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BRIEF REPORT

Unusual and Severe Complications of Acute Schistosomiasis in Travelers

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Acute schistosomiasis (ASC) is a hypersensitivity reaction seen mostly in nonimmune travelers and manifests mainly with fever, urticaria, and respiratory symptoms. We describe unusual severe presentations of ASC in 3 patients, including hip-monoarthritis, peri-myocarditis, and optic neuritis. In all 3 patients, clinical symptoms appeared or worsened after praziquantel administration.

Keywords. acute schistosomiasis; monoarthritis; myocarditis; retinitis; travelers.

Schistosomiasis is a waterborne helminthic disease, caused by the trematode of the genus *Schistosoma*. The 3 main species that infect humans are *Schistosoma mansoni* (Africa, South America, Caribbean, and Middle East) *Schistosoma haematobium* (Africa and Middle East), and *Schistosoma japonicum* (China and Southeast Asia), and recently few cases of autochthonous infections in Europe have been reported [1–3].

The parasite penetrates the skin of the host in contaminated fresh water sources that contain cercariae, the infective stage of the parasite. Migrating and maturing larvae may trigger allergic reactions, due to the formation of immune complexes (type 3) and proinflammatory cytokines, causing a syndrome named "acute schistosomiasis" (ASC) or "Katayama fever" [4]. Eventually the larvae mature into adult worms that further migrate to the destination—either urogenital venules for *S haematobium* or mesenteric venules for *S mansoni and S japonicum*, where they release eggs. The chronic disease is due to granulomatous immune response to eggs, leading to various clinical presentations depending on the involved organ [5].

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Schistosomiasis is not uncommon among travelers; in the GeoSentinel database, 16 cases of schistosomiasis were diagnosed per 1000 ill returning travelers, more than 80% of whom had contracted the disease in Africa [2]. Acute schistosomiasis is mostly seen in nonimmune travelers and typically appears 1–12 weeks after exposure, and it is rarely seen in residents or immigrants from endemic area. Acute schistosomiasis is manifested by fever, cough, rash, gastrointestinal complaints, and a range of other symptoms. However, chronic of schistosomiasis can be manifested from asymptomatic to devastating disease, caused by hepatic and pulmonary fibrosis, neuroschistosomiasis, bladder calcification, and fibrosis, depending on host, parasite, and environment factors [3, 4, 6].

The early manifestations of ASC are often nonspecific [4] and easily misdiagnosed, and they can present with unusual symptoms and signs, as illustrated in the following cases.

CASE 1: MONOARTHRITIS

A 24-year-old Israeli male was admitted to the hospital with fever and cough a day after returning from a 3-month trip to Africa, where he swam in Lake Victoria 2 months before presentation. On admission he was febrile; physical examination was unremarkable, and laboratory test revealed eosinophilia of 5.2 k/μL (38.8%) and mild hepatocellular enzyme elevation (Table 1). Thick smear and rapid antigen malaria tests were negative. A chest computed tomography (CT) showed small bilateral patchy infiltrates (Figure 1*A*). Schistosomiasis serology was positive, and stool and urine were negative for ova. The patient was treated with praziquantel (40 mg/kg), together with prednisone with gradual tapering off corticosteroid treatment and improvement in his symptoms. On the fourth day of prednisone treatment, he started feeling a gradually worsening pain in the left hip. On examination he had a restricted active and passive range of motion of the hip joint, without local redness, swelling, or warmth. Laboratory tests revealed white blood cell count of 13.5 k/μL with 2.3 k/μL (16.9%) eosinophils. Magnetic resonance imaging (MRI) of the hip showed joint effusion without involvement of the adjacent bone (Figure 1*B*).

He was treated with analgesics, and although the arthritis gradually resolved after 2 weeks, the cough persisted for another 2 months. Praziquantel (40 mg/kg) treatment was repeated 3 months after the patient's return to Israel.

