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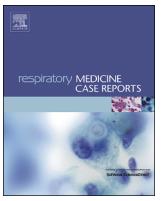

Case Report

Katayama syndrome disguised as eosinophilic asthma with acute systemic symptoms and pulmonary nodules

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ABSTRACT

Background: Katayama syndrome is an acute manifestation of schistosomiasis, a parasitic infection that manifests itself through a hypersensitivity reaction to migrating larvae and early egg deposition. Left undiagnosed and untreated, acute schistosomiasis can develop into chronic schistosomiasis which can lead to debilitating morbidity such as pulmonary hypertension. This case highlights that Katayama syndrome can also been seen in regions where the parasite is not endemic, as it occurs in travelers returning from endemic regions or in immigrants.

Case presentation: We describe the case of a 26-year-old asthmatic male, who presented with systemic symptoms including fever, myalgia, night sweats as well as gastro-intestinal and pulmonary complaints since five days. At presentation, there was a raised blood eosinophil count and nodular lesions were seen on computed tomography. After considering diagnoses such as tuberculosis, vasculitis and hypereosinophilic syndrome, it was repeated history taking that revealed that the patient had suffered from swimmer's itch during a stay in Guinea. A stool sample showed microscopic presence of Schistosoma mansoni eggs, confirming the diagnosis of Katayama syndrome. The patient was treated with tapered corticosteroids to suppress the hypersensitivity reaction and praziquantel was added to cure the parasitic infection. This led to a complete resolution of the patients' symptoms and radiological abnormalities. Negative stool samples confirmed the eradication of the schistosomes.

Conclusions: Swimmer's itch and Katayama syndrome are manifestations of acute schistosomiasis. It is important to recognize the syndrome, because early diagnosis and adequate treatment can prevent chronic disease and significant morbidity.

1. Background

Human schistosomiasis, also known as bilharzia – after Theodor Bilharz who discovered the disease in 1852 – is a parasitic infection caused by trematodes from the genus Schistosoma (S.). Six different species, amongst which the S. mansoni, have been described to infect humans. S. mansoni is endemic in the Caribbean, the Arabian Peninsula, the east of South America and the central to southern regions of the African continent [1]. It is estimated that two hundred thirty million people are affected worldwide [2]. However, in the Western world, this diagnosis is rarely made and the knowledge of physicians on its presentation and morbidity is limited [3].

Abbreviations: CT, Computed Tomography; S, Schistosoma.

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Two large European studies reported an incidence of 1.6 % over six months and 1.7 % over 4.5 years in international travelers [4], while one percent of immigrants was found to be infected in a recent study [5,6]. Immigrants usually present with chronic schistosomiasis due to early exposure and re-infection. In previously healthy travelers, however, the early disease manifestation of acute schistosomiasis (also called Katayama fever) is the more common presentation, usually occurring within the first 12 weeks after infection [7,8].

We report a case of acute schistosomiasis to highlight that also in regions where schistosomiasis is not endemic, the syndrome can occur in travelers and immigrants.

2. Case presentation

A 26-year-old male presented to the emergency room department of our institution in March 2020 with progressive dry cough, sore throat, dyspnea on exertion and night sweats since five days. He also reported recent onset gastrointestinal symptoms including watery diarrhea, hematochezia, nausea with vomiting and diffuse abdominal pain accompanied by anorexia, fever up to 39 °C, myalgia at the shoulders, fatigue and mild (2 kg) weight loss. He had already taken over-the-counter loperamide, probiotics and domperidone, with limited effect.

The patient had a history of asthma. Not taking any controller therapy, he had used his reliever with no effect. He denied any alcohol, recreational drug or tobacco use. Of interest, a work colleague had tested positive for Coronavirus Disease 2019 a few days earlier.

