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Broucke, S. van den; Schrijvers, R.; Esbroeck, M. van; Coppens, J.; Lieshout, L. van; Bottieau, E.

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Clinical Pearls

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Protracted Katayama syndrome in an immunocompromised traveller: the challenge of assessing cure

Steven Van Den Broucke, MD[1], Rik Schrijvers, PhD[2], Marjan Van Esbroeck, MD[1], Jasmine Coppens, MSc[1], Lisette Van Lieshout, PhD[3] and Emmanuel Bottieau, PhD[1]

[1]Department of Clinical Sciences, Institute of Tropical Medicine, Nationalestraat 155, 2000 Antwerp, Belgium, [2]Department of Microbiology, Immunology and Transplantation, Allergy and Clinical Immunology Research Group, KU Leuven, Herestraat 49, 3000 Leuven, Belgium and [3]Leiden University Center for Infectious Diseases (LUCID), Leiden University Medical Center (LUMC), Albinusdreef 2, 2333 ZA Leiden, the Netherlands

*To whom correspondence should be addressed. Email: svandenbroucke@itg.be

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Case presentation

A 17-year-old Dutch man was admitted to our hospital with high fever, cough and general body pains after returning from a 3-week trip to Malawi. The patient carried a genetic variant in TACI (*TNFRSF13B*), predisposing him to common variable immunodeficiency (CVID). The patient had received monthly intravenous immunoglobulins from the age of 2–12 years due to frequent infections. This treatment had been restarted preventively during the COVID-19 pandemic until 15 months before the current episode. Immunological re-evaluation at the age of 17 only showed temporarily lowered immunoglobulin G and A but otherwise no criteria for CVID.

In Malawi, the patient swam three times in Lake Malawi. Eleven days later, he experienced headache and nausea, and 23 days after the last freshwater exposure, he presented with fever of up to 40°C (see Figure 1 and Table 1), with slight non-productive cough and bifrontal headache.

At admission, his temperature was 38°C and palpation of the abdomen was tender. Laboratory investigation showed eosinophilia 660 cells/μL, platelets 113 000/μL and CRP 52 mg/L. Ceftriaxone and doxycycline were empirically started, but due to a lack of improvement and a rise in eosinophil count (up to 2030 cells/μL), prednisolone (0.5 mg/kg/day) was started for a tentative diagnosis of Katayama syndrome. Ivermectin was given once orally whilst awaiting *Stronglyloides* serology, which remained negative. Clinical evolution was favourable, but pain in the left forearm and both knees arose the day after stopping prednisolone, and eosinophil count peaked at 4250 cells/μL. Prednisolone was, therefore, restarted.

On day 35, post-exposure, the patient complained of persistent knee pain. Prednisolone was re-prescribed, with a 2-day course of praziquantel (60 mg/kg/day). No *Schistosoma* eggs were found in stool or urine, and *Schistosoma* serology was negative. A Dra1-targeted PCR (specific for *Schistosoma haematobium)* was positive on serum (Cycle threshold [Ct] value: 40.2), whilst Sm1-7 targeted PCR (specific for *Schistosoma mansoni*) was negative.[1] Serum tested positive for the schistosome circulating anodic antigen (CAA), determined by the Up-Converting Particle Lateral Flow (UCP-LF) test, at the Leiden University Medical Center (LUMC).[2]

On day 136, the patient came back for his second course of praziquantel but had meanwhile developed an urticaria-like rash on the abdomen, and the pain in the left elbow and knee had increased. Serology against *Schistosoma* was borderline positive at that time. Skin biopsy showed a predominantly lymphocytic dermatitis with dilated capillaries. Dra1-targeted PCR showed a lower Ct value (36.1).

Six weeks later, knee pain, urticaria and eosinophilia had hardly improved. As recurrent or protracted Katayama syndrome was suspected, possibly related to the immunodeficiency, a new course of praziquantel and prednisolone was prescribed, and symptoms improved again. An expert dermatologist concluded to the diagnosis of chronic idiopathic urticaria, possibly triggered by heat and added bilastine on top of prednisolone,

