

African Sleeping Sickness in Tourists Returning from Tanzania: The First 2 Italian Cases from a Small Outbreak among European Travelers

Diego Ripamonti,¹ Marco Massari,³ Claudio Arici,¹ Ermanno Gabbi,³ Claudio Farina,² Maria Brini,⁴ Carlo Capatti,⁵ and Fredy Suter¹

¹Infectious Diseases Unit and ²Microbiology Department, General Hospital of Bergamo, Bergamo, and ³Infectious Diseases Unit, ⁴Biochemistry Laboratory, and ⁵Microbiology Department, Arcispedale St. Maria Nuova, Reggio Emilia, Italy

A recent cluster of cases of African trypanosomiasis in humans (HAT) has been reported in tourists (most of whom were European) returning from Tanzania; we describe the first 2 patients (both of whom were Italian travelers) with HAT, who have been treated successfully. Because neither vaccine nor drug prophylaxis is currently recommended and/or available for persons traveling to areas of endemicity, physicians should be alerted about this uncommon but potentially life-threatening disease.

African trypanosomiasis in humans (HAT) is a protozoan disease caused by *Trypanosoma brucei* complex, which is transmitted by infected tsetse flies belonging to the genus *Glossina*. These insects, which are not found outside of Africa, acquire the infection by sucking the blood of wild and domestic infected animals. The illness (also known as “sleeping sickness”) may spread to the CNS during the late stage of disease. If untreated, it leads to coma and death [1].

It is estimated that at least 300,000 patients are currently infected with HAT in central Africa, and that >60 million persons live in areas where they are considered to be at high risk of infection [2, 3]. Although HAT is persistently endemic in the African continent, and although there has been a recent resurgence in infection [4], only a small number of cases (<15) have been reported in international travelers during the past 15 years. Most of these infected travelers had returned from short trips to national parks in Africa [5–15]. However, from

January through March 2001, TropNetEurop published warnings regarding a cluster of 6 patients (5 European travelers and 1 South African tourist) who acquired an acute form of sleeping sickness after a trip to Tanzania [16]. We describe in detail the first 2 Italian travelers to have acquired acute HAT, both of whom were included in the aforementioned warning.

Patient 1. A 33-year-old man was admitted to the hospital in February 2001 with high fever (temperature, 40.5°C), headache, nausea, and vomiting. Two days before admission, the patient had returned from a 15-day trip to Tanzania, Kenya, and Zanzibar. He had visited the Serengeti, Ngorongoro, and Lake Manyara national parks during 4 days, and he recalled receiving several insect bites during that time, none of which he considered particularly painful. The patient had been vaccinated for yellow fever 6 years before presentation, but he had not received any prophylaxis for malaria during his most recent trip.

At the time of admission to the hospital, the patient had a temperature of 40.5°C, pulse of 108 beats/min, and blood pressure of 110/60 mm Hg. An examination revealed a purulent and erythematous skin lesion (diameter, 4 cm) on his upper back (figure 1) that he had noticed the day after he left the national park areas. A right axillary lymph node (diameter, 2 cm) was palpable and painless. Liver and spleen findings were normal. Although the patient was distressed, he was alert and oriented. Findings on a chest radiograph were normal, but the patient’s arterial blood oxygen level was 51 mm Hg.

Laboratory examination revealed the following values: WBC count, 2.63×10^3 cells/ μ L (normal range, $4.8\text{--}10.8 \times 10^3$ cells/ μ L); platelet count, 53×10^3 cells/ μ L (normal, $150\text{--}400 \times 10^3$ cells/ μ L); hemoglobin, 14.7 g/dL (normal range, 14–18 g/dL); blood glucose, 84 mg/dL (normal range, 65–120 mg/dL); creatinine, 2.3 mg/dL (normal level, <1.2 mg/dL); aspartate aminotransferase, 167 IU/L (normal level, <46 IU/L); alanine aminotransferase, 20 IU/L (normal level, <46 IU/L); and total bilirubin, 2.7 mg/dL (normal level, <1.2 mg/dL). The fibrinogen level and prothrombin time were normal. The C-reactive protein level was 19 mg/dL (normal, <1 mg/dL), and the erythrocyte sedimentation rate was within normal range.

