Short Report: Human African Trypanosomiasis in a Traveler: Diagnostic Pitfalls

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Abstract. An Israeli traveler returning from Tanzania presented with a relapsing febrile illness. A diagnosis of *Trypanosoma brucei rhodesiense* infection was established by blood smear after nearly a month. Blood polymerase chain reaction failed to provide an early diagnosis of human African trypanosomiasis. Recognition of suggestive signs should prompt physicians to perform repeated tests before ruling out human African trypanosomiasis.

INTRODUCTION

Travelers to Africa may be at risk of acquiring human African trypanosomiasis (HAT)—one of the most important neglected tropical diseases.¹ Failure to recognize HAT in its early stages may lead to severe morbidity and even mortality. We present a case of HAT in an Israeli traveler, where the diagnosis was elusive despite suggestive clinical features.

CASE REPORT

A 31-year-old previously healthy Israeli woman traveled to Tanzania on an 11-day Safari. A week after leaving mainland Tanzania, and a day after her return to Israel she developed fever and severe headache. She was admitted to the Sheba Medical Center—a tertiary hospital in Israel. Routine laboratory tests showed mild leucopenia, thrombocytopenia, and mildly elevated transaminases (Table 1). Thick and thin blood smears were negative for malaria or other pathogens. Other evaluations, including chest radiography, brain computerized tomography, and a lumbar puncture, were all normal. Physical examination was unrevealing except for a small purplish painless lesion near the patient's buttock. This was considered a possible eschar, and the patient was started on doxycycline, for the purported diagnosis of African tick bite fever.

However, fever, headache, and vomiting continued unchanged; the cutaneous lesion grew in size; concern was raised for the possibility of HAT, and the patient recalled having been bitten by tsetse flies while on Safari in the Serengeti Reserve. A repeated malaria antigen test (BinaxNOW; Inverness Medical, Scarborough, ME) became positive, but was deemed false positive, because repeated blood smears were negative for malaria.

Blood smears were also negative for trypanosomes (although blood concentration techniques were not used). Microscopy from a biopsy from the lesion failed to show trypanosomes.

After nearly a week the patient's fever and headache resolved, the blood count and transaminase levels normalized, and the patient was discharged from the hospital. She remained asymptomatic for 10 days afterward, when fever recurred for 2 days and resolved spontaneously. Physical exam showed healing of the cutaneous lesion, and was otherwise negative. Routine laboratory tests showed only anemia and markedly increased C-reactive protein levels. Multiple

additional tests were unrevealing, including blood cultures, *Plasmodium*, and *Borrelia* blood polymerase chain reaction (PCR) tests. Chest computer tomography revealed a small pleural effusion on the left. A repeated serological test showed seroconversion to spotted fever rickettsiosis (specific *Rickettsia africae* serology is not available in Israel), but serology also showed a markedly positive antinuclear antibody level, and antimitochondrial and anticardiolipin antibodies (Table 1). Despite additional negative blood smears (taken while the patient was afebrile), concern for possible HAT increased. A PCR test for the presence of *Trypanosoma brucei* DNA was performed both on the patient's blood and on DNA eluted from the biopsy specimen taken earlier: both were negative.

A week later the patient had another 3 day bout of fever. This time on physical examination, mild, tender posterior-cervical lymphadenopathy was found, in addition to an unusual, large, non-pruritic annular pink macule at the base of the neck (Figure 1), compatible with a trypanid rash. A blood smear—taken this time during rigors—revealed trypanosomes, and a diagnosis of HAT was established. A serum sample taken at this time was also positive for *T. brucei* DNA on PCR. This sample was tested with two specific primers (as described elsewhere^{2,3}); it was positive for *Trypanosoma brucei rhodesiense* serum resistance-associated gene, and was negative for *Trypanosoma brucei gambiense*-specific glycoprotein, results compatible with infection with *T. b. rhodesiense*.

The patient was without any neurological symptoms. Lumbar puncture revealed normal cerebrospinal fluid. The patient was treated with a complete course of suramin. The first dose was followed by an evanescent, non-pruritic rash of large macules; further doses were without any adverse effects, and the patient recovered uneventfully. Six months later she was in good health; physical examination, routine laboratory tests, antinuclear antibody levels, and a repeated lumbar puncture were all normal (Table 1).

