Pulmonary nodules in African migrants caused by chronic schistosomiasis

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Schistosomiasis is a neglected tropical disease that can cause mainly hepatic and genitourinary damage, depending on the species. Involvement of the lungs has been commonly described in acute infection (Katayama syndrome) and chronic infection (pulmonary hypertension). Although rarely reported in the scientific literature, cases of lung nodules due to chronic schistosome infection are also possible and are probably more frequent than commonly thought. Here we report seven cases of African migrants who were diagnosed with chronic schistosomiasis and pulmonary nodules due to deposition of schistosome eggs, and we compare our findings to the case reports found in the scientific literature. We discuss the management of these patients in a non-endemic setting, beginning with a first fundamental step that is to include parasitic infections, namely schistosomiasis, in the differential diagnosis of pulmonary nodules in African immigrants. All patients responded to antiparasitic treatment with praziquantel after a relatively short time. We therefore conclude that lung biopsies and other invasive procedures (performed in the first cases to rule out other potential causes, such as tuberculosis or malignant nodules) can be avoided or postponed.

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Introduction

Schistosomiasis, caused by trematode parasites of the genus *Schistosoma*, is an infectious disease that affects more than 230 million people worldwide.[1] Three main species of schistosome infect human beings: *Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum*. *S mansoni* is present in Africa, Latin America, and in the Middle East, whereas *S haematobium* exists in Africa and the Middle East and *S japonicum* in Asia. Three other locally distributed species also cause human disease: *Schistosoma mekongi*, which exists in the Mekong river basin, and *Schistosoma guineensis* and *Schistosoma intercalutum*, which are found in west and central Africa.[1] Infected people shed schistosoma eggs into the environment through faeces or urine. Upon contact with freshwater, free-living, ciliated miracidia emerge from the eggs and seek out a compatible snail host (*Biomphalaria* spp, *Bulinus* spp, or *Oncomelania* spp, depending on the *Schistosoma* species).[2] In the infected snails, the miracidia enter a sporocystic stage and transform into cercariae, which can penetrate the skin of a human host and transform into schistosomula. The schistosomula migrate within the vascular system and are transported to the right side of the heart and to the lungs, from where they continue to the intrahepatic vasculature. The schistosomula mature in the hepatic portal venous system before pairing of male and female worms takes place. The final migration site is usually the mesenteric (*S mansoni* and *S japonicum*) or perivesical (*S haematobium*) venules. The eggs of *S mansoni* and *S japonicum* are usually found in stool, the intestinal tract, and liver, whereas *S haematobium* eggs can be found in urine and in the urinary tract.[2] The lifespan of an adult schistosome is about 3–5 years, but they can live up to 40 years.[3,4]

Available evidence suggests that the eggs, not the adult worms, induce the morbidity caused by schistosome infection.[5] In fact, the immunopathology of schistosomiasis is considered to be due to granuloma formation around tissue-deposited eggs—a complex relation exists between the severity of clinical disease, the intensity of infection, and the infecting species.[5]

In endemic regions, the most prevalent form of the disease is chronic schistosomiasis, resulting from repeated exposure to infectious cercariae, whereas acute schistosomiasis occurs most often in travellers or immigrants to schistosome-endemic regions who are exposed to schistosome antigens for the first time at an older age.[1]

In this Grand Round, we report seven cases of patients of African origin, diagnosed in Italy with chronic schistosomiasis and pulmonary nodules due to deposition of schistosome eggs. We discuss the gaps in knowledge of the pathophysiology of schistosomiasis and suggest an approach to treatment of patients with pulmonary lesions in chronic schistosomiasis, with a particular focus on patients in non-endemic countries.

