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References

1. Miller M, Michel A, van Helden P, Buss P. Tuberculosis in rhinoceros: an underrecognized threat? Transbound Emerg Dis. 2017;64:1071–8. http://dx.doi.org/10.1111/tbed.12489
2. Stetter MD, Mikota SK, Gutter AF, Monterroso ER, Dalovisio JR, Degraw C, et al. Epizootic of *Mycobacterium bovis* in a zoologic park. J Am Vet Med Assoc. 1995;207:1618–21.
3. Espie IW, Hlokwe TM, Gey van Pittius NC, Lane E, Tordiffe ASW, Michel AL, et al. Pulmonary infection due to *Mycobacterium bovis* in a black rhinoceros (*Diceros bicornis minor*) in South Africa. J Wildl Dis. 2009;45:1187–93. http://dx.doi.org/10.7589/0090-3558-45.4.1187
4. Hlokwe TM, van Helden P, Michel AL. Evidence of increasing intra and inter-species transmission of *Mycobacterium bovis* in South Africa: are we losing the battle? Prev Vet Med. 2014;115:10–7. http://dx.doi.org/10.1016/j.prevetmed.2014.03.011
5. Department of Environmental Affairs, Republic of South Africa. Minister Molewa highlights process on integrated strategic management of rhinoceros. 2017 Feb 27 [cited 2018 Aug 14]. https://www.environment.gov.za/mediarelease/molewa_progressonintegrated_strategicmanagement_ofrhinoceros
6. Miller M, Buss P, van Helden P, Parsons S. *Mycobacterium bovis* in a free-ranging black rhinoceros, Kruger National Park, South Africa, 2016. Emerg Infect Dis. 2017;23:557–8. http://dx.doi.org/10.3201/eid2303.161622
7. Goosen WJ, Miller MA, Chegou NN, Cooper D, Warren RM, van Helden PD, et al. Agreement between assays of cell-mediated immunity utilizing *Mycobacterium bovis*–specific antigens for the diagnosis of tuberculosis in African buffaloes (*Syncerus caffer*). Vet Immunol Immunopathol. 2014;160:133–8. http://dx.doi.org/10.1016/j.vetimm.2014.03.015
8. Dippenaar A, Parsons SDC, Miller MA, Hlokwe T, Gey van Pittius NC, Adroub SA, et al. Progenitor strain introduction of *Mycobacterium bovis* at the wildlife-livestock interface can lead to clonal expansion of the disease in a single ecosystem. Infect Genet Evol. 2017;51:235–8. http://dx.doi.org/10.1016/j.meegid.2017.04.012
9. Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. Int J Tuberc Lung Dis. 2004;8:286–98.
10. Michel AL, Lane EP, de Klerk-Lorist L-M, Hofmeyr M, van der Heijden EMDL, Botha L, et al. Experimental *Mycobacterium bovis* infection in three white rhinoceroses (*Ceratotherium simum*): susceptibility, clinical and anatomical pathology. PLoS One. 2017;12:e0179943. http://dx.doi.org/10.1371/journal.pone.0179943

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Lung Involvement in Chronic Schistosomiasis with Bladder Squamous Cell Carcinoma

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We report a case of chronic *Schistosoma haematobium* infection with pseudometastatic pulmonary nodules and high-grade squamous cell carcinoma in a 30-year-old man in Mali. Lung biopsies revealed chronic pulmonary involvement of *S. haematobium* and ruled out lung metastases.

A 30-year-old man from Mali, who had immigrated to France a year before, was hospitalized for acute urinary retention. The patient reported isolated hematuria over the preceding month with recent dysuria. He was afebrile and had normal vital signs. Physical examination revealed pelvis tenderness and guarding. The only biologic abnormality was a hypereosinophilia (1,640 cells/mm^3). Unenhanced computed tomography (CT) revealed linear calcifications on the bladder wall, with a large intraluminal mass infiltrating the left ureter (Figure, panel A). Cystoscopy was typical of schistosomiasis. Anatomopathology revealed urinary schistosomiasis complicated by a high-grade, well-differentiated, keratinized squamous cell carcinoma (SCC) (Figure, panel B). Within the wall, ovoid structures, sometimes calcified,