COMMENT

Human African trypanosomiasis is among the most important of the “neglected” tropical diseases. And although numbers of *gambiense* HAT are in decline,¹ this trend does not affect *rhodesiense* HAT, where the number of reported HAT cases in travelers appears to be increasing, usually acquired in game parks in Tanzania, Kenya, or Malawi.^{4–6}

Untreated, *rhodesiense* HAT is uniformly fatal, and significant morbidity and mortality may ensue even with appropriate therapy. Despite its severity and prevalence, there has been little change in its management and treatment during the last century.

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TABLE 1
Main laboratory parameters during acute *rhodesiense* HAT case

Parameter	1st admission (during 1st bout of fever)	2nd admission (after 2nd bout of fever)	3rd admission (during 3rd bout of fever)	4th admission (6 months after treatment)
Hemoglobin (gr/dL)	12.7	9.5	8.6	13.2
Leukocytes (X10 ⁹ /L)	3.3	6.9	7.7	7.5
Platelets (X10 ⁹ /L)	93	342	286	297
C reactive protein (mg/L)	178	104	171	1.9
Serum globulin (gr/L)	3.3	5.8	5.7	2.6
Alanine transaminase (IU/L)	81	15	13	11
Alkaline phosphatase (IU/L)	262	73	64	64
<i>Rickettsia</i> serology	Negative	Positive	ND	ND
Antinuclear antibodies	ND	Positive	Positive	Negative
Anticardiolipin antibodies	ND	Positive	Positive	Negative

Shaded cells = abnormal results; ND = not done.

Our patient may be regarded as a classical presentation of *rhodesiense* HAT. All the clinical features, including the initial skin lesion, the relapsing fever pattern, the posterior cervical lymphadenopathy (Winterbottom's sign), and the trypanid rash (Figure 1) would have been easily recognizable 90 years ago.⁷ And yet, the diagnosis proved to be elusive despite the high level of suspicion.

Trypomastigotes can sometimes be diagnosed from a biopsy of the initial chancre, however their absence—as in our case—does not rule out HAT.

Serological tests—the main screening tool for *gambiense* HAT—are not used in *rhodesiense* HAT. This in part reflects the inherent delay for seroconversion (3–4 weeks).⁸ In addition, occasional cases of false positive serology in travelers have been documented.⁹

Multiple blood smears were taken during our patient's illness, but were negative until the third bout of fever. This may have been caused by either intermittent parasitemia or low level parasitemia (below the detection level of blood smears, especially since blood concentration techniques were not used). In light of the patient's negative blood smears, we attempted to use blood PCR to diagnose HAT. However, PCR did not improve on microscopy, and was false negative between fever bouts. Blood PCR has recently been shown to be a promising test for the diagnosis (but not for follow-up) of *gambiense* HAT,¹⁰ but there is no data regarding its use in *rhodesiense* HAT. Its role should therefore be

considered as investigational: a negative PCR result does not preclude HAT.

Diagnostic efforts in our case were further complicated by false positive serological reactions. *Rickettsia africae* infection, which was the first diagnosis considered in our patient, was theoretically confirmed by seroconversion. In addition, a false positive malaria antigen test emerged during illness, and several autoantibodies were positive as well (Table 1). The patient could easily have been misdiagnosed as a case of probable lupus erythematosus (as per American Rheumatology Association [ARA] criteria: autoantibodies, lymphopenia, serositis = pleural effusion and rash). Immunosuppressive therapy in that case could have resulted in the patient's demise from “lupus cerebritis,” when HAT would have moved to its neuroinvasive phase.

