Atypical presentation of cerebral schistosomiasis four years after exposure to Schistosoma mansoni#
Case Report

Atypical presentation of cerebral schistosomiasis four years after exposure to Schistosoma mansoni

Matthew F. Rose a,⁎,1, Eli E. Zimmermanb,1, Liangge Hsc, Alexandra J. Golby c,d, Emam Salehd, Rebecca D. Folkerta, Sandro S. Santagataa, Danny A. Milner Jr.a, Shakti H. Ramkissoona

a Department of Pathology, Brigham and Women’s Hospital, Harvard Medical School, USA
b Department of Neurology, Brigham and Women’s Hospital, Harvard Medical School, USA
c Department of Radiology, Brigham and Women’s Hospital, Harvard Medical School, USA
d Department of Neurosurgery, Brigham and Women’s Hospital, Harvard Medical School, USA

A R T I C L E   I N F O
Available online 12 February 2014

Keywords:
Cerebral schistosomiasis
Neuroschistosomiasis
Schistosoma mansoni
Generalized tonic-clonic seizure
Granuloma

A B S T R A C T

Schistosomiasis is the second most socioeconomically devastating parasitic disease worldwide, affecting over 240 million people in 77 countries on 5 continents and killing 300,000 people annually in sub-Saharan Africa alone. Neuroschistosomiasis is caused by granuloma formation around eggs that lodge in the CNS, with Schistosoma mansoni and Schistosoma haematobium usually affecting the spinal cord and Schistosoma japonicum causing most reported cerebral disease. We report a case of a previously healthy 25-year-old woman native to the United States who presented with a single generalized tonic-clonic seizure without other neurologic symptoms four years after spending a semester in Ghana where she went swimming once in a river. Brain MRI showed areas of signal abnormality and mottled nodular linear enhancement in the left temporal and right posterior temporal/parietal lobes and right cerebellum without mass effect. A biopsy of the left temporal lesion showed prominent granulomas with dense mixed inflammatory infiltrates composed of eosinophils, plasma cells, and lymphocytes surrounding refractile egg shells containing characteristic embryonal cells and von Lichtenberg’s spines in the granulomas displaying the pathognomonic spine shape of S. mansoni. Serum ELISA and antibody immunoblots confirmed exposure to S. mansoni. In summary, we describe the atypical combination of cerebral schistosomiasis due to S. mansoni, after a prolonged interval of four years, from a single known exposure.

© 2014 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

1. Introduction

Schistosomiasis has afflicted humans for thousands of years and is now the second most socioeconomically devastating parasitic disease worldwide, affecting over 240 million people in 77 countries on 5 continents and killing an estimated 300,000 people annually in sub-Saharan Africa alone [1,2]. Nearly 800 million people are currently at risk of developing schistosomiasis worldwide [1]. The three main species of Schistosoma (digenetic blood trematode flatworms) infecting humans are Schistosoma haematobium, Schistosoma mansoni, and Schistosoma japonicum. Schistosoma mansoni and S. haematobium are endemic across much of Africa and the Middle East, often in overlapping geographic distributions. S. mansoni is also prevalent in areas of South America and the Caribbean. In contrast, S. japonicum is primarily found in the Far East. Two other species, Schistosoma mekongi and Schistosoma intercalatum, are more geographically restricted with S. mekongi found very focally in Southeast Asia and S. intercalatum found mainly in central West Africa [3,4].

Infection by schistosomes requires contact with freshwater where mobile larval forms emerge from intermediate host snails and penetrate the skin, sometimes provoking an urticarial rash lasting several days. Adult worms migrate to the venous plexuses of specific host tissues, where they form mating pairs and copulate throughout their 3- to 5-year lifespan, laying eggs to be eliminated in either feces or urine (Fig. 1). The different species of Schistosoma show some correlation with specific tissue types, which in turn correspond to the mode of egg elimination. Schistosoma japonicum and S. mansoni show preference for the mesenteric venules of the bowel/rectum, while S. haematobium shows preference for the venous plexus of the bladder [5–7].

Much of the pathology of schistosomiasis results from inflammatory reactions to the eggs and resulting damage of the surrounding organs.

This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-No Derivative Works License, which permits non-commercial use, distribution, and reproduction in any medium, provided the original author and source are credited.