Case description

Between May 1, 2014, and Oct 31, 2015, we diagnosed seven migrants coming from sub-Saharan Africa with chronic schistosomiasis and pulmonary nodules. Six of these patients presented to the Centre for Tropical Diseases (CTD) in Negrar, Italy, and one patient presented to the Infectious Diseases Clinic of Udine, Italy. All patients were men coming from west Africa, and their age ranged from 18 to 28 years (mean 22·3 years). Two patients had no symptoms and presented to the CTD for a screening programme available for migrants, which includes chest radiographs. The other five patients presented with various signs and symptoms (table 1), and were treated accordingly. None of the patients had HIV or hepatitis C virus infections. Only one patient was found to have tuberculosis, and two patients had chronic hepatitis B virus infection. The median value of eosinophil count was 1020 cells per µL

	Age, years	Country of origin	Years since patient left a schistosome endemic area	Comorbidities and symptoms	Absolute eosinophils count, cells per mL	IgE, IU/mL	Schistosome eggs in urine or stool	Other tests for *Schistosoma* spp	Lung biopsy	Number of lung lesions at CT scans (maximum diameter of lung lesions, mm)
Patient 1	27	Mali	5	Pulmonary tuberculosis, hepatitis B virus hepatopathy, abdominal pain	750 (13·9%)	4950	*Schistosoma mansoni*	None	*S mansoni* eggs	2 (13)
Patient 2	25	Guinea	1	None	440 (9·6%)	1440	None	Negative PCR* and CCA ICT	*Schistosoma* spp eggs	2 (10)
Patient 3	28	Côte d'Ivoire	1	Abdominal pain, cough	790 (12·9%)	2930	*Schistosoma haematobium; S mansoni*	Positive CCA ICT	*Schistosoma* spp eggs	More than 10 (10)
Patient 4	19	Senegal	5	Strongyloidiasis, haematuria	2040 (31%)	497	*S haematobium*	Positive PCR*; negative CCA ICT	*Schistosoma* spp eggs	9 (20)
Patient 5	21	Mali	1	Haematuria, abdominal pain, chest pain	2290 (36·4%)	19 000	*S haematobium*	None	*Schistosoma* spp eggs	More than 10 (11)
Patient 6	18	Mali	1	Hepatitis B virus hepatopathy, asymptomatic	1960 (22%)	408	*S haematobium; S mansoni*	Positive PCR* and CCA ICT	Not done	3 (11)
Patient 7	18	Nigeria	1	Cough, chest pain, abdominal pain	400 (6·6%)	1040	*S haematobium*	Negative PCR* and CCA ICT	Not done	5 (15)

CCA ICT=circulating cathodic antigen immunochromatographic test. *PCR was done on stool.

***Table 1*: Demographics, clinical characteristics, eosinophil count, and IgE values of seven patients diagnosed with schistosomiasis and pulmonary nodules in Negrar and Udine, Italy**