CASE 2: PERIMYOCARDITIS

A 24-year-old Israeli male developed a sudden onset of retrosternal chest pain accompanied by presyncope and dizziness, 1 month after swimming in the Nile in Jinja, Uganda. On

Table 1. Initial Laboratory Results at Presentation

Laboratory Test	Normal Range	Case 1: Monoarthritis	Case 2: Myocarditis	Case 3: Optic Neuritis
White blood count (k/μL)	4–11	13.4	11	8.3
Hemoglobin (g/dL)	13–17	14.4	13.1	15.5
Eosinophil Count (k/μL, %)	0–0.5 (0%–7%)	5.21 (38.8%)	1.01 (8.1%)	1.30 (16.0%)
Aspartate aminotransferase/alanine transaminase (IU/L)	5–34/0–55	55/81	35/42	18/15
Blood sedimentation rate (mm/hour)	0–22	Not available	11	13
CRP (mg/L)	0–5	Not available	69	Not available
Microscopic examination for ova	Stool	Negative	Not available	Negative
	Urine	Negative	Not available	Not available
Additional laboratory results		Antigen and thick smear negative for malaria	Troponin-I and N-terminal pro-B-type-natriuretic peptide elevated PCR negative for plasmodium, salmonella, rickettsia, dengue, chikungunya, West Nile virus, and *Leptospira*	Antigen and thick smear negative for malaria. Negative serology for HIV, *Leptospira*, syphilis, *Bartonella henselae*, toxoplasma, and toxocara.

Abbreviations: HIV, human immunodeficiency virus; PCR, polymerase chain reaction.

physical examination he was afebrile, arterial pressure was 90/60, and heart rate was 100/minute; the rest of the physical examination was unremarkable. Laboratory test results were remarkable for eosinophilia of 1.0 k/μL (8.1%), elevated troponin, and C-reactive protein (CRP) (Table 1). Electrocardiogram showed low voltage, an incomplete right bundle branch block, and poor R wave progression. Angio CT was negative for pulmonary embolism but showed a small right pleural effusion (Figure 1*C*). The echocardiogram revealed thickened myocardium, which was bright and with a speckled pattern, especially in the inferior wall. Additional findings included a small pericardial effusion and an ejection fraction of 50%.

Our thorough evaluation (see Supplement) of the tests revealed positive serology for schistosome infection, but stool and urine were not tested for ova. The MRI revealed late gadolinium enhancement with inferolateral epimyocardial distribution consistent with myocarditis (Figure 1*D*). Troponin and CRP gradually normalized spontaneously. However, on day 5, the patient was treated with praziquantel (40 mg/kg), which resulted in the re-emergence of eosinophilia and re-elevation of troponin levels. The patient was then treated with prednisone, which resulted in the normalization of troponin, CRP, and eosinophil counts. Praziquantel (40 mg/kg) was prescribed again 3 months later. At that time, echocardiography and cardiac MRI showed no signs of perimyocarditis.

CASE 3: OPTIC NEURITIS

A 23-year-old Israeli male was admitted to the hospital with a 3-day history of blurred vision in his right eye, accompanied by mild headaches and a pruritic rash on his forehead, 3 months after his return from a 4-month backpacking trip in sub-Saharan Africa. He traveled to Northern Ethiopia in the first 3 months and in Uganda in the following month. During his stay in Uganda, he swam in a several lakes at several points of time. One month after his return, he was treated with praziquantel (40 mg/kg) because his *Schistosoma* serology screening test was positive although he was asymptomatic, and 2 months later his symptoms described above appeared. On examination, he was afebrile, and an eruption consisting of discrete papules, without vesicles, were noted above the right eye (Figure 1*E*). An ophthalmic examination revealed a decrease in visual acuity of 6/15 in the right eye with a mild afferent pupillary defect in the right eye. Acuity in the left eye was 6/6. Anterior segments and intraocular pressure were normal in both eyes. On fundus examination of the right eye, posterior vitreous opacities, swollen pale optic disc with cotton wool spots, and hemorrhages were noted, along with macular edema with macular star-figure hard exudates and retinal vein dilatation. The fundus of the left eye was normal. These findings were compatible with neuroretinitis of the right eye (Figure 1*F*). Blood count revealed eosinophilia of 1.3 k/μL (16%). A further search for other causes of neuroretinitis was negative (see Supplement). Chest CT revealed multiple nodular lesions compatible with ASC (Figure 1*G*). Brain MRI results were compatible with optic neuritis (Figure 1*H*); no granulomas were discernible and/or visible.