⁎ Corresponding author at: Department of Pathology, Brigham and Women’s Hospital, 75 Francis Street, Boston, MA 02115, USA.
E-mail addresses: mfsrose@rics.bwh.harvard.edu (M.F. Rose), sramkissoon@partners.org (S.H. Ramkissoon).
1 These authors contributed equally to this work.

E-mail addresses: mfsrose@rics.bwh.harvard.edu (M.F. Rose), sramkissoon@partners.org (S.H. Ramkissoon).

Schistosoma haematobium is a risk of developing schistosomiasis worldwide [1]. The three main species of Schistosoma are found mainly in central West Africa [3,4]. Nearly 800 million people are currently at risk of developing schistosomiasis worldwide [1]. The three main species of Schistosoma (digenetic blood trematode flatworms) infecting humans are Schistosoma haematobium, Schistosoma mansoni, and Schistosoma japonicum. Schistosoma mansoni and S. haematobium are endemic across much of Africa and the Middle East, often in overlapping geographic distributions. S. mansoni is also prevalent in areas of South America and the Caribbean. In contrast, S. japonicum is primarily found in the Far East. Two other species, Schistosoma mekongi and Schistosoma intercalatum, are more geographically restricted with S. mekongi found very focally in Southeast Asia and S. intercalatum found mainly in central West Africa [3,4]. Infection by schistosomes requires contact with freshwater where mobile larval forms emerge from intermediate host snails and penetrate the skin, sometimes provoking an urticarial rash lasting several days. Adult worms migrate to the venous plexuses of specific host tissues, where they form mating pairs and copulate throughout their 3- to 5-year lifespan, laying eggs to be eliminated in either feces or urine (Fig. 1). The different species of Schistosoma show some correlation with specific tissue types, which in turn correspond to the mode of egg elimination. Schistosoma japonicum and S. mansoni show preference for the mesenteric venules of the bowel/rectum, while S. haematobium shows preference for the venous plexus of the bladder [5–7]. Much of the pathology of schistosomiasis results from inflammatory reactions to the eggs and resulting damage of the surrounding organs.
Hence, the tissue preferences of specific Schistosoma species lead in turn to some correlations between specific species and the incidence of particular organ injury. For instance, the pathology of S. mansoni and S. japonicum includes hepatic perisinusoidal egg granulomas/Symmers' pipe stem periportal fibrosis, portal hypertension, as well as Katayama fever. In contrast, the pathology of S. haematobium revolves around the urinary tract with frequent hematuria, bladder/lower ureter scarring, and calcification with resulting renal parenchymal damage and kidney failure as well as an association with squamous cell carcinoma of the bladder [3,5,8]. All three Schistosoma species can also affect the central nervous system as neuroschistosomiasis [4,9].

Neuroschistosomiasis results when eggs, instead of being eliminated in feces or urine, spread to the central nervous system and induce the formation of granulomas. Involvement of the brain (cerebral/encephalic schistosomiasis or cerebral granulomatous disease) often leads to seizures, whereas involvement of the spinal cord (spinal cord schistosomiasis or schistosomal myeloradiculopathy) can cause cord compression resulting in paralysis. Similar to the organ distribution described above, different Schistosoma species have prevalence for affecting either the brain or spinal cord. Schistosoma japonicum primarily involves the brain, while S. mansoni and S. haematobium primarily affect the spinal cord. However, occasional cases of cerebral schistosomiasis due to S. mansoni continue to be reported, and it is possible that its frequency of cerebral involvement may be underreported [10–13]. In areas where S. haematobium is endemic, spinal schistosomiasis is the leading cause of spinal cord damage. Involvement of the CNS is thought to be most frequently due to embolization of eggs, but some cases of adult schistosomes traveling to the CNS vasculature have been reported. Symptoms can present soon after infection in the case of acute schistosomal encephalopathy, but delayed reactions for months and sometimes for years have been reported in cerebral schistosomiasis [3,4,9].