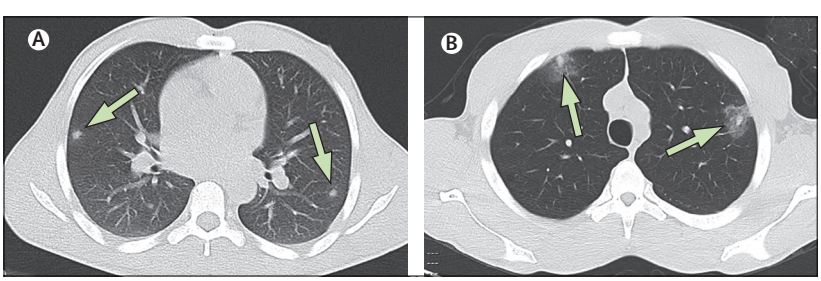

***Figure 1*: Lung nodules at CT scan**
Patient 3 (A) and patient 4 (B).

(range 400–2290 cells per µL), and the median IgE concentration was 2185 IU/mL (range 408–19 000 IU/mL). The index of suspicion for parasitic infection was high, so the patients underwent a parasitological examination of urine and stool as well as serological tests, which included an ELISA assay for *S mansoni* (*Schistosoma mansoni* ELISA, Bordier Affinity Products, Switzerland). The test results were positive in all patients, and all but one patient (patient 2) presented schistosome eggs at microscopic examination of urine, stool, or both (table 1). Patient 2, one of the two patients who were asymptomatic, also tested negative to schistosome real-time PCR on stool and to the circulating cathodic antigen immunochromatographic test. Chest radiographs showed pulmonary lesions (described as nodules, microcalcifications, or interstitial thickening) in all patients, necessitating a CT scan to improve the definition of the findings. All patients had multiple nodules (2–15 nodules per patient, 5–25 mm in diameter; figure 1). Biopsies of the pulmonary nodules were taken from the first five patients, and histological examination revealed the presence of schistosome eggs (figure 2). A presumptive diagnosis was made for patients 6 and 7. Patient 1 was also diagnosed with pulmonary tuberculosis: PCR on sputum was positive for *Mycobacterium tuberculosis*, and PCR on lung nodule biopsy was positive for *Mycobacterium* spp (this case has been described previously[6]). Moreover, this patient had an *S mansoni* infection, with eggs present in stool and in a lung nodule (figure 2), but also, presumably, a second species (one egg atypical in shape was found in a lung nodule; figure 2). Although processing of sections for histological analysis (vertical, horizontal, or tangential) can sometimes distort the shape of the eggs, the image could suggest a distorted *S haematobium* egg or even a hybrid (ie, between *S haematobium* and *Schistosoma bovis*), as observed in the Corsican outbreak.[7] All patients were treated with praziquantel (40 mg/kg per day in two doses) for 3 days. This dosing schedule is different from the one recommended by WHO,[8] but it is routinely used at CTD on the basis of concerns raised after a meta-analysis[9] of the cure rate with a single dose of praziquantel. 6 months after treatment, the CT scan showed resolution of all pulmonary lesions in the five patients who underwent the pulmonary biopsy. The other two patients who were treated empirically underwent a closer radiological follow-up: a CT scan done 3 months after treatment showed complete

resolution of the pulmonary lesions in patient 6 (figure 3), and in patient 7 the lesions had almost disappeared 50 days after treatment (figure 3).

Review and discussion

Schistosomiasis and the lung

Schistosomiasis can cause lung disease both in the acute and in the chronic phase.[1] Acute schistosomiasis, also called Katayama syndrome, is a systemic hypersensitivity reaction against the migrating schistosomula and eggs, occurring a few weeks to months after the primary infection.[10] The acute phase is usually asymptomatic, but clinical signs of varying intensity include fever, chills, weight loss, headache, anorexia, dry cough, nausea, vomiting, diarrhoea, hepatomegaly, and splenomegaly. Symptoms last from a few weeks to 3 months before gradually waning. Eosinophilia is often present and serves as a diagnostic clue.[11] Findings with chest radiograph include an interstitial pattern with micronodules, as well as pleural and pericardial effusion.[10] Pulmonary nodules with ground-glass attenuation areas are commonly found by CT scan.[12–17] Lambertucci[14] and Taliberti[18] reported CT scan results for two patients with acute schistosomiasis, which revealed micronodules and macronodules disseminated in the lungs. Katayama syndrome is usually diagnosed either by serology or, less frequently, by detecting schistosome eggs in urine or stool (depending on the species).[11] Moreover, Coron and colleagues[19] reported eggs of *S haematobium* in a pulmonary biopsy from a French traveller with Katayama syndrome. Schwartz[20] considered three different possible scenarios for acute pulmonary schistosomiasis: symptomatic cases with radiological findings (either by chest radiograph or CT scan) evident at presentation; symptomatic patients without radiological findings (probably with small lesions, not visible by chest radiograph); or asymptomatic cases with radiological findings, with an unknown incidence, because radiology is usually not performed in the absence of symptoms. The most common findings were small, nodular lesions with ill-defined borders; reticulo-nodular patterns were less common. Chest CT scan revealed more nodular lesions than radiograph.[20]

Clinical manifestations of chronic schistosomiasis vary with the characteristics of the established infection, such as egg burden and duration of infection. Manifestations also differ with *Schistosoma* species. *S haematobium* can cause a chronic genitourinary disease with a wide spectrum of clinical syndromes: haematuria, ureteral obstruction, nephrolithiasis, and squamous cell bladder carcinoma. Chronic intestinal schistosomiasis, defined as the presence of parasites in stool without portal hypertension, and chronic hepatosplenic schistosomiasis, defined as the presence of parasites in stool with portal hypertension and periportal fibrosis, are mainly caused by *S mansoni* and *S japonicum*.[21] The latter has also been associated with dwarfism and granulomatous disease of the large intestine (colonic tumoroid proliferation) in the advanced stage of the disease.[22] The involvement of the lungs in the chronic phase is usually described in relation to pulmonary hypertension. The pathophysiological mechanisms that might cause pulmonary hypertension are hepatosplenic disease, leading to portal hypertension

