy progressing to somnolence, fevers, and weight loss.

The patient was born in Cameroon, attended college in Nigeria, and thereafter returned to Cameroon to work as a missionary. In 2001, he traveled to Mali, Senegal, Algeria, and Guinea, before immigrating to the United States (US). In 2013, he traveled back to Cameroon, as well as Nigeria, South Africa, Ghana, Central African Republic, and many other non-African countries. He last visited Cameroon in 2017. In November 2018 he visited Kumasi, Ghana, where he spent time outdoors and recalled a possible insect bite on his thigh. He noted mild erythema and pain at the site and received steroids, with improvement of the lesion. During this time, he also developed weakness and fatigue, which he described as similar to prior illness with malaria. His weakness and fatigue improved, until May 2019, when he developed fever, night sweats, and weight loss. However, he continued traveling, visiting Jerusalem in June 2019, where he had a syncopal episode requiring hospitalization, though the details were unavailable.

Upon returning to the US in July 2019, he sought care at a local hospital for fever, weight loss, and generalized weakness. A computed tomography (CT) scan of the chest, abdomen, and pelvis showed diffuse lymphadenopathy; a supraclavicular lymph node biopsy was reported as "benign reactive lymph node" without evidence of malignancy. The patient was treated

Received 15 May 2021; editorial decision 8 July 2021; accepted 14 July 2021.

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Open Forum Infectious Diseases®2021

https://doi.org/10.1093/ofid/ofab377

with ceftriaxone with little improvement and was discharged home without a clear diagnosis.

The symptoms progressed, with fever up to 39.4°C, usually at night. The patient became increasingly confused and weak, stopped working, and required a wheelchair. When the patient was hospitalized at UT Southwestern Medical Center in September 2019, he appeared confused, had difficulty answering questions, reported a 35-pound (~15.8 kg) weight loss, and had long periods of somnolence.

On admission, he appeared cachectic and frail and was febrile to 38.9°C; heart rate was regular at 93 beats per minute, blood pressure was 114/82 mm Hg, and oxygen saturation was 99% on room air. On examination, he had no evidence of posterior cervical or other lymphadenopathy. Cardiac examination revealed normal heart sounds without murmurs, and no abnormalities were noted on respiratory or skin examination. He did not have abdominal tenderness or hepatosplenomegaly. No focal abnormalities were noted on neurological examination; however, he was somnolent and slow to respond.

Results of complete blood count, differential count, and tests for renal and hepatic function were normal. A broad workup for fever of unknown origin was pursued, including infectious and noninfectious causes. Results of blood cultures, Giemsa stain of peripheral blood smear for parasites, *Mycobacterium tuberculosis* interferon-γ release assay (QuantiFERON-TB Gold), screening tests for *Treponema pallidum*, Epstein-Barr virus polymerase chain reaction (PCR), cytomegalovirus PCR, urine histoplasma antigen, endemic fungal antibody tests, serum β-D-glucan, serum galactomannan, serum cryptococcal antigen, *Rickettsia* antibody, West Nile virus, and Lyme disease testing were all negative. Human immunodeficiency virus (HIV) type 1 and 2 testing revealed an indeterminate HIV-2 antibody, though confirmatory testing confirmed this was a false-positive result, and CD4 count was normal (1491 cells/μL). Laboratory tests for autoimmune antibodies were positive only for antinuclear antibodies present at a titer of 1:160. Serum protein electrophoresis revealed a polyclonal gammopathy, with a normal immunoglobulin A level of 285 mg/dL (reference range, 70–400 mg/dL), elevated total immunoglobulin G (IgG) of 2340 mg/dL (reference range, 767–1590 mg/dL), and elevated immunoglobulin M (IgM) of 953 mg/dL (reference range, 40–230 mg/dL).

Lumbar puncture performed on day 2 of admission revealed cerebrospinal fluid (CSF) with 638 nucleated cells/μL (100% lymphocytes), and cytology did not reveal any malignant cells (Table 1). Results of CSF testing for arboviruses, Venereal Disease Research Laboratory test, herpes simplex virus, varicella zoster virus, and enterovirus were all negative (Table 1). No morula cells of Mott were noted on CSF analysis. CT of the chest, abdomen, and pelvis showed scattered bilateral axillary and inguinal adenopathy up to 1 cm in size, and magnetic resonance imaging of the brain was normal without any brainstem abnormalities. Given an increasing clinical suspicion for HAT, blood and CSF smears were reviewed by an infectious diseases pathologist/microbiologist. However, this additional review was also unrevealing. Unfortunately, the patient's original lymph node aspirate was unavailable to review at our hospital, and he did not have significant palpable lymphadenopathy to perform another aspiration.