Cardiopulmonary and abdominal examination was normal. Parameters were within normal range except for a temperature of 37.4 °C. Biology showed moderate inflammation with a c-reactive protein of 72 mg/dl, mild leukocytosis (10600/μl) and elevated blood eosinophil count (1654/mm^3). Kidney and liver function tests, as well as arterial blood gasses were within normal range. A chest computed tomography (CT) scan was performed which showed numerous bilateral randomly distributed pulmonary (micro) nodules evoking the diagnosis of miliary tuberculosis (Fig. 1). Other potential differential diagnoses included vasculitis and even hypereosinophilic syndrome because of the combination of asthma, eosinophilia, pulmonary nodules and systemic symptoms in our patient.

The patient was admitted to the pulmonology ward in an isolation chamber. Sputum samples with polymerase chain reaction and microscopic examination were repeatedly negative for mycobacterium tuberculosis. Further history taking revealed that the patient had spent two weeks in Guinea (Konakri) for a humanitarian project six weeks prior to his hospitalization. During his stay in Africa, he had taken a prophylactic treatment for malaria. A blood smear for malaria turned out negative. Serology for dengue fever and chikungunya virus was also negative. Total immunoglobulin E was elevated at 1645 kIU/l with a positive radioallergosorbent test for dermatophagoides pteronysinus (>100 kU/l, class 6) and for gx3 mixture of grasses (>0.7 kU/l). Because of the travel history and diarrhea, a stool sample was examined and revealed the presence of S. mansoni (Fig. 2). On further inquiry, our patient mentioned a diffuse itchy feeling (without noticing a rash) that had occurred after having swum in a freshwater lake during his stay in Guinea and that had lasted only a few minutes.

Based on all these findings, we were able to diagnose our patient with Katayama fever and swimmer's itch.

As soon as the diagnosis of acute schistosomiasis syndrome was confirmed, treatment with oral corticosteroids was initiated at a dose of 16 mg methylprednisolone once a day. During his hospital stay, blood eosinophil count rose to 4803/mm^3 despite treatment with oral corticosteroids, however, accompanied by a quick and favorable evolution of clinical symptoms.

The patient was discharged from the hospital after three days. After one week, the methylprednisolone dose was tapered off to 8 mg once a day and the next week to 4 mg daily. The latter dose was maintained until four weeks after discharge. By that time, the patient's fever, respiratory and gastrointestinal symptoms had completely resolved. Praziquantel at a dose of 50 mg/kg (in this case two

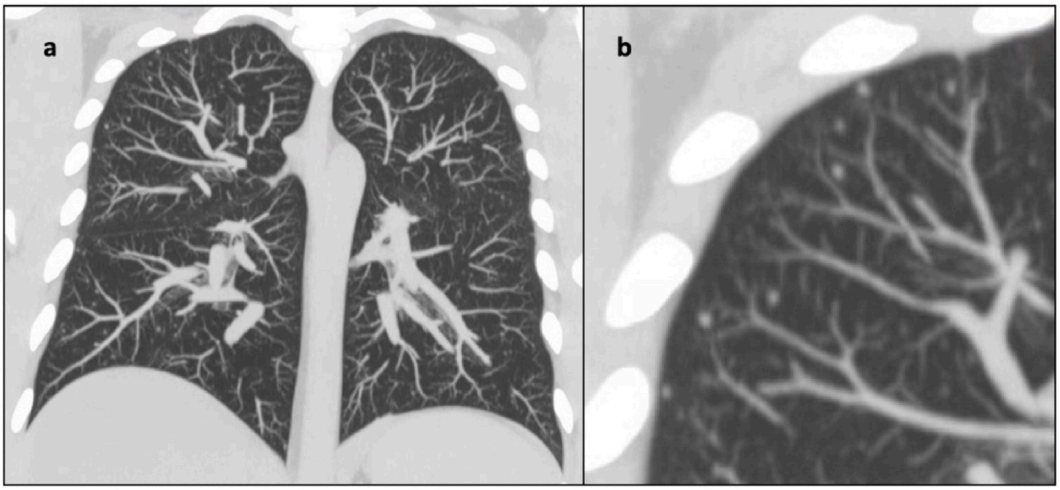

Fig. 1. Computed tomography images at presentation. **a.** Coronal overview. **b.** Zoomed in portion of right apical corner.