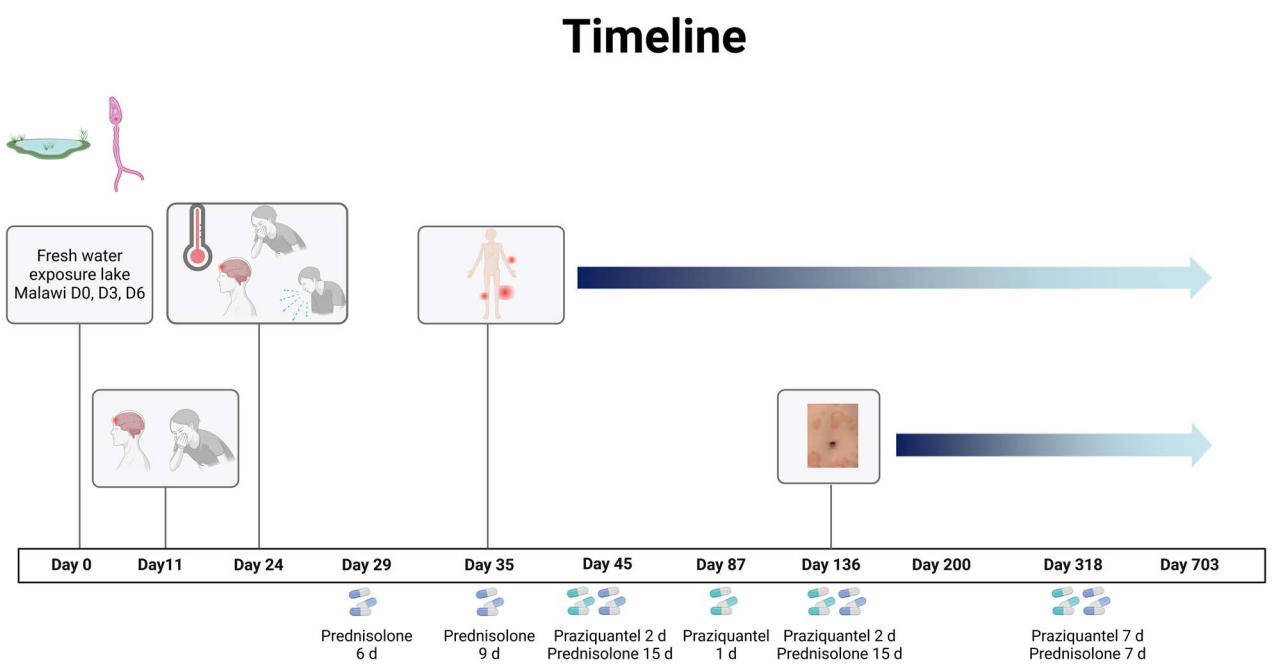

Figure 1 Timelines of symptoms and treatment

Table 1 Timeline of laboratory values

	D 24	D 29	D 35	D 45	D 87	D 136	D 200	D 318	D 703
Eosinophils (eo's/μl)	660	2030	4250	1030	590	560	340	790	710
Serum PCR Dra1 (Ct value)	0	46.01		40.22	36.12		33.59	41.34	Neg
Serum PCR Sm 1-7 (Ct value)	0		0	0					
ELISA (nl. <1.00)				0.86 (neg)	1.07 (pos)	0.63 (neg)	0.51 (neg)	0.24 (neg)	0.16 (neg)
IHA				Neg	Neg	Neg	Neg	Neg	Neg
Serum CAA				Pos		Neg		Neg	

ELISA = elisa enzyme linked immunosorbent assay, IHA = immune hemagglutination assay.

with symptom improvement. About 30 weeks (day 200) after exposure, a Dra1 PCR showed no dramatic improvement (Ct value: 33.6), with a negative serum CAA. A few weeks later, pain in the left knee increased again, and eosinophilia rose to 790/μL, prompting the administration of an additional course of praziquantel and prednisolone, but this time without clinical or laboratory effect. Re-administration of intravenous immunoglobulins was considered but finally not administered as symptoms remained controlled with symptomatic treatment. Two years after the exposure, the knee pain, urticaria and eosinophilia were still present, but both PCR and CAA in serum were negative, supporting a final diagnosis of mechanical arthralgia and idiopathic urticaria.

Discussion

Our case highlights the challenges related to the follow-up of acute schistosomiasis, which often presents nonspecific. In hindsight, the persisting symptoms and laboratory abnormalities were likely unrelated to the *Schistosoma* infection. However, the immunocompromised status, persistence of features suggestive of Katayama syndrome and fluctuating/decreasing Dra1 PCR Ct values led to additional testing and repeated treatments. Eosinophilia might have been correlated with immunodeficiency,[3] but its absence before the travel likely refutes this hypothesis. Whilst persistence of serum PCR positivity has been reported in a subset of adequately treated (and likely cured) patients, the decreasing trend of the Ct values made us consider a recurrent or protracted course of Katayama syndrome. This entity is poorly defined and difficult to manage.[4] *Schistosoma* DNA detection in blood demonstrated high sensitivity and specificity for early diagnosis of acute schistosomiasis but, contrary to PCR on stools or urine, remains positive for many months after treatment.[2,5] Hence, our serum PCR serum does not necessarily reflect the persistence of living worms. However, no studies investigated the evolution of PCR results for schistosomiasis infection in immunocompromised patients, making interpreting consecutive Ct values particularly challenging. In our case, the Ct value was lowest 6 months after the initial praziquantel treatment.

