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CASE REPORT

Clinical and serologic responses to human 'apathogenic' trypanosomes

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Summary We describe a female patient suffering from a benign self-healing febrile disease with strongly positive serology for *Trypanosoma brucei*. The patient showed a clinical picture with similarities to that of human African trypanosomiasis (HAT). HAT due to *T. b. gambiense* and *T. b. rhodesiense* were ruled out. We performed serologic tests because the patient was worried about HAT after receiving tsetse bites. The possibilities of an infection with human 'apathogenic' trypanosomes such as *T. b. brucei, T. congolense* or *T. vivax* are discussed.

1. Case report

A 75-year-old Caucasian woman sustained multiple tsetse fly bites in Tarangire Park in northern Tanzania on 15 September 2003. She returned to Switzerland 1 month later and 5 weeks after the insect bites developed a febrile condition with a non-itching skin rash on the abdomen, which was not related to the localization of the tsetse bites. Cetrizine was given on the assumption of an unspecific insect bite reaction. The symptoms subsided under treatment with prednisolone at a dosage of 20 mg for 3 days. We first saw the patient on the second day of the steroid treatment. A macular skin rash on the trunk and the arms was observed, and a tympanal body temperature of 37.6 °C was recorded. The diameter of the macules was up to 4 cm. The next day, the rash had disappeared.

C-reactive protein (CRP) was slightly elevated at 17 mg/ml (normal value <8 mg/ml). ALT, AST, Gamma GT, creatinine, blood sugar, haemoglobin and white blood cell count (including differentiated WBC) were inconspicuous. Rheumatologic tests for antinuclear antibodies and c-/p-ANCA were negative.

Serology (IFAT) for *Trypanosoma brucei* was highly positive (1280; normal <160). Cross-reactions with leishmania or malaria were ruled out serologically and parasitologically. Serologies for helminthic infections were negative, including trichinellosis, toxocarosis, echinococcosis, schistosomiasis, filariasis, strongyloidiasis and gnathostomiasis. Serologies for *T. b. gambiense* (IFAT and CATT) and *T. b. rhodesiense* were negative.

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Parasitological blood examinations performed for the first time 56 days after receiving tsetse bites were repeatedly negative. Trypanosomes were not detected in direct microscopy (thin and thick film), concentration methods (QBC, Anion exchange system), culture, or after animal inoculation.

The rash disappeared and the patient did not develop any further symptoms or signs of human African trypanosomiasis (HAT) in the following year. One year later, serology for *T. b. brucei* was close to normal values (1:160).

2. Description of serologic methods

2.1. Serology for *T. brucei*

Heparinized blood of mice infected with *T. brucei brucei* was diluted 1:2.5 with phosphate-saline-glucose (PSG) and run over a DE 52 column (Lanham and Godfrey, 1970), in order to isolate trypanosomes. After centrifugation (2500 rpm/10 min) the pellet was re-suspended in PBS pH 7.2 + 0.5% BSA (Roche Diagnostics, Switzerland), dripped onto slides, dried overnight, wrapped in aluminium foil and stored at −80 °C. For immunofluorescence, the slides were dried and fixed with acetone. Incubations were done at 37 °C in a humid chamber using an FITC F(ab′)2 anti-human IgGAM (H + L) conjugate (Bio-Rad S.A., Marnes-la-Coquette, France), and slides were read under a fluorescent microscope.

2.2. CATT-Test/IFAT for *T. b. gambiense* (Institut voor Tropische Geneeskunde, Klinik Leopold II, Antwerpen)

The antigen consisted of lyophilized bloodstream forms of *T. b. gambiense* variable antigen type LiTat 1.3. Antigen production is based on the isolation of trypanosomes from infected rat blood, as described above. The trypanosomes were fixed, stained with Coomassie Blue and freeze-dried.

2.3. IFAT for *T. b. rhodesiense* (Institut voor Tropische Geneeskunde, Klinik Leopold II, Antwerpen)

The antigen consisted of cloned trypanosomes ETat 1.18 and ETat 1.1.