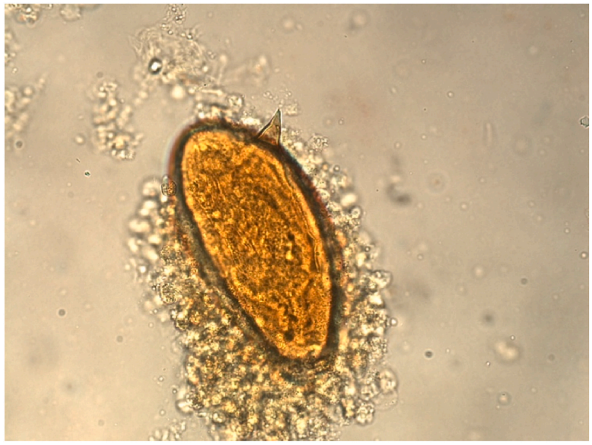

Fig. 2. Schistosoma mansoni egg on stool sample microscopy.

times four tablets of 600 mg per day) was given to consolidate the treatment. A low dose of oral corticosteroids was continued for another four days to prevent flare-ups. Blood eosinophil counts three weeks and nine weeks after hospital discharge were respectively 4830/mm^3 and 594/mm^3. Two stool samples were collected ten weeks after discharge and thus six weeks after treatment with praziquantel. Both were negative for the presence of parasites. A chest x-ray three weeks after discharge, showed complete resolution of pulmonary radiological abnormalities (Fig. 3).

An overview of the timeline of this case is provided in Fig. 4.

3. Discussion

Schistosoma trematodes have an average life span of three to ten years with a life cycle that necessitates an intermediate and definitive host. After hatching of the eggs in freshwater, ciliated miracidia penetrate the snail intermediate host, followed by asexual replication. Cercariae are subsequently released from the snail after on average 30 days under the influence of sunlight in freshwater with an infectious potential to penetrate the human skin of up to three days. After passing through the lungs via the venous circulation, maturation of larvae (schistosomula) in the portal vein takes up to seven weeks. Afterwards, the adult schistosoma form mating pairs, travel to their target organ and start to produce eggs. These are either retained in the tissue, breach the intestinal or bladder mucosa to leave the body, or travel downstream to the portal bloodstream [2].

Dermatological symptoms include swimmer's itch and cercarial dermatitis. The former is caused by the entry of cercariae into the skin and presents with a hardly visible wheel consisting mainly of edema and dilated capillaries [9,10]. The reaction is more pronounced in infection with schistosoma species that are not able to infect humans because these cercariae cannot migrate to the vascu-

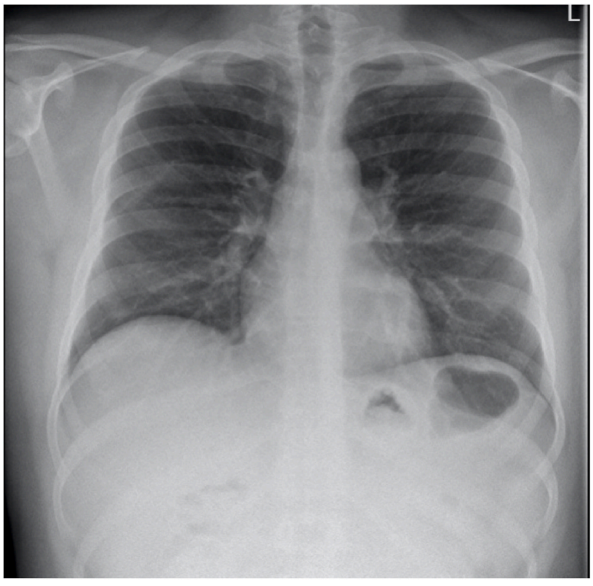

Fig. 3. Thoracic x-ray image after treatment with praziquantel showed resolution of pulmonary nodules.