He was treated again with praziquantel (40 mg/kg per day) for 3 consecutive days. After the first dose he developed shortness of breath, cough, and fever, all of which resolved after treatment with prednisone (1 mg/kg).

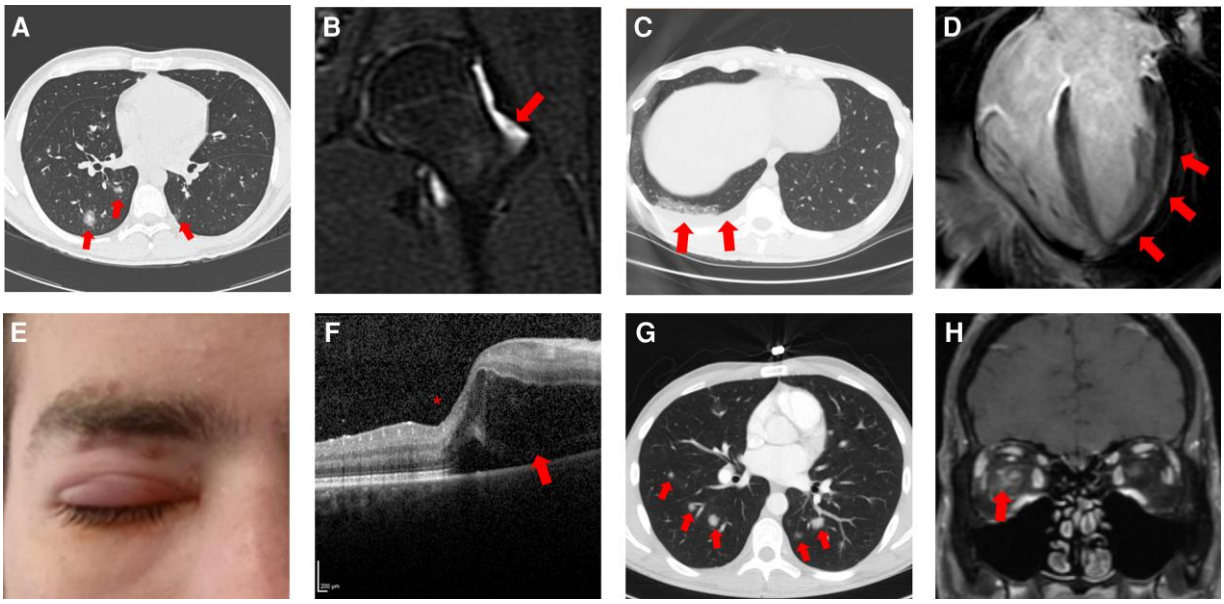

Figure 1. Imaging and clinical findings. Patient 1: (*A*) Chest computed tomography (CT) showing bilateral small patchy infiltrates. (*B*) Coronal short tau inversion recovery (STiR) sequence of the pelvis with left hip effusion (arrow). Patient 2: (*C*) Chest CT shows mild pleural effusion (arrows) of the right lung. (*D*) Cardiac magnetic resonance imaging (MRI) shows late gadolinium enhancement with inferolateral epicardial distribution (arrows) consistent with myocarditis. Patient 4: (*E*) Right papular periorbital rash. (*F*) Spectral domain optical coherence tomography of the right eye demonstrates cystoid macular edema mostly in nasal part of the macula (arrow), with foveal involvement (asterisk) and subretinal fluid. (*G*) Chest CT shows multiple nodular lesions (arrows). (*H*) Coronal gadolinium-enhanced fat-suppressed T1-weighted MRI shows enhancement of the right optic nerve (arrow) compared with the normal contralateral nerve.

PATIENT CONSENT STATEMENT

The patients' written consent was obtained. The design of the work has been approved by the Institutional Review Board (IRB) at the Sheba Medical Center (IRB approval No. SMC- 4378-17).