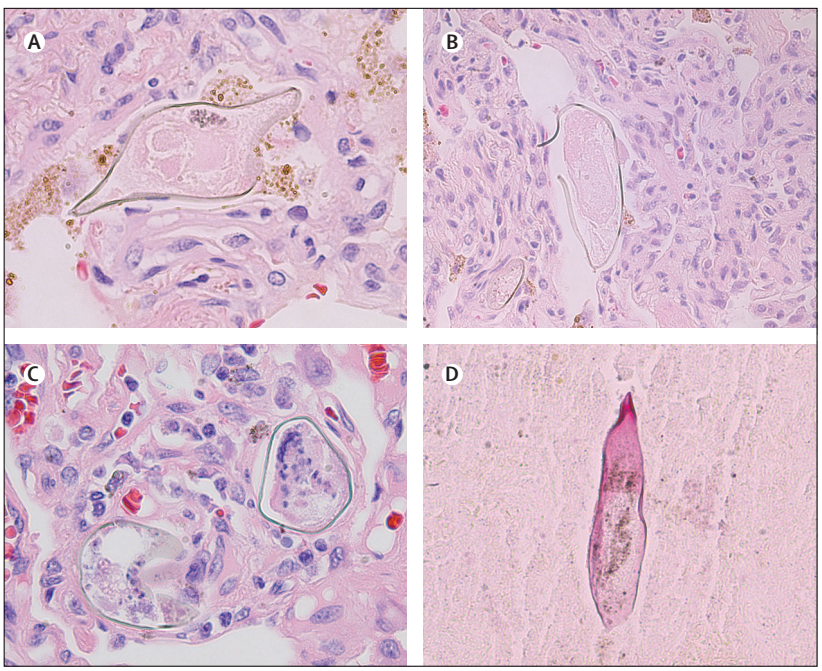

***Figure 2*: Lung specimens showing schistosome eggs**
Schistosoma spp eggs, haematoxylin and eosin stain, 300× magnification (A, C). *Schistosoma mansoni* egg, haematoxylin and eosin stain, 200× magnification (B). *Schistosoma* spp egg, Ziehl-Nielsen stain, 300× magnification (D).

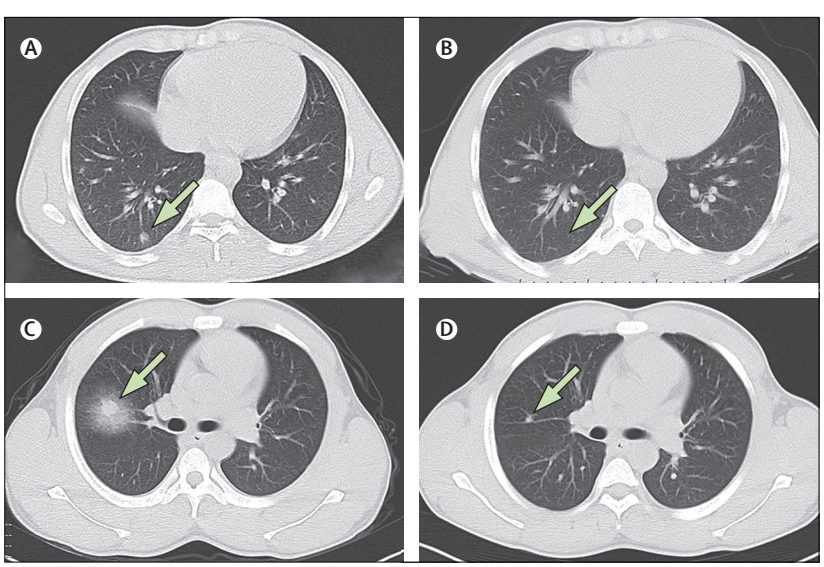

***Figure 3*: Pulmonary CT scan images**
CT scans of patient 6 were done at first presentation (A) and 3 months after treatment (B). CT scans of patient 7 were done at presentation (C) and 50 days after treatment (D).