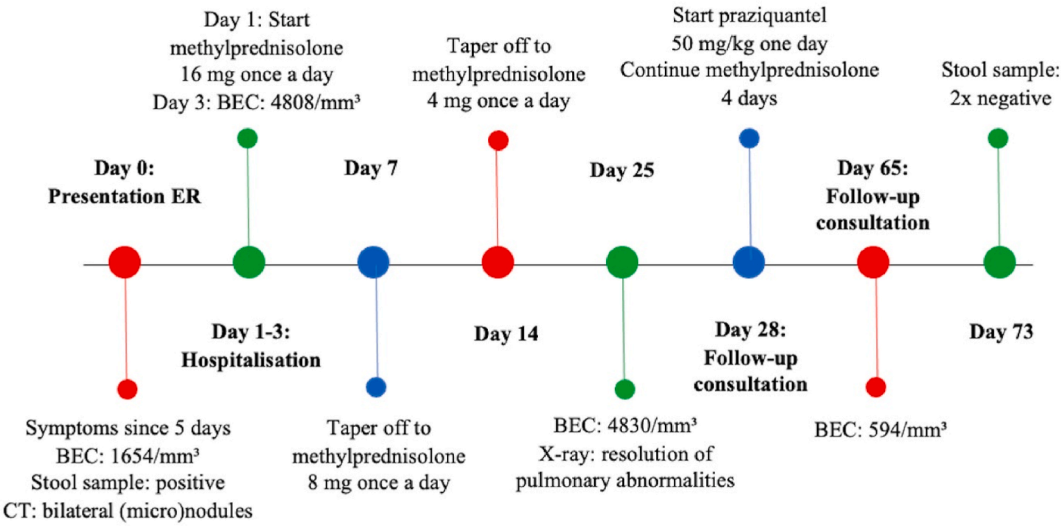

Fig. 4. Timeline of the case. *BEC* Blood Eosinophil Count, *CT* Computed Tomography, *ER* Emergency Room.

lar system and thus stay longer in the dermis. The latter, cercarial dermatitis is a disease manifestation that also occurs within hours or a few days or, in case of delayed-onset dermatitis, 1–12 weeks later. It is pathogenically similar to swimmer's itch but develops due to re-exposure to schistosoma species that are not able to infect humans. It manifests as a maculopapular rash or as angioedema or urticarial in case of delayed onset [9,10].

Katayama syndrome, also known as snail fever, can occur four to eight weeks after infection with S. mansoni, S. haematobium or S. japonicum due to a delayed hypersensitivity reaction to the maturation and migration of the parasites and the start of egg production [8]. Possible symptoms are fever, sweats and chills, myalgia, non-productive cough and headache. Clinical examination may show lymphadenopathy and/or hepatosplenomegaly [7]. Blood tests usually show marked eosinophilia, except in case of early presentation [10].

The acute pulmonary symptoms (such as dyspnea and cough in our patient) may be caused, as in Katayama syndrome, by a hypersensitivity reaction to egg deposition, the migration and maturing of schistosomula alone or the combination of the two. Another hypothesis is that it can be explained by a Loeffler-like reaction not specific to either the eggs or the larvae [8]. Indeed, in schistosomal infection, portocaval shunts develop that allow passage of the eggs from the portal circulation towards the lungs. This process causes a hyperdynamic circulation with increased flow and sheer stress and an increased shunting of eggs as well. Formation of granuloma, endothelial proliferation and dysfunction, and vascular remodeling might eventually result in obstructive pulmonary hypertension. Previous case studies report a prevalence of pulmonary arterial hypertension due to chronic schistosomiasis between 7.7 % and 33 % [11,12].