Fig. 1. Schistosome life cycle. The stages of the schistosome life cycle (1–10) include (1) elimination from the host as eggs in feces or urine (diagnostic stage), (2) hatching of miracidia, (3) infection of species-specific aqueous snail intermediate hosts, (4) proliferation of sporocysts within snails, (5) release of cercariae into water (infective stage), (6) infection of host by skin penetration, (7) development into schistosomulae, (8) circulation, (9) maturation within portal vasculature, and (10) migration of paired adult worms to target organs. Elimination of schistosome eggs in either feces or urine depends on whether the adults reside in the mesenteric venules of the bowel/rectum (primarily (A) skin penetration, (7) development into schistosomulae, (8) circulation, (9) maturation within portal vasculature, and (10) migration of paired adult worms to target organs. Elimination of schistosome eggs in either feces or urine, spread to the central nervous system and induce the formation of granulomas. Involvement of the brain (cerebral/encephalic schistosomiasis or cerebral granulomatous disease) often leads in turn to some correlations between specific species and the incidence of particular organ injury. For instance, the pathology of S. mansoni and S. japonicum includes hepatic perisinusoidal egg granulomas/Symmers' pipe stem periportal fibrosis, portal hypertension, as well as Katayama fever. In contrast, the pathology of S. haematobium revolves around the urinary tract with frequent hematuria, bladder/lower ureter scarring, and calcification with resulting renal parenchymal damage and kidney failure as well as an association with squamous cell carcinoma of the bladder [3,5,8]. All three Schistosoma species can also affect the central nervous system as neuroschistosomiasis [4,9].

2. Case presentation

The patient is a previously healthy 25-year-old female native of Massachusetts, U.S., who presented to the Brigham and Women’s Hospital emergency department after the first seizure in her life. She had been feeling fatigued on the train that morning, and her symptoms worsened over the day. A coworker had her sit down, at which point she had difficulty answering questions. She then fell off a chair and had a witnessed generalized tonic–clonic seizure, which lasted for 3 min (without incontinence), followed by 30 min of more pronounced fatigue and confusion. In the emergency department, she was fully alert and oriented, followed all commands without difficulty, and had fluent speech. Concentration, attention, and memory were intact, as was her ability to read, name, and analyze a picture. The remainder of her neurologic exam was normal. A CT scan at that time also showed no abnormalities.

Her past medical history is notable only for headaches and eczema. Her headaches, which began in childhood, are infrequent and occur only once or twice per year. They are usually preceded by a scintillating scotoma and often resolve without medications. She also had a tick bite prior to her current course, though she had no subsequent rash and had a negative Lyme titer. In her family, she has a maternal uncle with epilepsy (unknown type), a maternal aunt with migraines, and a mother with cardiac arrhythmias. She is a vegetarian and does not smoke, drink, or use illicit drugs. She is HIV-negative. She has traveled to England twice and lived in Ghana for one semester of college, four years prior to the onset of symptoms. During that trip, she lived mainly in the university town of Legon, 12 km northeast of the capital city of Accra, and she reported swimming once during the trip in a freshwater river that runs parallel to the ocean, east of the capital city. She did not recall swimming in any lakes. She recalled no particular symptoms during her stay, apart from one episode of dysuria that lasted less than a day. In the last 4 years, she has been perfectly well until this episode.
She was subsequently followed in the clinic at weekly intervals and experienced an episode of altered consciousness (possibly a partial seizure) prior to the 4th visit. Peripheral blood showed no abnormal findings: WBC: 9.3, HGB: 12.9, HCT: 39.8, PLT: 226 (POLY: 58, BAND: 0, LYMPH: 31, MONO: 7, EOS: 2, and BASO: 0). Likewise, serum chemistries were within normal ranges: glucose: 91, BUN: 6, creatinine: 0.64, sodium: 140, potassium: 3.8, chloride: 100, total CO2: 26, alkaline phosphatase: 54, ALT: 11, AST: 17, total bilirubin: 0.2, total protein: 7.5, albumin: 4.6, calcium: 9.4, and magnesium: 1.9.

A lumbar puncture was performed, and CSF showed no abnormal findings: glucose: 55, protein: 19, WBC: 2 (91% lymphocytes), and RBC: 0. Likewise, hematologic labs were within normal ranges: CRP: 0.6, MPO: 0, PR3: 4, and ANA and ANCA: negative. She was started on the antiepileptic drug levetiracetam to prevent further seizures.

Electroencephalography (EEG) showed good organization at rest, but occasional abnormal left temporal theta slowing was noted, maximal at T3. There were no definite epileptiform abnormalities (Fig. 2). These findings are suggestive of mild left temporal dysfunction.

Brain MRI imaging showed areas of abnormal T2 and FLAIR signal at the medial and lateral aspects of the anterior left temporal and right posterior temporal parietal lobes (with the left more affected than the right), as well as a similar small area of abnormality of the right cerebellum (Figs. 3A–C). After contrast administration, all these areas showed mottled nodular linear enhancement without significant mass effect (Figs. 3D–F). No associated diffusion abnormality or mineralization or hemorrhage was seen. Likewise, there was no asymmetric hippocampal volume loss or gray matter heterotopia, and ventricles were normal in size. Possible etiologies of these imaging findings could include a spectrum of vasculitides, lymphomatoid granulomatosis, infection, and, less likely, granulomatous disease or tumor.