The results of a peripheral blood smear for malaria were negative, but trypanosomes and high-grade parasitemia were detected (1.8 parasites per field; magnification, $\times 40$; figure 2). A CT scan of the brain did not reveal any abnormalities except for a mild diffuse cerebral edema. A lumbar puncture was performed to assess possible CNS involvement. Examination of the CSF specimen revealed only 3 cells, with a total protein level of 24 mg/dL (normal range, 15–45 mg/dL) and a glucose

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Reprints or correspondence: Dr. Diego Ripamonti, Divisione di Malattie Infettive, Ospedali Riuniti, Largo Barozzi, 1, Bergamo, 24100 Italy (djnrip@tin.it).

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Figure 1. Erythematous plaque on the upper back of a 33-year-old man (patient 1) who returned from a trip to East Africa

level of 61 mg/dL (normal, 50–80 mg/dL); no trypanosomes were detected. Three consecutive blood cultures and a skin lesion swab yielded coagulase-negative *Staphylococcus* species, and the patient was successfully treated with second-generation cephalosporin.

Serologic testing for *Trypanosoma brucei* was performed using indirect hemoagglutination. The results were negative at the time of admission to the hospital, but they became positive (titer, 1:512) 2 weeks later. On the day of hospitalization, pending the arrival of suramin from Switzerland, the patient received iv pentamidine (300 mg). The following morning, the parasitemia was markedly reduced (5 trypanosomes per slide) and the patient was given iv suramin (1 g) after a test dose. The drug was well tolerated, despite transient and asymptomatic arterial hypotension with a skin rash (which was most prominent on the legs) during infusion. Beginning on the third day after hospitalization, the patient was healthy and the results of peripheral blood smears for parasites were persistently negative. The patient received a second dose (1 g) of suramin on day 9 of his hospital stay. Blood chemistry findings normalized within a few days after admission to the hospital, and the skin lesion healed completely 10 days after the start of treatment. After discharge, the patient received the same dose of suramin once per week for 3 more weeks. No adverse events occurred after these subsequent doses of suramin therapy. One month after he received the last dose of suramin, the patient was clinically healthy.

Patient 2. A 30-year-old man was admitted to the hospital in February 2001 shortly after he had returned from a 15-day trip to Kenya and Tanzania. During the first 6 days of his trip, he consecutively visited the East Tzavo, Lake Manyara, Ser-

engeti, and Ngorongoro national parks. The patient underwent yellow fever vaccination before travel, and he was receiving malaria prophylaxis with mefloquine.

Four days after he left the park area, the patient noticed an ulcerating skin lesion on his left ankle with local edema and erythema; the patient did not recall having received an insect bite on that skin area. He also had high fever (temperature, 39.7°C), which apparently resolved after a short course of amoxicillin. A blood smear for malaria was performed in Kenya, the results of which were negative. The patient was hospitalized after he returned home because of dark urine, mild jaundice, petechial exanthema, and a persistent skin lesion (figure 3).

At the time of admission to the hospital, the patient presented with multiorgan failure and disseminated intravascular coagulation. An examination revealed a skin lesion (diameter, 5.5 cm) on the left ankle. The patient had hepatomegaly, his spleen was not palpable, and no lymphadenopathy was found. The patient was distressed, but alert and oriented. Findings of a neurological examination were unremarkable. His temperature was 37.2°C, his pulse was 92 beats/min, and his blood pressure was 100/65 mm Hg. Laboratory tests revealed the following values: WBC count, 5.6×10^3 cells/ μ L; hemoglobin, 14.8 g/dL (normal range, 14–18 g/dL); platelet count, 63×10^3 cells/ μ L (normal range, $150\text{--}400 \times 10^3$ cells/ μ L); blood glucose, 101 mg/dL (normal range, 60–120 mg/dL); creatinine, 4.5 mg/dL (normal level, <1.3 mg/dL); blood urea, 47 mg/dL (normal level, <23 mg/dL); total bilirubin, 6.4 mg/dL (normal level, <1.2 mg/dL); lactate dehydrogenase level, 2032 IU/L (normal level, <460 IU/L); aspartate aminotransferase level, 192 IU/L (normal, <40