3. Discussion

HAT was suspected with fever and skin rash after multiple tsetse fly bites. The further course was self-limiting. West African HAT was ruled out by epidemiology, lack of demonstration of the parasite and negative serology for *T. b. gambiense*. East African HAT is endemic in Tanzania, has a short incubation period (<16 days) and is an acute, life-threatening disease with high fever and headache, often presenting a chancre and sometimes skin rashes (Apted et al., 1963; Moore et al., 2002; Sinha et al., 1999). Trypanosomes can easily be detected in East African HAT because of a persistent parasitaemia. The observation of asymptomatic healthy carriers (Wurapa et al., 1984), oligosymptomatic patients (Apted et al., 1963) and regions in which healthy humans have tested serologically positive has caused discussion on the potential presence of *T. rhodesiense* strains with low pathogenicity (Songa et al., 1991). However, mild or asymptomatic infections with spontaneous cure have not been described in tourists. The lack of demonstration of the parasite even using concentration methods, culture and inoculation of animals, as well as the negative serology for *T. b. rhodesiense*, the untypical clinical picture and the spontaneous disappearance of the patient's symptoms, all speak against the diagnosis of East African HAT in this Caucasian tourist. An oligosymptomatic *T. b. rhodesiense* infection with spontaneous cure cannot be ruled out but appears to be unlikely.

The character of the skin rash, its localization and its coincidence with a febrile reaction presented by the patient appear to be similar to the trypanosomal rash (=trypanid) described by Duggan among Europeans with sleeping sickness (Duggan and Hutchinson, 1966): ''This exanthema, which may appear at any time after the first febrile episode, consists of blotchy irregular erythematous macules up to four inches across. A large proportion of the macules develop a central area of normal-coloured skin, giving the rash a circinate or serpiginous outline. The trunk is chiefly affected and the erythema is seldom marked. The rash is evanescent, fading in one place and reappearing in another over a period of several weeks. It is not tender and does not itch''.

Besides the tsetse fly bites there was no history of a possible allergen causing an urticaria, and no other cause for the skin rash was found. Although an atypical urticaria could not be ruled out, the aspect of the skin lesions and the lack of itching were not in favour of urticaria.

Whereas chancres at the inoculation site have been reported by various authors (Iborra et al., 1999; Jelinek et al., 2002; Moore et al., 2002; Oscherwitz, 2003; Ripamonti et al., 2002), the trypanosomal rash or trypanid are only rarely reported in East African HAT among Europeans. An enlarged,

painless, non-itching skin lesion lasting 2 days, and a soft tissue thickening observed using magnetic resonance imaging in the areas of trypanids were described in travellers with East African HAT (Moore et al., 2002; Oscherwitz, 2003).

The serologic tests for the presented patient are directed against *T. brucei* spp. and cross-react with *T. b. gambiense* and *T. b. rhodesiense*. The strongly positive serology for *T. brucei* spp. could be the result of an immunological reaction for *T. b. brucei* or a cross-reaction towards trypanosome species such as *T. congolense* or *T. vivax*. Cross-reactions of trypanosomes with malaria or leishmania are well known, but were ruled out by negative serology and the parasitological absence of these diseases. An interference with a rheumatologic disease is unlikely, because there was no clinical sign of rheumatic disease. CRP was close to normal, and the antinuclear antibodies and the ANCA tests were negative. Therefore, the high serological antibody titre and its fall after 1 year cannot be explained by a known cross-reaction.

The question arises whether *T. b. brucei* itself or another trypanosome, such as *T. congolense* or *T. vivax*, may have caused the serologic response and the mild self-limiting disease. Little is known about the pathology of these trypanosomes, and they are generally reported as not being infective for humans. However, recent studies discuss the possibility of the infectious potential and genetic mutability of trypanosomes. The pathogenic potential of *T. congolense* was described by Truc et al. in a severely ill patient as mono-infection or as co-infection (Truc et al., 1998).

Usually, a self-limiting febrile episode is not investigated further. The diagnostic efforts in this patient were pursued because she was worried about HAT after the tsetse fly bites and wanted to have an infection ruled out. Serology was used as a screening test in addition to examining the blood for parasites.

The coincidence of a history of multiple recent tsetse fly bites, a self-healing disease with a skin rash similar to a trypanid and fever, combined with a high serological response to *T. b. brucei* that returned to normal values after 1 year allows the hypothesis that a non-pathogenic trypanosome, *T. b. brucei*, *T. vivax* or *T. congolense*, may have induced this clinical and serological picture, even in the absence of the parasite.

Conflicts of interest statement

The authors have no conflicts of interest concerning the work reported in this paper.

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