RESULTS

One year after presentation, visual acuity was 0.9 in the right and 1.0 in the left eye. Normal anterior segments and clear vitreous chambers were noted in both eyes. The right optic disc showed sharp margins and the macula edema was completely absorbed, leaving a small, pigmented scar and a few hard exudates.

The diagnosis in all cases was confirmed by a soluble egg antigen enzyme-linked immunosorbent assay (IVD Research Inc., Carlsbad, CA) that is not species specific [7]. All 3 cases are described in more details in the Supplement.

DISCUSSION

Three cases of severe unusual manifestations of acute schistosomiasis are described here. To the best of our knowledge, monoarthritis has never been reported among patients with ASC. Rheumatic manifestations, although uncommon, were typically described among patients with chronic schistosome infection. The common presentation among those patients resembles reactive arthritis, seronegative spondyloarthropathies, large-joint asymmetric oligoarthritis, sacroiliitis, or rheumatoid arthritis-like inflammation effecting small peripheral joints. These manifestations stem either from the presence of parasite ova or are caused by an immune mechanism often called parasitic rheumatism or parasitic reactive arthritis [8].

In our case, the arthritis appeared during acute schistosomiasis, without evidence of ova and granuloma formation, suggesting an immune phenomenon caused and/or exacerbated by praziquantel treatment and lasting only for 2 weeks.

Although cardiac involvement in ASC has scarcely ever been reported, myocarditis was reported in 2 cases of ASC acquired in the Dogon area of Mali, presumably due to infection with *S hematobium* [9]. Pericarditis was diagnosed in 6 of the 31 ASC patients infected with *S mansoni* contracted in the Abaís lake, Brazil [10]. Another case of pericarditis and endomyocardial fibrosis was described in a patient with ASC with *S mansoni* contracted in Madagascar [11]. Cardiac involvement thus seems to be uncommon and unrelated to schistosome species or to geographic distribution.

To the best of our knowledge, optic neuritis during ACS has never been reported. Nevertheless, 2 cases of retinal and periorbital involvement were reported, and both biopsies were found to contain Schistosomal ova [12, 13]. In our case, the patient presented with ocular inflammatory process without ova detection or any granulomas, which therefore was likely to be caused by hypersensitivity reaction to the pathogen and not by inflammatory reaction and granuloma formation in a trapped ova. Indeed,

the presence of multiple nodular lung lesions revealed in a chest CT, relatively shortly after the repeated praziquantel treatment, also suggested ASC as a likely diagnosis [14]. These severe complications, even uncommon, first and foremost emphasize the importance of traveler's education to avoid swimming in fresh water, especially in Africa and in other endemic areas.

In all 3 cases, the clinical complication or worsening was noticed after praziquantel treatment. This phenomenon has been well documented. In 2 series of ASC among travelers, describing a total of 22 cases, symptoms were exacerbated in 40% of cases after treatment [15, 16]. Although exacerbation was mostly related to respiratory symptoms, more severe complications, such as cerebral vasculitis, also occurred [17]. It should be noted that a worsening of cardiac and retinal manifestations of ASC may have devastating outcomes.

The diagnosis of ACS is still challenging. In this phase of disease, eggs are not detectable, and therefore based on serologic test, which has relatively low sensitivity (80%), they may have an approximate 2-week seronegative window, which requires further serological testing to confirm seroconversion. Molecular methods are in development are not yet fully validated [18, 19].

The treatment with praziquantel during ASC is debatable, because early treatment with praziquantel during ASC does not effectively prevent chronic schistosomiasis and may exacerbate the symptoms [15]. Therefore, the common recommendation is to give praziquantel 3 months after the last exposure. However, if time from exposure to ACS is excessive, as in the third case presented here, we recommend to postpone and provide the praziquantel treatment 4 to 6 weeks later [20, 21].