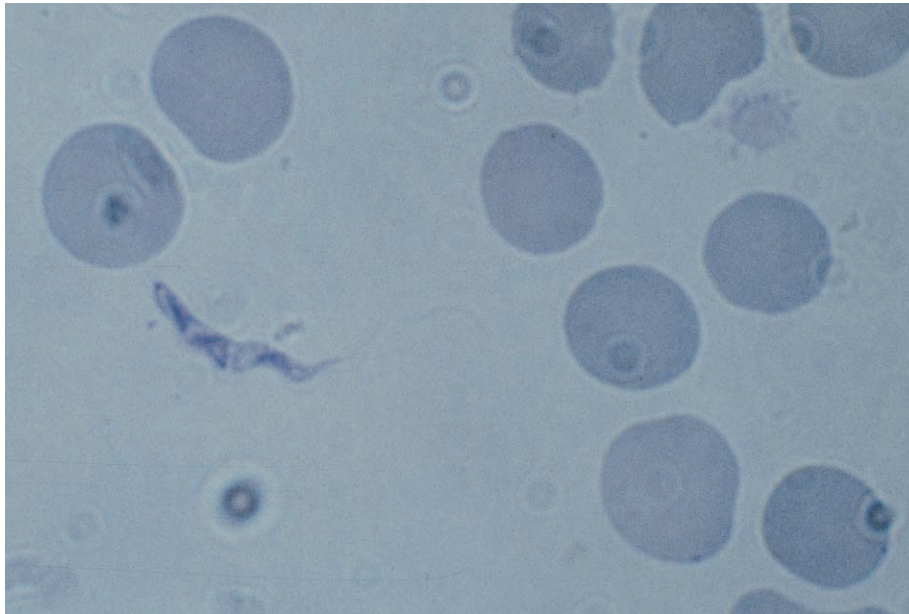


Figure 2. Peripheral blood smear (Giemsa stain; magnification, $\times 40$) showing *Trypanosoma brucei rhodesiense* (patient 1)

IU/L); alanine aminotransferase level, 208 IU/L (normal, <40 IU/L); and prothrombin activity, 63%.

Peripheral blood smear for parasites revealed numerous trypanosomes (3.8 parasites per field; magnification, $\times 100$). Suramin was not available, so the patient was given iv pentamidine (4 mg/kg every 48 h), which is the standard dosage for patients with renal impairment. After the patient received 2 doses of pentamidine, the results of blood smears for trypanosomes became persistently negative. However, during the subsequent days, his temperature increased to 37.8°C , his creatinine level increased to 7.7 mg/dL, and he underwent hemodialysis. His total bilirubin level was 19.7 mg/dL (mostly conjugated), with several hypoglycemic crises that had possibly been caused by pentamidine. He had severe thrombocytopenia (6.0×10^3 cells/ μL) with prolongation of clotting time and increased D-dimer levels. He developed mild respiratory distress, with bilateral effusions secondary to acute renal failure, but he remained hemodynamically stable during his entire stay at the hospital. The findings of neurological examinations were persistently normal. Blood cultures did not yield any organisms. Lumbar puncture was deferred to day 9 of the hospital stay because of severe thrombocytopenia. Examination of a CSF specimen revealed 8 cells (100% lymphocytes) and normal glucose and protein levels, but there was a slight increase in IgG level, to 100 mg/L (normal level, <40 mg/L). No trypanosomes were detected.

A second CSF specimen was examined on day 18 of hospitalization; no abnormalities were revealed and parasites were absent. Coagulation disorders resolved gradually without any apparent acute bleeding. Hepatic and renal functions recovered completely 15 and 38 days after treatment began, respectively.

The patient underwent hemodialysis 15 times (total duration of hemodialysis, 25 days). The results of 2 consecutive serologic tests for trypanosomes (ELISA and indirect hemoagglutination), which were performed 2 weeks apart, were negative. The patient was discharged to his home after 35 days of hospitalization. Two weeks after discharge, he was still clinically healthy.

Discussion. Approximately 60 million people who live in sub-Saharan countries are at risk for HAT, and the situation now is worse than it was 50 years ago [4]. The breakdown of the tsetse fly-control programs due to the recurrent political turmoil and economic crisis is considered to be an important determinant of this recrudescence [17]. The occurrence of several cases of HAT this close together, as was recently reported in European travelers [16], confirms the resurgence of this disease. The high number of international tourists who travel to such regions of endemicity has brought this clinical entity to the attention of physicians who also reside outside the tropical area. HAT is caused by 2 species of trypanosomes: *Trypanosoma brucei rhodesiense*, which is responsible for the acute form of the disease and which is prevalent in eastern and southern Africa, and *Trypanosoma brucei gambiense*, which causes the chronic form of illness and which is prevalent in western and central Africa. The 2 species cannot be distinguished morphologically, and they are managed with different treatments. Differential diagnosis is made on the basis of geographical area of travel and the clinical course of disease [1].