Additional functional MRI (fMRI) brain mapping was performed for presurgical planning and showed findings consistent with left-sided language lateralization but also showed the functional language regions to be apart from the areas of left temporal lobe signal abnormality. An image-guided left temporal craniotomy for open biopsy of the area of signal abnormality was performed. Upon inspection, the surface of the brain was abnormal with some speckled appearance and some increased vascularity. A 0.5-cm biopsy was taken from the anterior/ inferior left temporal lobe and appeared grossly abnormal with areas of possible necrosis. In addition, tissue was sent for microbiologic cultures.

Initial intraoperative consultation with frozen section/smear evaluation showed collections of histiocytes concerning for granulomas, vascular involvement, and necrosis suspicious for an infectious process (Figs. 4A–B). Subsequent evaluation of paraffin-embedded permanent sections showed brain tissue with extensive granuloma formation and dense mixed inflammatory infiltrates comprised of eosinophils, plasma cells, histiocytes, and lymphocytes (Figs. 5A–B). Review of multiple tissue sections revealed refractile shell fragments at the center of each granuloma with occasional intact shells showing the pathognomonic acanthic spine shape of S. mansoni (Fig. 6A) [14].

Serum ELISA and antibody immunoblots performed at the Center for Disease Control and Prevention (CDC) confirmed exposure to S. mansoni and showed lack of exposure to S. haematobium, the other most prevalent schistosome species in Ghana. The S. mansoni AB FAST-ELISA produced a score of 100 (positive score considered >10; 99% sensitivity for S. mansoni; 90% sensitivity for S. haematobium; 95% specificity for schistosomal infection). The S. mansoni AB immunoblot was positive, while the S. haematobium AB immunoblot was negative. Hence, the patient was diagnosed with cerebral schistosomiasis (neuroschistosomiasis) due to S. mansoni. Stool and urine were repeatedly negative for ova.

The patient was started on dexamethasone to control inflammation and received praziquantel (2 doses) immediately after the histologic diagnosis in order to kill any remaining adult schistosomes. The steroids were tapered over one month, at which point she received another course of praziquantel (2 doses). She was maintained on levetiracetam for seizures. She has had no additional symptoms in the subsequent

![Fig. 2. Electroencephalography shows left temporal dysfunction. This electroencephalogram (EEG), performed with anterior temporal and standard 10–20 electrodes during the waking, drowsy, and sleeping states, is abnormal because of occasional left temporal theta slowing. These findings are suggestive of mild left temporal dysfunction. There are no definite epileptiform abnormalities.](https://example.com/fig2.png)
twelve months. Subsequent serum analysis showed no eosinophilia, and stools continue to be negative for ova.

3. Discussion

Cerebral (encephalic) schistosomiasis was first described by Yamagiwa, a student of Rudolf Virchow, in 1889[15]. It is most often associated with S. japonicum infection in East Asia, where that species is most prevalent, and has only occasionally been reported to be caused by S. mansoni or S. haematobium. In contrast, both S. mansoni and S. haematobium, but not S. japonicum, are endemic to Ghana, the likely source of infection for the current case[3]. Hence, this presentation of cerebral schistosomiasis due to S. mansoni four years after a single known exposure is an atypical presentation.

Cerebral schistosomiasis can present with variable clinical and imaging characteristics that can overlap with that of epilepsy, brain tumors, vasculitis, stroke, granulomatous disease, and other disorders [4]. Patients can present with a combination of partial or generalized tonic-clonic seizures, increased intracranial pressure, focal neurological deficits, and headache [16]. Electroencephalogram can help localize the disease in some cases but can also be normal in some patients [4,17].

The lesions of neuroschistosomiasis can occur in both the cerebral hemispheres and cerebellum/brain stem. On postcontrast MRI, the lesions can appear as a large mass comprising multiple intensely enhancing nodules or as a central linear enhancement surrounded by multiple enhancing punctate nodules sometimes appearing “arborized.” Occasionally, they have also been reported to appear as nonenhancing irregular “finger-like” areas of abnormal signal consistent with increased
edema [18–20]. However, the imaging characteristics of cerebral schistosomiasis due to *S. mansoni*, as in the current case, are not well described because of its comparable rarity. In the current case as well as in three other reported cases of cerebral schistosomiasis due to *S. mansoni*, the imaging does appear to show a similar pattern of enhancing punctate nodules clustered irregularly around some linear enhancement, with surrounding edema. Thus, this imaging pattern may be generally applicable to cerebral schistosomiasis due to both *S. mansoni* and *S. japonicum* [10,11].