	Category	Sex	Age, years	Country of acquisition of the infection	Years from exposure to diagnosis	Comorbidities and symptoms	Absolute eosinophils count, cells per mL
Mallah and Hashem[30]	Autochthonous	Male	47	Egypt	0	Chest pain, cough, haemoptysis	1020 (12%)
Abdel-Hakim and Elwi[31]	Autochthonous	Male	32	Egypt	0	Fever, cough, dyspnoea	NA
Tizes et al[32]	Migrant	Female	45	Puerto Rico	17	Chest pain, tuberculosis	NA
Besson et al[33]*	Migrant	Female	..	Cameroon	1	Thoracic pain, haemoptysis	Eosinophilia
Grunstein et al[34]	Autochthonous	Female	56	Martinique	0	Pulmonary chronic heart, weight loss	2200 (20%)
Al-Fawaz et al[35]*	Autochthonous	Female	13	Saudi Arabia	0	Fever, weight loss, abdominal pain, haematuria, hepatosplenomegaly	NA
Schaberg et al[36]	Migrant	Male	35	Angola	0	None	510 (12%)
Fatureto at al[37]	Autochthonous	Male	47	Brazil	25	None	NA
Lambertucci et al[38]	Autochthonous	Female	33	Brazil	33	Control after chemotherapy	NA
N'Dong et al[39]*	Autochthonous	Female	47	Gabon	0	Pneumonia, chest pain, haemoptysis	NA
Ryan et al[40]	Migrant	Male	51	Brazil	>20	Gastric adenocarcinoma, chest pain	693 (9%)
Cavalcanti Rodrigues et al[41]	Autochthonous	Male	50	Brazil	0	Chest pain, weight loss, dry cough	130 (2%)
De Gorgolas et al[42]	Tourist	Female	34	Mali	1	Chemotherapy for dysgerminoma	25†
Oliveira et al[43]	Autochthonous	Female	25	Brazil	0	Pulmonary mass, dysphagia, weight loss	NA
Tang et al[44]	Autochthonous	Male	93	China	>50	Congestive heart failure and pleural effusion in tuberculosis	NA
Chaudhry et al[45]	Tourist	Male	60	Egypt	26	No symptoms or comorbidities	NA

NA=data not available. *Data refers to the abstract of the paper, the full text was not available. †The percentage cannot be retrieved from the original report.

***Table 2*: Demographics, clinical characteristics, and eosinophil count of patients diagnosed with schistosomiasis and pulmonary lesions described in the scientific literature**

and eventually pulmonary hypertension; embolisation of the pulmonary arteries by parasite eggs, resulting in the formation of granulomas and pulmonary arterial obstruction, and inducing consequent fibrosis and tissue destruction; and an immune-mediated inflammatory cascade, resulting in substantial pulmonary vascular changes, including inflammation, medial thickening, and intimal remodelling.[21] Pulmonary hypertension might result from all these mechanisms, and each mechanism could be prominent in different stages of the infection. This hypothesis could also explain the distribution of the schistosome-induced pulmonary hypertension in two main age groups: young patients (with high burden of recent infection causing massive egg embolisation), and the elderly individuals (for whom the immune-mediated inflammatory cascade and the portal hypertension might have a major role).[21] The clinical presentation of chronic pulmonary schistosomiasis can be divided into three main categories: asymptomatic cases with eggs in the pulmonary beds, with or without granuloma formation; granuloma formation with pulmonary hypertension; and granuloma formation with pulmonary hypertension and cor pulmonale.[20,23] Patients who progress to cor pulmonale present signs and symptoms that are analogous to those presented by patients with pulmonary hypertension and cor pulmonale due to other causes. Whether all individuals with schistosome-induced pulmonary hypertension tend to develop cor pulmonale with time is unknown. Some characteristics of the infection (such as egg load and density of egg release) and the species of schistosome might affect the different patterns of clinical progression.[20]

Schistosomiasis-induced pulmonary hypertension is common in areas of high endemicity,[2] with prevalence estimated at 8–25%.[21] Gonçalves and colleagues,[24] in their series of 1863 consecutive autopsies in Belo Horizonte, Brazil, reported 313 (16·8%) cases of *S mansoni* infection, with eggs found in almost all organs. Eggs were also found in the lungs of 93 (29·7%) of 313 cases with schistosomiasis. Nodular areas were not mentioned.