The patients' travel destinations and the acute onset of the disease indicated that both patients were infected with *T. b. rhodesiense* trypanosomiasis. Tourists can acquire the infection through the bites of infected tsetse flies. The bites are not nec-



Figure 3. Erythematous and ulcerated plaque on the inner left ankle of a 30-year-old man (patient 2) with African trypanosomiasis

essarily painful (as was the case in our 2 patients), and patients may not recall having received them. Because no vaccination is available, persons traveling to areas of endemicity should be alerted and take general precautions (such as wearing long sleeves, long trousers, and insect repellent) to protect themselves against tsetse flies. History of recent travel to an area where HAT is endemic and the presence of fever and skin lesions (trypanosomal chancre) are highly consistent with this infectious complication.

The trypanosomal chancre is normally not purulent but circumscribed, rubbery, and indurated [1, 9]. The presence of coagulase-negative *Staphylococcus* species in the first patient's skin lesion and blood sample was a peculiarity of this presentation. The definitive diagnosis of HAT requires demonstration of the parasite in blood or CSF specimens or in enlarged lymph nodes. Moreover, in both the primary stage (with chancre as the main cutaneous manifestation) and the secondary stage (with tripanids) of disease, biopsy specimens and/or fluid samples from the skin lesions should be obtained and directly examined under a microscope for the parasite [1, 9, 18]. With respect to serologic testing, because of the great variation of trypanosome antigens, serologic assays have variable specificity and sensitivity and, thus, are not reliable for diagnostic purposes [9]. Therefore, negative test results—even if confirmed over time—do not rule out the diagnosis. As was the case in patient 2, decisions regarding treatment should be made on the basis of the demonstration of the parasite in appropriate specimens.

A highly sensitive method for the detection of *T. b. rhodesiense* is the inoculation of specimens of blood, CSF, or lymph node aspirate into mice or rats, in which parasitemia develops

in 1–2 weeks. This particular approach is particularly useful to rule out occult CNS involvement when CSF abnormalities (increase in cell counts and/or protein levels) are present and a microscopic examination reveals no evidence of trypanosomes [1]. Frank and occult CNS involvement have strong implications for therapy, as described below. With regard to the finding of a mild cerebral edema on the CT scan of the brain of patient 1, the interpretation may be more difficult. It may have been related to the patient's 3-day history of high fever or, possibly, to early stage CNS invasion. However, the patient did not have any neurological signs, and his CSF was found to be normal and without any evidence of parasites.

In all suspected cases of trypanosomal infection, lumbar puncture is mandatory and should be repeated 3–6 months after treatment is finished to confirm the absence of CNS involvement. However, any abnormalities in CSF in patients with HAT should be considered to be an indicator of CNS involvement and managed appropriately. Suramin is the first-line treatment for early stage *T. b. rhodesiense* trypanosomiasis. It is an old antitrypanosomal compound (it was discovered in 1917), but it is still effective. Adverse events associated with its use are neurological disorders, skin rash, renal impairment, coagulopathy, and hematological toxicity [19].

For treatment of frank late-stage sleeping sickness, as well as for occult CNS involvement, melarsoprol is the drug of choice, because neither suramin nor pentamidine crosses the blood-brain barrier adequately [1, 9, 20]. Unfortunately, its commercial production is at risk because the market is limited [17, 21]. Melarsoprol has a relatively high toxicity and is associated with reactive encephalopathy, in particular. This condition can

occur in up to 18% of patients who receive melarsoprol, and it can be fatal [1]. Pentamidine is the alternative recommended drug, but only for management of early stage trypanosomiasis caused by *T. b. rhodesiense*. It has a lower cure rate than does suramin. Eflornithine, a very expensive drug (the current cost of treatment per patient is \$700), is highly effective for management of both hemolymphatic and late-stage disease, but only for the *T. b. gambiense* form [17, 20, 22]. Although suramin is the drug of choice for management of early stage *T. b. rhodesiense* disease when the CNS is not affected, in both of our patients, pentamidine effectively reduced parasitemia after 1 or 2 doses; for the second patient, pentamidine also cured the disease, despite the patient's severe clinical presentation.

Because, to our knowledge, <15 cases of trypanosomal infection have been reported outside of Africa during the past 15 years, the first-line treatment for trypanosomal infection (suramin) is seldom available at local hospital pharmacies in Europe [23]. For this reason, the appropriate treatment is usually deferred, even when the diagnosis is made promptly [10, 13–16, 24]. In light of the recent outbreak in international travelers, and in light of the resurgent epidemic in regions of Africa, physicians should be alerted about HAT, because prompt diagnosis and appropriate treatment are highly effective. Moreover, because HAT can rapidly become life threatening, and because patients may have a severe presentation (as did patient 2) [15], the most effective antitrypanosomal drugs should be made available in reference hospitals, at the least.