Table 1. Cerebrospinal Fluid Testing Results

Test	Reference Range	On Admission
Opening pressure, cm of water	6–18	16
Color	Colorless	Colorless
Turbidity	Clear	Clear
Glucose, mg/dL	50–75	51
Total protein, mg/dL	5–55	67
Red cell count, per μL	0–5	2
Nucleated cell count, per μL	0–5	638
Differential, %		
Neutrophils	60–70	0
Lymphocytes	40–80	100
Monocytes	<20	0
VDRL	Negative	Negative
Lyme Ab IgG	Negative	Negative
MTB PCR Probe	Negative	Negative
CMV PCR	Negative	Negative
HSV types 1 & 2 PCR	Negative	Negative
EBV PCR	Negative	Negative
Eastern equine encephalitis Ab panel	Negative	Negative
Western equine encephalitis Ab panel	Negative	Negative
West Nile virus Ab panel	Negative	Negative

Abbreviations: Ab, antibody; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; IgG, immunoglobulin G; MTB, Mycobacterium tuberculosis; PCR, polymerase chain reaction; VDRL, Venereal Disease Research Laboratory.

The patient had intermittent fever, almost daily for the first week, then sporadically every 3–4 days. His somnolence worsened despite treatment with vancomycin, ceftriaxone, piperacillin-tazobactam, acyclovir, and doxycycline. A bone marrow aspiration performed on day 10 of admission revealed normocellular marrow with necrotizing granulomatous inflammation, though fungal and acid-fast bacilli stains were negative. Two trypanosomes were identified on the marrow aspirate smear, with morphology consistent with *Trypanosoma brucei* (Figure 1).

Given the bone marrow findings, travel, and clinical history, a diagnosis of HAT (*T brucei gambiense*) was made, further confirmed by detection of specific antibody using the card agglutination test for trypanosomiasis (CATT) (McGill University Centre for Tropical Diseases). Treatment was coordinated with the Centers for Disease Control and Prevention (CDC), and nifurtimox and eflornithine were obtained after completion of an investigational new drug application with the US Food and Drug Administration. On hospital day 24, the patient started therapy with eflornithine 200 mg/kg administered every 12 hours for 7 days as a 2-hour intravenous infusion, in combination with oral nifurtimox 5 mg/kg every 8 hours for

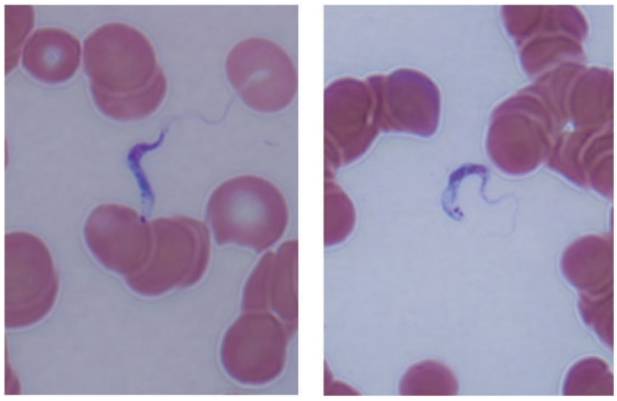

Figure 1. Bone marrow aspirate smear with *Trypanosoma brucei* (Wright-Giemsa stain). Magnification ×100.

10 days, given simultaneously, without significant side effects. His mental status improved 4 days into therapy, with no further fevers. Upon completion of treatment, on hospital day 34, he was discharged from the hospital, fully oriented and without neurological deficits. He remains fully recovered, 15 months after discharge, and continues his missionary work.

DISCUSSION

Human African trypanosomiasis, or African sleeping sickness, is an infectious disease endemic to sub-Saharan Africa and is fatal when untreated. HAT is caused by the parasite *Trypanosoma brucei*, transmitted by the tsetse fly (*Glossina* spp) vector. There are 2 forms of the disease caused by different subspecies of the parasite: *T brucei gambiense*, endemic to West and Central Africa, causes a slowly progressive illness leading to progressive symptoms and death over months to years; and *T brucei rhodesiense*, endemic in eastern and southern Africa, causes a more acute illness that evolves over a span of weeks, leading to death within months [1]. The disease has 2 stages: a hemolymphatic stage characterized by intermittent or undulating fevers, headache, and lymphadenopathy; followed by a meningoencephalitic stage, in which the trypanosomes cross the blood-brain barrier. Neurological symptoms typical of the second stage include mental confusion, abnormal behavior, logorrhea, ataxia, tremor, motor weakness, speech impairment, abnormal gait, and abnormal movements and seizures, with somnolence being a dominant feature [1].