Direct pathologic evaluation of the involved tissue, as in the current case, is still the gold standard for diagnosis. Observation of the spine placement on the egg shell (lateral for *S. mansoni*, midline for *S. haematobium*, and absent for *S. japonicum*) is pathognomonic for each species. However, a combination of the serum indirect hemagglutination (IHA) test and enzyme-linked immunosorbent assay (ELISA) shows high sensitivity and specificity for *S. mansoni*, and both are often used in addition to histologic evaluation to confirm the species diagnosis, especially if intact eggs are not identified on histologic sections [16,21]. Other tests such as evaluation of stool and urine for ova can be very useful if positive but are often negative. Overall, as in our case, a combination of these diagnostic approaches is required [4].

Schistosomiasis pathology is driven by host inflammatory response to the eggs and hence correlates with where the eggs are deposited. *Schistosoma mansoni* and *S. japonicum* can cause Katayama fever, hepatic perisinusoidal egg granulomas, and periporal fibrosis and portal hypertension, whereas *S. haematobium* is more frequently associated with hematuria and bladder wall scarring [3,5]. Moreover, specific schistosome species are associated with the development of specific cancers, such as the correlation between *S. haematobium* infection and the development of squamous cell carcinoma of the bladder. In areas where *S. haematobium* is endemic, squamous cell carcinoma of the bladder is the leading form of cancer in the population. Other studies have likewise suggested links between *S. japonicum* and hepatocellular carcinoma and between *S. mansoni* and colorectal adenocarcinoma, although more evidence is needed [8].

Treatment of schistosomiasis consists of antischistosomal therapy (i.e., praziquantel) plus corticosteroids to control the inflammation [22]. Some cases involving the posterior fossa with resulting mass effect may also require treatment with surgical resection [20]. While the current patient showed involvement of both the cerebral cortex and cerebellum, there was no significant mass effect, and the patient was treated successfully with medical therapy after the diagnostic biopsy. Anticonvulsants are frequently needed for a period of time, but studies suggest that long-term antiepileptic therapy is not required in most cases of cerebral schistosomiasis [17]. Unfortunately, neuroschistosomiasis can sometimes result in significant postexposure chronic sequelae including medically refractory epilepsy that may require surgical treatment in the case of cerebral schistosomiasis and paralysis in the case of spinal cord schistosomiasis [4,23]. The worst outcomes have been seen in spinal cord schistosomiasis where some studies have reported that only 15% of treated patients experience a complete recovery, while other studies have shown that early aggressive treatment can lead to full recovery in up to 65% of patients [4,24].
Of note, other schistosome species are found indigenously in the U.S. but die after penetrating human skin, giving rise to a similar initial allergic condition called “swimmer’s itch”, or cercarial dermatitis, but not progressing to the other manifestations of the disease. The primary hosts for these other species are instead water fowl (Austrobilharzia variglandis, Microbilharzia sp., Trichobilharzia ocellata, Trichobilharzia physella, Trichobilharzia stagnicolae) and rodents (Schistosomatium douiti) [25]. Because the specific snail species required as intermediates for S. japonicum, S. mansoni, and S. haematobium are not present in the United States, the transmission of these organisms in the United States waterways is currently unlikely [25].

4. Conclusions

In summary, we describe the atypical combination of cerebral schistosomiasis due to S. mansoni, after a prolonged four-year interval, from apparently a single exposure. The imaging characteristics of irregular nodular enhancement seen in this case mirror those reported in the United States in the apparent single exposure. The imaging characteristics of irregular nodular enhancement seen in this case mirror those reported in the United States waterways is currently unlikely [25].

Disclosures

All authors report no disclosures.

Acknowledgments

We thank the Longwood Neuropathology Training Program of Brigham and Women’s Hospital, Boston Children’s Hospital, Beth Israel Deaconess Medical Center, and Harvard Medical School. We also thank Marian Slaney and Sebastian Valentin of the Brigham and Women’s Hospital neuropathology laboratory for their technical expertise in histological preparation.

References