References

- Mandell G, Bennett JE, Dolin R. Mandell, Douglas, and Bennet's principles and practice of infectious diseases. 5th ed. New York: Churchill Livingstone, 2000.
- Control and surveillance of African trypanosomiasis: report of a WHO Expert Committee. World Health Organ Tech Rep Ser 1998; 881:1–114.
- World Health Organization. The programme for surveillance and control of African Trypanosomiasis. Available at: http://www.who.int/emc/diseases/tryp/sleeping_sickness.pdf.
- Ekwanzala M, Pèpin J, Khonde N, et al. In the heart of darkness: sleeping sickness in Zaire. Lancet 1996; 348:1427–30.
- Bakken JS, Arroe M. African trypanosomiasis: report on a patient [in Norwegian]. Tidsskr Nor Laegeforen 1985; 23:1501–2.
- Arroe M, Willumsen L, Tvede M, et al. Acute African trypanosomiasis imported into Denmark [in Danish]. Ugeskr Laeger 1985; 147:2915–6.
- Niemen RE, Kelly JJ, Waskin AH. Severe African trypanosomiasis with spurious hypoglycemia. J Infect Dis 1989; 159:360–2.
- Braendli B, Dankwa E, Junghans T. East African sleeping sickness (*Trypanosoma rhodesiense* infection) in two travellers to the tropics [in German]. Schweiz Med Wochenschr 1990; 120:1348–52.
- Panosian CB, Cohen L, Bruckner D, et al. Fever, leukopenia and a cutaneous lesion in a man who had recently travelled in Africa. Rev Infect Dis 1991; 13:1131–38.
- Ponce-de-León S, Lisker-Melman M, Kato-Maeda M, et al. *Trypanosoma brucei rhodesiense* infection imported to Mexico from a tourist resort in Kenya. Clin Infect Dis 1996; 23:847–8.
- Sabbah P, Brosset C, Imbert P, et al. Human African trypanosomiasis: MRI. Neuroradiology 1997; 39:708–10.
- Iborra C, Danis M, Bricaire F, Caumes E. A traveller returning from Central Africa with fever and a skin lesion. Clin Infect Dis 1999; 28: 679–80.
- Jones J. African sleeping sickness returns to UK after four years. BMJ 2000; 321:1177.
- Sanner BM, Doberaurer C, Tepel M, Zidek W. Fulminant disease simulating bacterial sepsis with disseminated intravascular coagulation after a trip to East Africa. Intensive Care Med 2000; 26:646–7.
- Sinha A, Grace C, Kemper Alston W, et al. African trypanosomiasis in two travellers from the United States. Clin Infect Dis 1999; 29:840–4.
- TropNetEurop: European Network of Imported Infectious Disease Surveillance. Available at: http://www.tropnet.net/special%20reports/tryps_ex_serengeti.pdf.
- World Health Organization. TDRnews: African trypanosomiasis update. Available at: <http://www.who.int/tdr/diseases/tryp/update.htm>.
- McGovern TW, Williams W, Fitzpatrick JE, Cetron MS, Hepburn BC, Gentry RH. Cutaneous manifestations of African trypanosomiasis. Arch Dermatol 1995; 131:1178–82.
- Suramin sodium: CI 1003, Metaret, suramin, suramin hexasodium. Drugs R D 1999; 2:431–5.
- Donnelly H, Bernard EM, Rothkotter H, Gold JWM, Armstrong D. Distribution of pentamidine in patients with AIDS. J Infect Dis 1988; 157:985–9.
- Pepin J, Milord F. The treatment of human African trypanosomiasis. Adv Parasitol 1994; 33:1–47.
- Dumas M, Bouteille B. Treatment of human African trypanosomiasis. Bull World Health Organ 2000; 78:1474.
- European Network of Imported Infectious Disease Surveillance. TropNetEurop survey: stocks of anti-trypanosomiasis drugs within Europe. Available at: http://www.tropnet.net/special%20reports/Survey_anti-tryps-stocks2.pdf.
- Maddocks S, O'Brien R. Images in clinical medicine: African trypanosomiasis in Australia. N Engl J Med 2000; 342:1254.