Different radiological patterns can be found. Formation of lung nodules is found in the presence and in the absence of inflammatory pulmonary symptoms [8]. Rocha et al. [13] reported in 56.7 % of their cases beaded micronodulation on x-ray. A small study by Schwartz et al. [14] found nodular lesions to be the most prevalent abnormality on x-ray and CT; the latter finding was also reported in another small case series [15]. Other CT findings are bronchial wall thickening, reticulo-nodular pattern and bilateral ground-glass opacities [16].

Chronic schistosomiasis can cause a significant morbidity. It occurs when schistosomula follow the venous circulation of the lungs, mature in the hepatic sinusoids and migrate to the mesenteric vessels of the intestinal or urogenital system. Egg deposition causes a T-helper 1 mediated inflammatory granulomatous reaction that transforms into a fibrotic T-helper 2 reaction [8,17]. This can lead to intestinal strictures, periportal fibrosis and obstructive uropathy, as well as hydroureter and -nephrosis [10]. Cases of proliferative glomerulonephritis, secondary amyloidosis and squamous cell cancer have been described related to schistosomal infection. Central nervous system involvement can lead to meningoencephalitis and transverse myelitis [9,10].

A lab diagnosis can be made based on microscopy on tissue biopsy, urine or feces (as in our case). The limitations of this method are low sensitivity and lack of ability to distinguish viability. Other current available methods include schistosomal deoxyribonucleic acid detection, serology for antibodies against schistosomal antigens via western blotting, and detection of circulating schistosomal antigen via dot enzyme-linked immunosorbent assay on blood [18].

As the first part of the treatment of acute schistosomiasis, oral corticosteroids are given to reduce the hypersensitivity inflammatory reaction, with a proposed dose of 1.5–2.0 mg/kg prednisolone per day for three weeks [18]. Secondly, anti-parasitic treatment is given, preferably with praziquantel [18,19]. Praziquantel acts only against adult worms. Hence, to treat acute schistosomiasis, a time interval of 5–7 weeks after exposure should be kept in mind, in order to allow for maturation of the cercariae into schistosomes. A dose of 40 mg/kg is effective in S. mansoni, S. haematobium and S. intercalatum, whilst a higher dose of 60 mg/kg is necessary to treat S. japonicum and S. mekongi. A cure rate of 60 %–95 % has been described for S. mansoni [18]. The adverse effects of treatment are related to the host parasite burden and include abdominal pain, headache, dizziness and hematochezia. Of note, concomitant ad-

ministration of corticosteroids can diminish plasma levels of praziquantel by 50 % [8]. If necessary, praziquantel can be repeated after three to six weeks. A diagnostic and treatment flow chart proposed by Gray et al. [18] suggests follow-up microscopy after four weeks with an additional dose of praziquantel if positive. In our patient, there was an interval of six weeks between treatment and negative stool samples.

Other therapies have been proposed for the treatment of schistosomiasis, with the combination of praziquantel and artemisinin showing the most promising results [19]. Furthermore, several vaccines have already shown efficacy in clinical trials [20].

4. Conclusions

The combination of asthma, eosinophilia, pulmonary infiltrates and systemic symptoms in our patient evoked a broad differential diagnosis. However, it was the thorough medical history that led to the diagnosis of acute schistosomiasis, a rare condition outside the regions where schistosomiasis is endemic. All around the world, the disease should be suspected in immigrants and travelers from endemic regions. Careful medical history taking, inquiring specifically about the typical swimmer's itch can facilitate an early diagnosis and prevent important morbidity.

- Health professionals should be mindful of Katayama syndrome beyond endemic regions.
- A thorough medical history is key to identifying typical symptoms.
- The presence of swimmer's itch can provide a clue to the diagnosis.
- Initial treatment with corticosteroids can ease the acute inflammatory symptoms.
- A correct time interval should be respected for administration of anti-parasitics.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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CRediT authorship contribution statement

Femke Demolder: Writing – original draft, Methodology, Conceptualization. **Samuel De Bontridder:** Data curation. **Shane Hanon:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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