Controlled human infection models as a tool for malaria and schistosomiasis vaccine research

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CHAPTER 6

Katayama syndrome without *Schistosoma mansoni* eggs.

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Background

Katayama syndrome is a self-limited illness that occurs several weeks after infection with schistosome larvae (cercariae). Its symptoms are typical of an acute inflammatory response.

Objective

To provide insight into the cause of Katayama syndrome.

Case Report

We exposed 2 human participants to male cercariae of *Schistosoma mansoni* in an experimental infection that met all applicable laws and regulations, was approved by the Ethical Research Committee of Leiden University Medical Center (study P16.111), and was registered at ClinicalTrials.gov (NCT02755324).

The first patient was a healthy 24-year-old medical student with a history of hay fever and mild atopic dermatitis. We exposed her to 30 male cercariae of *S. mansoni* on her lower arm for 30 minutes. She felt itching and developed a typical localized cercarial rash that lasted 2 weeks. Four weeks after exposure, she started having fever, night sweats, myalgia, and headache, but no cough. Her temperature increased above 38.5 °C for 10 days (Figure, top). At that time, her complete blood count showed lymphocytopenia without eosinophilia, but her eosinophil count increased 1 week later (Figure, bottom). A chest radiograph was normal, and bacterial blood and urine cultures were negative. Serum aminotransferase levels increased to 4 times the upper limit of detection. We found no acute viral infections in serologic studies or in repeated molecular diagnostic tests on throat swabs. At week 6, the patient's fever decreased to between 37.5 and 38.0 °C in the evenings; she had night sweats for 3 weeks and reported fatigue, malaise, and mild to severe headaches for a total of 8 weeks. These symptoms were relieved by intermittent acetaminophen and nonsteroidal anti-inflammatory drugs and did not require corticosteroids.

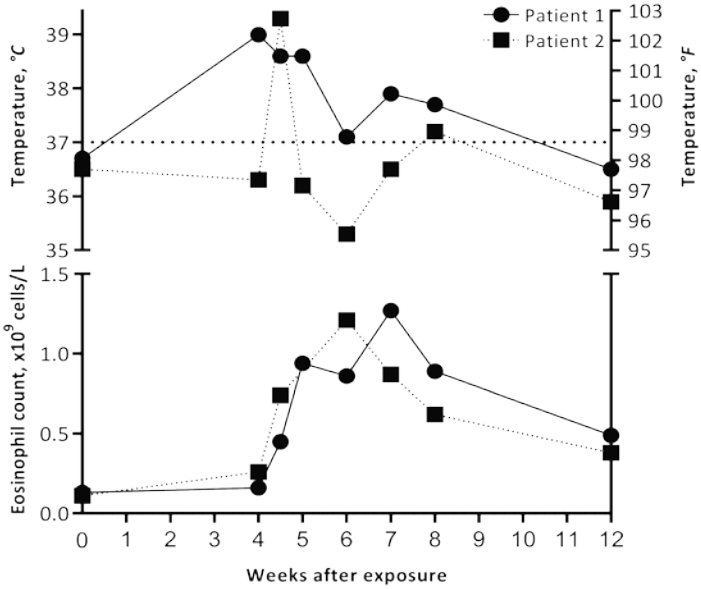

Figure. Highest temperature recorded by the physician or trial participant (top) and eosinophil count (bottom). The horizontal dashed line represents normal body temperature.

The second patient was a healthy 26-year-old psychology student who also had a history of hay fever and mild atopic dermatitis. We exposed her to 30 male cercariae of *S. mansoni* on her lower arm for 30 minutes. She developed nonitching cercarial dermatitis that lasted 6 weeks. Four weeks after exposure, she reported fever and severe headaches for 2 days (Figure, top). Molecular diagnostic tests could not identify viral infections on a throat swab. After the patient's fever abated, she had mild headaches for 5 days. One week after onset of symptoms, her complete blood count showed eosinophilia (Figure, bottom) and she reported periorbital edema of the left eye. We treated her with cetirizine for 2 days, and the edema resolved.

All symptoms eventually subsided, and both patients recovered completely. At the end of the study (week 12), we treated them with praziquantel, 40 mg/kg of body weight, as part of the study protocol.

Table. Quantitative Data of the Anti–Adult Worm IgM (IFA) and Anti-Egg IgG (EIA) in Serum and of the Parasite Antigen Detection Assays for CCA in Urine and CAA in Serum.

Test	week						
	0	4	5	6	7	8	12
Patient 1							
Schistosoma serology							
IFA*	<1:16	1:32	1:256	1:1024	>1:1024	>1:1024	>1:1024
EIA†	<1:32	<1:32	-	-	-	-	<1:32
Parasite antigen							
Urine POC-CCA	Negative	Trace	-	-	-	Trace	Negative
Serum UCP-LF CAA	Negative	Trace	Positive	Positive	Positive	Positive	Positive
Patient 2							
Schistosoma serology							
IFA*	<1:16	<1:16	1:64	1:1024	>1:1024	>1:1024	>1:1024
EIA†	<1:32	<1:32	-	-	-	-	<1:32
Parasite antigen							
Urine POC-CCA	Negative	Trace	-	-	-	Trace	Negative
Serum UCP-LF CAA	Negative	Negative	Negative	Positive	Positive	Positive	Positive

EIA = enzyme immunoassay; IFA = immunofluorescent assay; POC-CCA = point-of-care–circulating cathodic antigen; UCP-LF CAA = upconverting phosphor-lateral flow circulating anodic antigen. *Cutoff, 1:16. †Cutoff, 1:32.

Discussion

Both participants developed Katayama syndrome, as evidenced by typical illness at the expected time after exposure without detectable viral or bacterial pathogens (1). In addition, both were diagnosed with schistosomiasis by parasite antigen testing in serum (upconverting phosphorlateral flow circulating anodic antigen) and had antiworm IgM antibodies detectable by immunofluorescent assay 1 week after the onset of fever (Table) (2, 3). Selection of male cercariae by molecular tests for the experimental infection ensured that *Schistosoma* egg production would not occur (4). In addition, the monosexual infection was supported by the absence of IgG antibody responses to egg antigens on enzyme immunoassay (Table) and the lack of detectable *Schistosoma* DNA in feces (3).

Katayama syndrome has been described as an immune complex–mediated hypersensitivity response to schistosomes or their eggs in previously unexposed persons (1). The antigens that trigger the syndrome are unknown. Our cases prove that it can occur in the absence of eggs and suggest that newly expressed antigens on developing worms may be the cause. The classic type 1 immunologic responses in Katayama syndrome (for example, urticaria; angioedema; and particularly periorbital edema, which occurred in one participant) suggest that worm-specific IgE has a role in this process. These IgE-mediated conditions often respond well to antihistamines and corticosteroids (5).

Katayama syndrome can be remarkably heterogeneous in terms of clinical signs and symptoms (1). Because symptoms are generally mild, transient, and nonspecific, the diagnosis is easily overlooked. Our cases show that both eosinophilia and seroconversion may become apparent after severe symptoms have subsided, that Katayama syndrome can be diagnosed as early as 5 weeks after exposure, and that it is not necessarily related to egg deposition.

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