Autoantibodies are known to occur in many infections. In HAT patients, the presence of antinuclear antibodies (ANAs) has been described in the past, with up to 84% of *gambiense* HAT cases positive for ANAs, probably reflecting an intense, polyclonal B cell activation.¹¹ A misdiagnosis of systemic lupus erythematosus and a delay in antitrypanosomal treatment has been described in the past in *gambiense* HAT cases.¹² To our knowledge, this is the first documentation of ANAs in human *rhodesiense* HAT, however monkeys experimentally infected with *T. b. rhodesiense* invariably developed high titers of ANAs within a month of infection.¹³

CONCLUSIONS

A relapsing fever pattern in a traveler returning from a sojourn in East Africa should alert the clinician to the possibility of *rhodesiense* HAT. Typical physical findings may take weeks to evolve, and multiple blood smears may be required to make the diagnosis. HAT may be associated with multiple false positive infectious and autoimmune serologies, and the risk of a misdiagnosis is real. A possible association between blood smear positivity and its timing in relation to the onset of rigors should be further explored. The role of blood PCR in the diagnosis of *rhodesiense* HAT remains to be established.

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FIGURE 1. Human African trypanosomiasis—trypanid rash.

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REFERENCES

1. WHO, 2011. Human African trypanosomiasis: number of new cases drops to historically low level in 50 years. Geneva: World Health Organization.
2. Radwanska M, Chamekh M, Vanhamme L, Claes F, Magez S, Magnus E, de Baetselier P, Buscher P, Pays E, 2002. The serum resistance-associated gene as a diagnostic tool for the detection of *Trypanosoma brucei rhodesiense*. *Am J Trop Med Hyg* 67: 684–690.
3. Radwanska M, Claes F, Magez S, Magnus E, Perez-Morga D, Pays E, Buscher P, 2002. Novel primer sequences for polymerase chain reaction-based detection of *Trypanosoma brucei gambiense*. *Am J Trop Med Hyg* 67: 289–295.
4. Mighelsen SJ, Büscher P, Hoepelman AI, Schallig HD, Adams ER, 2011. Human African trypanosomiasis: a review of non-endemic cases in the past 20 years. *Int J Infect Dis* 15: e517–e524.
5. Gautret P, Clerinx J, Caumes E, Simon F, Jensenius M, Loutan L, Schlagenhauf P, Castelli F, Freedman D, Miller A, Bronner U, Parola P, 2009. Imported human African trypanosomiasis in Europe, 2005–2009. *Euro Surveill* 14: 1–3.
6. Jelinek T, Bisoffi Z, Bonazzi L, van Thiel P, Bronner U, de Frey A, Gundersen SG, McWhinney P, Ripamonti D, 2002. Cluster of African trypanosomiasis in travelers to Tanzanian national parks. *Emerg Infect Dis* 8: 634–635.
7. Manson P, 1918. *Tropical Diseases: A Manual of the Diseases of Warm Climates*. London: Cassel & Co.
8. Chappuis F, Loutan L, Simarro P, Lejon V, Buscher P, 2005. Options for field diagnosis of human African trypanosomiasis. *Clin Microbiol Rev* 18: 133–146.
9. Blum J, Beck BR, Brun R, Hatz C, 2005. Clinical and serologic responses to human “apathogenic” trypanosomes. *Trans R Soc Trop Med Hyg* 99: 795–797.
10. Deborggraeve S, Lejon V, Ekangu RA, Mumba Ngoyi D, Pati Pyana P, Ilunga M, Mulunda JP, Büscher P, 2011. Diagnostic accuracy of PCR in *gambiense* sleeping sickness diagnosis, staging and post-treatment follow-up: a 2-year longitudinal study. *PLoS Negl Trop Dis* 5: e972.
11. Kazyumba G, Berney M, Brighthouse G, Cruchaud A, Lambert PH, 1986. Expression of the B cell repertoire and autoantibodies in human African trypanosomiasis. *Clin Exp Immunol* 65: 10–18.
12. Kirrstetter M, Lerin-Lozano C, Heintz H, Manegold C, Gross WL, Lamprecht P, 2004. Trypanosomiasis in a woman from Cameroon mimicking systemic lupus erythematosus. *Dtsch Med Wochenschr* 129: 1315–1317.
13. Lindsley HB, Kysela S, Steinberg AD, 1974. Nucleic acid antibodies in African trypanosomiasis: studies in Rhesus monkeys and man. *J Immunol* 113: 1921–1927.