Cattle and wild animals may serve as reservoirs for *T brucei rhodesiense*; however, for *T brucei gambiense*, humans are the primary reservoir and the long duration of infection has helped maintain the transmission cycle. In the last century there have been devastating epidemics of HAT, with the last major resurgence occurring in the 1990s. In the last 20 years, there have been concerted efforts to diagnose, treat, and eliminate the disease, with the World Health Organization (WHO) targeting the interruption of transmission of *T brucei gambiense* by 2030. Currently, the disease is reported from small endemic foci in sub-Saharan Africa in primarily rural areas [2]. In 2019 there were 874 cases of *gambiense* HAT reported worldwide, with no cases reported from Ghana and 20 cases reported from Cameroon [3]. Single cases were reported from Ghana in 2000 and 2013 [3]. No other cases have since been reported in Ghana, despite a well-established surveillance system. The GeoSentinel surveillance network monitors returning travelers and *T brucei gambiense* HAT is rare, with only a single case reported among 42 173 ill returning travelers seen between 2007 and 2011 [4]. Although the majority of HAT cases in disease-endemic countries (DECs) are caused by *T brucei gambiense*, most cases in non-DECs are caused by *T brucei rhodesiense*, often associated with safari tourism, with symptoms appearing shortly after return [5].

CATT is a fast and sensitive test to screen for *T brucei gambiense* antibodies in blood, plasma, or serum [6]. PCR in blood is highly sensitive and specific [7]. Serological and PCR tests for HAT are not available in the US but can be performed at several reference laboratories outside the US. Definitive diagnosis relies on microscopic visualization of the parasite. When lymphadenopathy is present, rapid diagnosis is possible by observation of motile trypanosomes on wet mount of fresh lymph node aspirate. The sensitivity varies between 40% and 80%, depending on the parasite strain and stage of the disease (sensitivity is higher during the first stage) [6]. Alternatively, examination of Giemsa-stained peripheral blood smear may be used, although sensitivity is very low (10%–30%), especially when level of parasitemia is low. Trypanosomes may potentially be seen in CSF if parasite load is high during the second stage of disease [8]. Examination of bone marrow is of low yield in detecting trypanosomes [6], and bone marrow smear as a means of diagnosis is rare [9, 10]. Polyclonal activation of B cells is a hallmark of HAT, resulting in elevated IgG and IgM levels, as well as false-positive antibodies for pathogens, and autoantibodies [11].

Significant progress has been made in the development of new oral drugs capable of curing both stages of *gambiense* HAT. Fexinidazole is now considered the drug of choice in most cases of *gambiense* HAT but is currently not available in the US. It is used in patients without clinical features of severe meningoencephalitic disease (or with CSF white blood cell [WBC] count <100 cells/μL) [12]. WHO interim guidelines for treatment of severe *T brucei gambiense* HAT with detected CSF trypanosomes (or CSF WBC count >100 cells/μL) recommend chemotherapy with nifurtimox-eflornithine (NECT) [12]. In the US, eflornithine is only available through the CDC Parasitic Diseases Drug Service and was last released 10 years prior for treatment of a patient diagnosed with HAT. This is the first time that combination therapy NECT has been used for treatment of meningoencephalitic stage of *T brucei gambiense*