CAA testing proved to be the most reliable parameter predicting active infection post-treatment, as demonstrated in studies where this marker has been quantitatively determined on stored clinical samples.[6,7] Unfortunately, the UCP-LF CAA serum test

is only available in LUMC as a diagnostic laboratory procedure. This is challenging for clinical care, not only because the serum UCP-LF CAA test is currently performed in batch twice a month only, but also because shipping international samples implies logistical hurdles and transport costs. This results in high thresholds for sending samples and delays in receiving results.

Immune response to schistosomiasis entails mostly T helper 2 mediated immunity in concert with IgE, eosinophils and macrophages, whereas susceptibility to reinfection has been associated with the development of parasite-specific blocking IgG4 immunoglobulins, counteracting the effect of IgE.[8] It is unclear if and to what extent the humoral immunodeficiency in our patient, with a transient course of immunodeficiency, would have contributed to the protracted course. Despite schistosomiasis being a relatively common infection, no reports link inborn errors of immunity with a potential predisposition to schistosomiasis or persistent Katayama syndrome, although there might be considerable underreporting from areas where schistosomiasis is endemic.

Our case underscores the difficulty of managing Katayama syndrome in an immunocompromised patient, and especially the challenging clinical and laboratory follow-up of such cases in the absence of an immediately available test of cure. Given the mounting evidence that CAA is the most reliable parameter of schistosomiasis activity, there is a pressing need to make this assay more widely available for the travel clinic practice and to evaluate it in sound clinical strategies.

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Author contributions

Steven Van Den Broucke (Conceptualization [Lead], Data curation [Lead], Formal analysis [Lead], Investigation [Lead], Visualization [Lead], Writing—original draft [Lead], Writing—review & editing [Equal]), Rik Schrijvers (Investigation [Equal], Writing—review & editing [Supporting]), Marjan Van Esbroeck (Data curation [Supporting], Writing—review & editing [Supporting]), Jasmine Coppens (Writing—review & editing [Supporting]), Lisette van Lieshout (Writing—review & editing [Supporting]) and Emmanuel Bottieau (Conceptualization [Supporting], Writing—review & editing [Supporting]).

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Ethical approval

Informed consent was obtained from the patient for the publication of this case report.

Consent for publication

The patient gave his informed consent to publish the case report with all accompanying clinical data.

References

1. Cnops L, Soentjens P, Clerinx J, Van Esbroeck M. A Schistosoma haematobium-specific real-time PCR for diagnosis of urogenital schistosomiasis in serum samples of international travelers and migrants. *PLoS Negl Trop Dis* 2013;**7**:e2413.
2. Hoekstra PT, Dam, Lieshout. Context-specific procedures for the diagnosis of human schistosomiasis – a mini review. *Front Trop Dis* 2021;**2**:1–10.
3. Navabi B, Upton JEM. Primary immunodeficiencies associated with eosinophilia. *Allergy Asthma Clin Immunol* 2016;**12**:27. BioMed Central Ltd.
4. Bottieau E, Clerinx J, de Vega MR *et al.* Imported Katayama fever: clinical and biological features at presentation and during treatment. *J Infect* 2006;**52**:339–45.
5. Hoekstra PT, van Esbroeck M, de Dood CJ *et al.* Early diagnosis and follow-up of acute schistosomiasis in a cluster of infected Belgian travellers by detection of antibodies and circulating anodic antigen (CAA): a diagnostic evaluation study. *Travel Med Infect Dis* 2021;**41**:102053. https://doi.org/10.1016/j.tmaid.2021.102053.
6. Hoekstra PT, Chernet A, de Dood CJ *et al.* Sensitive diagnosis and post-treatment follow-up of Schistosoma mansoni infections in asymptomatic Eritrean refugees by circulating anodic antigen detection and polymerase chain reaction. *Am J Trop Med Hyg* 2022; **106**:1240–6.
7. Tamarozzi F, Ursini T, Hoekstra PT *et al.* Evaluation of microscopy, serology, circulating anodic antigen (CAA), and eosinophil counts for the follow-up of migrants with chronic schistosomiasis: a prospective cohort study. *Parasit Vectors* 2021;**14**:1–11.
8. Colley DG, Secor WE. Immunology of human schistosomiasis. *Parasite Immunol* 2014;**36**:347–57.