Ectopic sites of schistosome eggs

Although pulmonary hypertension has been described as a common finding in chronic schistosomiasis, localised pulmonary masses or nodules are unusual, and are classified as ectopic sites. In general, ectopic sites are defined as adult worms, eggs, or both outside the urinary

	Serology	Schistosome eggs in urine or stool	Findings at chest radiograph	Findings in lung biopsy	Number of lesions at CT scan	Maximum diameter of lesions at CT scan (CT) or pneumectomy (P), mm
Mallah and Hashem[30]	NA	Not found	Single coin lesion	*Schistosoma* spp eggs	NA	60 (P)
Abdel-Hakim and Elwi[31]	NA	NA	Not homogeneous opacity	*Schistosoma* spp eggs	NA	60 (P)
Tizes et al[32]	NA	NA	Single coin lesion	*Schistosoma mansoni* eggs	NA	20 (P)
Besson et al[33]*	NA	*Schistosoma haematobium* eggs	Single coin lesion	*S mansoni* eggs	2	NA
Grunstein et al[34]	Positive	Not found	Several coin lesions	*S mansoni* eggs	NA	NA
Al-Fawaz et al[35]*	NA	*S haematobium* eggs	Parenchymal opacity and mediastinal mass	*Schistosoma* spp eggs	1	NA
Schaberg et al[36]	Positive	Not found	Cavitary infiltration	*S mansoni* eggs	1	NA
Fatureto at al[37]	NA	Not found	Single coin lesion	*S mansoni* adult worm	1	5 (CT)
Lambertucci et al[38]	NA	NA	Single coin lesion	*S mansoni* eggs	1	10 (CT)
N'Dong et al[39]*	NA	NA	Opacity	*Schistosoma* spp eggs	1	NA
Ryan et al[40]	Positive	NA	Single coin lesion	*S mansoni* eggs degenerated adult worm	Less than 5	4 (CT)
Cavalcanti Rodrigues et al[41]	NA	Not found	Irregular mass	*S mansoni* eggs	1	50 (CT)
De Gorgolas et al[42]	Positive	Not found	Multiple nodular lesions	*Schistosoma* spp eggs and adult worm	More than 5	4 (CT)
Oliveira et al[43]	NA	NA	Large mass	*S mansoni* eggs	1	80 (CT)
Tang et al[44]	NA	NA	Irregular mass	*Schistosoma japonicum* eggs	1	70 (CT)
Chaudhry et al[45]	Negative	NA	Opacity	*Schistosoma* spp adult worm	1	20 (CT)

NA=data not available. *Data refers to the abstract of the paper, the full text was not available.

***Table 3*: Laboratory and radiology findings of patients diagnosed with schistosomiasis and pulmonary lesions described in the scientific literature**

tract and the portal–mesenteric system.[24] Some investigators have postulated that ectopic locations appear when the parasite burden is high because the subsequent portal hypertension might permit the embolisation of schistosome eggs through the collateral portal–systemic circulation. However, this hypothesis could better explain a homogeneous spread of eggs to many organs rather than the formation of masses localised to one anatomical site. Other hypotheses seem more plausible in relation to the latter condition: the adult worms might deposit the eggs in the ectopic site, reaching end venules either through collateral vessels or through the vertebral venous system, which provides a natural, valveless intercommunicating channel from portal and caval veins to all parts of the body.[25]

Adult worms have been discovered ectopically in the circumphlex branch of the left coronary artery,[26] in a branch of the superior ophthalmic vein,[27] in cervical polyps,[28] and in many other organs including the lung.[29] By contrast, *S japonicum* eggs (and, rarely, adults) have occasionally been found in ectopic sites almost all over the body.[22]

In the scientific literature, we found 16 cases of patients with an in-vivo diagnosis of pulmonary lesions due to chronic schistosomiasis. In four of these patients, adult worms were found by histological examination of biopsy specimens (tables 2 and 3).[30–45] Chest radiographs showed coin lesions, irregular masses, and even cavitations. CT scan findings were available for 12 patients.