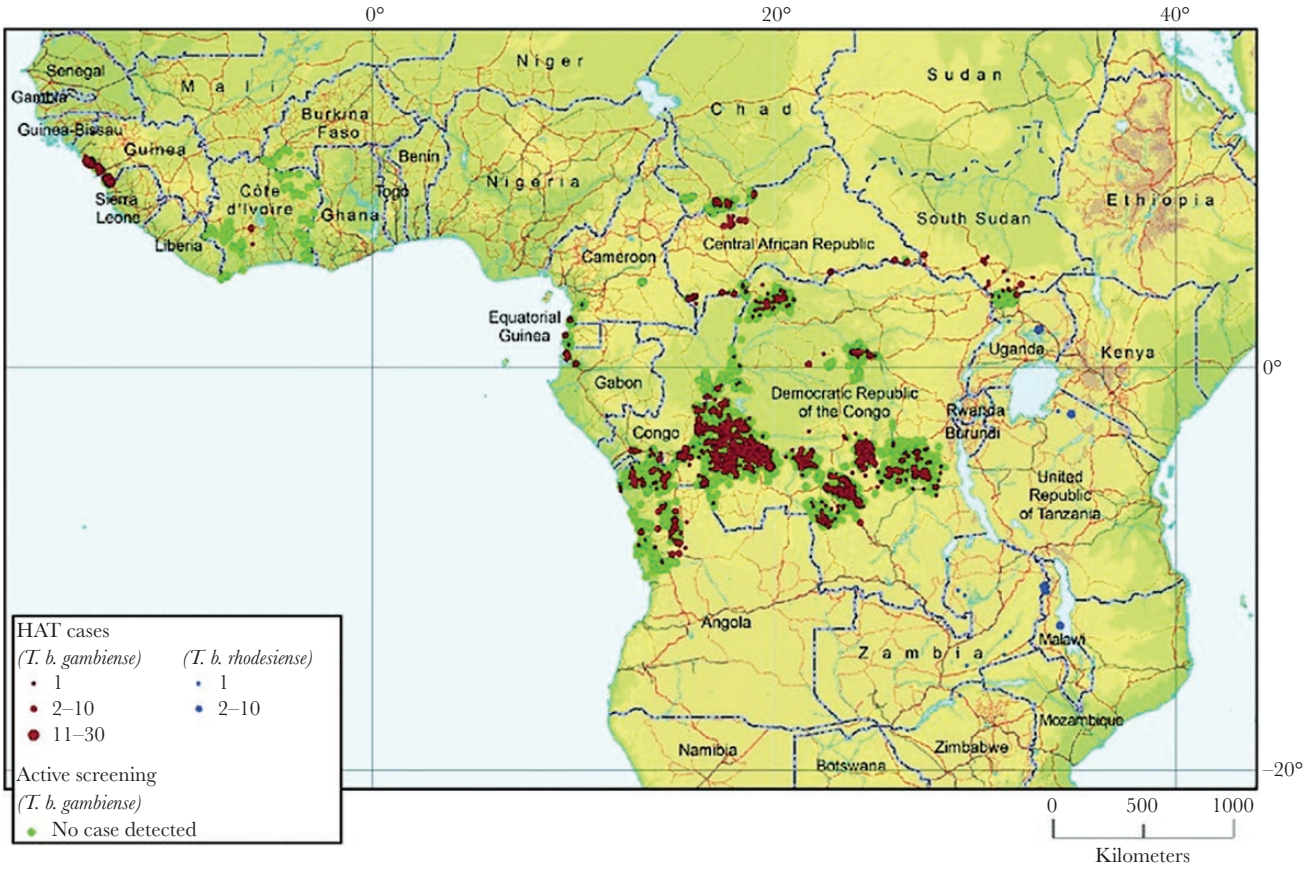

Figure 2. Geographic distribution of human African trypanosomiasis (HAT) Period 2017–2018. Reference: Franco JR, Cecchi G, Priotto G, et al. Monitoring the elimination of human African trypanosomiasis at continental and country level: update to 2018. PLoS Negl Trop Dis 2020; 14:e0008261.

HAT in the US (Rebecca Chancey, MD, personal communication, March 2021).

Our patient had an extensive travel history and had been ill for several months. HAT was considered unlikely, since he reported travel to only urban areas in both Ghana and Cameroon, where HAT is thought to have been eliminated (Figure 2) [2]. While the patient's history of a possible insect bite and lesion in Ghana raised the possibility that this was the location of exposure, it was felt to be unlikely as no cases had been reported to surveillance systems in the region since 2013 [3]. In 2017, the patient visited Mamfe, Limbe, and Buea, Cameroon; Mamfe is an endemic focus reporting occasional cases. However, the last case reported in the region was in 2009 (José Franco-Minguell, MD, personal communication, December 2019).

This case was reported to the WHO for further review. Although the patient reported travel to only urban areas in Ghana and Cameroon, the distinction between urban and rural areas in Mamfe, Cameroon is blurred, and transmission has been described in periurban areas. Therefore, it is possible that the patient acquired this infection during his visit to Mamfe. Our experience highlights that disease surveillance is imperfect, and changes in the environment as well as population susceptibility can affect vector-borne diseases [13]. As the incidence of HAT continues to decline, clinicians should remain vigilant for HAT in a patient with compatible clinical manifestations and exposure history.

Notes

Acknowledgments. We thank Dr José Ramón Franco-Minguell and Dr Gerardo Priotto of the World Health Organization (WHO) for their expertise and advice on the manuscript.

We also thank the Centers for Disease Control and Prevention's (CDC) Division of Parasitic Diseases and Malaria for expertise in confirming the patient's diagnosis.

Patient consent statement. The patient's written consent was obtained.

Disclaimer. The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the WHO or the CDC.

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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