CONCLUSIONS

In conclusion, the cases described above illustrate that diagnosis and treatment of ASC remain a challenge. Acute schistosomiasis may cause debilitating clinical manifestations that can be exacerbated after treatment with praziquantel.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Bisoffi Z, Buonfrate D, Beltrame A. Schistosomiasis transmission in Europe. Lancet Infect Dis **2016**; 16:878–80.
2. Nicolls DJ, Weld LH, Schwartz E, et al. Characteristics of schistosomiasis in travelers reported to the GeoSentinel Surveillance Network 1997–2008. Am J Trop Med Hyg **2008**; 79:729–34.
3. Poddighe D, Castelli L, Pulcrano G, et al. Urinary schistosomiasis in an adolescent refugee from Africa: an uncommon cause of hematuria and an emerging infectious disease in Europe. J Immigr Minor Health **2016**; 18:1237–40.
4. Leshem E, Maor Y, Meltzer E, Assous M, Schwartz E. Acute schistosomiasis outbreak: clinical features and economic impact. Clin Infect Dis **2008**; 47:1499–506.
5. Gryseels B. Schistosomiasis. Infect Dis Clin North Am **2012**; 26:383–97.
6. Mawa PA, Kincaid-Smith J, Tukahebwa EM, Webster JP, Wilson S. Schistosomiasis morbidity hotspots: roles of the human host, the parasite and their interface in the development of severe morbidity. Front Immunol **2021**; 12:635869.
7. Hinz R, Schwarz NG, Hahn A, Frickmann H. Serological approaches for the diagnosis of schistosomiasis –A review. Mol Cell Probes **2017**; 31:2–21.
8. Peng SL. Rheumatic manifestations of parasitic diseases. Semin Arthritis Rheum **2002**; 31:228–47.
9. Epelboin L, Jauréguiberry S, Estève JB, et al. Myocarditis during acute schistosomiasis in two travelers. Am J Trop Med Hyg **2010**; 82:365–7.
10. de Jesus AR, Silva A, Santana LB, et al. Clinical and immunologic evaluation of 31 patients with acute schistosomiasis mansoni. J Infect Dis **2002**; 185:98–105.
11. Assimeng J, Segbefia CI, Neequaye J. Endomyocardial fibrosis associated with Schistosoma haematobium infection. Ghana Med J **2014**; 48:225–7.
12. Dickinson AJ, Rosenthal AR, Nicholson KG. Inflammation of the retinal pigment epithelium: a unique presentation of ocular schistosomiasis. Br J Ophthalmol **1990**; 74:440–2.
13. Guirou N, Resnikoff S, Yakoura AKH, et al. Orbital migration of schistosome eggs: a case report. BMC Ophthalmol **2021**; 21:189.
14. Schwartz E, Rozenman J, Perelman M. Pulmonary manifestations of early schistosome infection among nonimmune travelers. Am J Med **2000**; 109:718–22.
15. Grandière-Pérez L, Ansart S, Paris L, et al. Efficacy of praziquantel during the incubation and invasive phase of Schistosoma haematobium schistosomiasis in 18 travelers. Am J Trop Med Hyg **2006**; 74:814–8.
16. Meltzer E, Artom G, Marva E, Assous MV, Rahav G, Schwartzt E. Schistosomiasis among travelers: new aspects of an old disease. Emerg Infect Dis **2006**; 12: 1696–700.
17. Caumes E, Vidailhet M. Acute neuroschistosomiasis: a cerebral vasculitis to treat with corticosteroids not praziquantel. J Travel Med **2010**; 17:359–60.
18. Meningher T, Lerman G, Regev-Rudzki N, et al. Schistosomal MicroRNAs isolated from extracellular vesicles in sera of infected patients: a new tool for diagnosis and follow-up of human schistosomiasis. J Infect Dis **2017**; 215:378–86.
19. Wichmann D, Panning M, Quack T, et al. Diagnosing schistosomiasis by detection of cell-free parasite DNA in human plasma. PLoS Negl Trop Dis **2009**; 3: e422.
20. Jauréguiberry S, Caumes E. Clinical management of acute schistosomiasis: still challenging! J Travel Med 18:365–6.
21. Jauréguiberry S, Paris L, Caumes E. Acute schistosomiasis, a diagnostic and therapeutic challenge. Clin Microbiol Infect **2010**; 16:225–31.