Our case series and the 16 cases reported in the scientific literature show that radiological presentation of ectopic lung lesions is more similar to the one case of Katayama syndrome than to the classical radiological presentation of chronic pulmonary schistosomiasis. This finding contrasts with the traditional view of acute and chronic schistosomiasis causing distinct lung pathology, with different clinical pictures and different pathogenic mechanisms.[20] Moreover, similarly to known cases of acute pulmonary schistosomiasis, ectopic lesions disappeared after treatment with praziquantel in all our cases, whereas the lesions commonly described in chronic pulmonary schistosomiasis are only partly reversible.[20]

Gaps in knowledge about the mechanisms that lead to the development of lung nodules or masses in chronic schistosomiasis still exist, and the proposed theories open unexpected scenarios, such as the possibility that migration of adult schistosomes throughout the organism might not be uncommon, leading them to organs that are outside their traditional pathways.

Misdiagnosis might occur frequently, given that schistosomiasis in non-endemic settings is a diagnostic conundrum and the clinical and radiological presentation

is not characterised by typical features. Moreover, some patients are asymptomatic and would never be diagnosed if they did not undergo radiological imaging for other purposes.

Our experience provides a clear example of how difficult it is to include unusual pathogens in the differential diagnosis of clinical or radiological presentations that are already included in predefined diagnostic pathways. The first four patients that presented to the CTD and the patient diagnosed in Udine underwent a pulmonary biopsy because, at the time, we doubted that pulmonary nodules could be caused by schistosomes and suspected more common causes (in fact, patient 1 also had pulmonary tuberculosis). In light of previous experience and after a thorough review of the scientific literature, we opted for a non-invasive approach to the patients. In this sense, other non-invasive procedures that could help to attribute lung nodules to schistosome infection might be implemented. For instance, although we did not find any schistosome eggs in the sputum of the three patients who underwent sputum analysis, it would be interesting to test the possibility of retrieving eggs in patients with lung nodules caused by schistosomes. Moreover, the use of molecular biology for the diagnosis of schistosomiasis in the sputum could be worth exploring further. To our knowledge, no PCR methods have been validated for the detection of schistosome infection in this biological material.

CTD is the regional reference centre for tropical diseases, and in the 18 months we observed the six cases reported here, we diagnosed a total of 120 cases of schistosomiasis (hence the pulmonary nodular cases accounted for 5% of all schistosomiasis cases seen in our centre during the study period). However, we did not consider schistosoma to be a possible cause of pulmonary nodules until we had the histological evidence from the first four patients. Moreover, we found additional possible cases retrospectively. In fact, we reviewed the medical records of patients discharged from CTD during the study period to estimate the ratio of pulmonary nodules due to schistosoma to the number of pulmonary nodules due to tuberculosis. We found eight patients with a clinical and radiological suspicion of pulmonary tuberculosis. Four cases with microbiologically confirmed tuberculosis did not show a nodular pattern by chest radiograph. Four patients had a nodular (single or multiple nodules) presentation: one patient had a non-tuberculous mycobacterial infection, detected by granulomatous inflammation and PCR of a histological sample, whereas the other three cases were presumptively attributed to tuberculosis, without microbiological confirmation—surprisingly, these three patients also had schistosome infection; hence, these patients received both praziquantel treatment as well as treatment for tuberculosis, but we now suspect that the latter therapy could have been avoided, or at least postponed.

Conclusion

Our findings have relevant implications for the management of patients with pulmonary lesions coming from endemic areas for schistosomiasis. A screening for schistosome infection should be recommended and, in cases of positive serology, circulating cathodic antigen detection in urine, or both, or the presence of schistosome eggs in urine, stool, or both, treatment with praziquantel and radiological follow-up should be done. Biopsy and other invasive procedures can be avoided if the index of suspicion for other severe disorders (eg, tuberculosis or malignancies) is low. The clinician could wait for the results of the follow-up and, if the lesions have disappeared, take no further action.

Contributors

FG, DB, and ZB conceived the work. FG and DB searched the literature and wrote the draft of this manuscript. AA, AB, LB, SD, VM, SM, MM, GM, and AT collected data. FG, DB, AA, AB, MB, GB, SC, MG, and ZB interpreted the data. All authors revised the manuscript and approved the final version of the manuscript.

Declaration of interest

We declare no competing interests.

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