Figure. Schistosomiasis-induced squamous cell carcinoma of the bladder with pseudometastatic pulmonary nodules in a 30-year-old man from Mali. A) An unenhanced computed tomography axial image shows diffuse calcification of the bladder wall (arrow). A soft-tissue mass arises from the left posterolateral wall, breaching the calcifications and reaching the perivesical fat (asterisk). B) Anatomopathology slide stained with hematoxylin and eosin (original magnification ×10) of the bladder wall showing massive infiltration by a carcinomatous proliferation of the epidermoid type arranged in islands, or in broad cords in depth (arrows). The cells are large and polygonal, with eosinophilic cytoplasm. The papillomatous malpighian epithelium infiltrates the entire thickness of the chorion and the muscularis into the perivesical fat with venous vascular emboli (asterisk). Within the wall are observed bilharzia eggs, sometimes calcified (small arrow). The chorion is, on the other hand, the seat of a moderate mononuclear inflammatory infiltrate. C) Eggs of *Schistosoma haematobium* in a wet mount of urine concentrate, showing their characteristic terminal spine (original magnification ×400). D, E) Axial (D) and sagittal (E) reconstruction chest computed tomography of the lungs showing blurred ground glass nodules scattered over both lungs. F) A lung subpleural nodule of 0.2 cm greater axis shows at low magnification (original magnification ×4) a fibrous nodule surrounded by lymphoid follicles. G) Hematoxylin and eosin staining of the lung nodule (original magnification ×20) shows inflammatory population, mainly represented by eosinophils and a structure corresponding to a bilharzia egg. No territory suspected of malignancy was visualized.
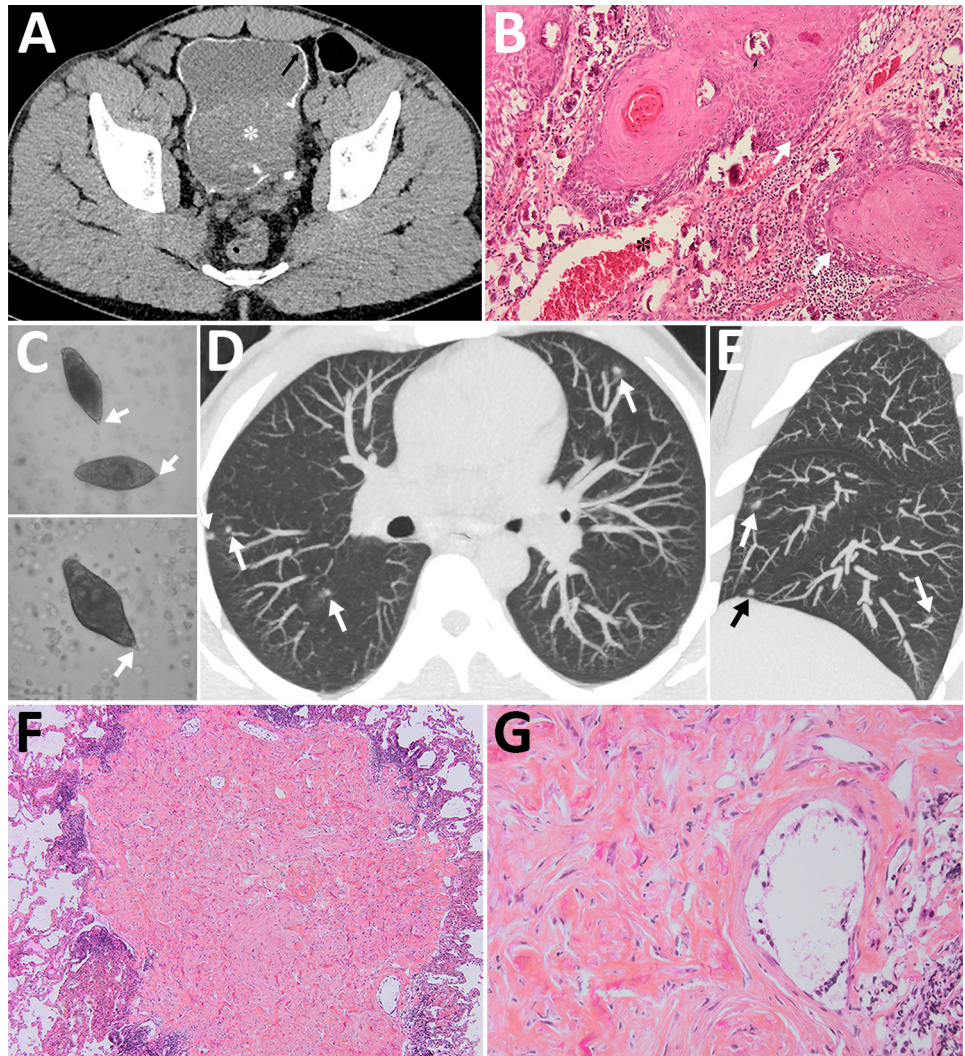
corresponded to bilharzia eggs. We found calcified eggs with a terminal spine resembling *Schistosoma haematobium* in the urine (Figure, panel C). Stool examinations were negative. Schistosomiasis serologic tests were positive in hemagglutination and ELISA and were confirmed by immunoblotting. Chest CT revealed multiple, bilateral, diffuse, infracentimetric, pulmonary, ill-defined nodules (Figure, panels D, E), suggesting metastases. Because secondary lesions contraindicate cystectomy and require aggressive chemotherapy, we performed further investigations.

The patient was HIV-negative. We excluded tuberculosis on the basis of direct examination and culture of sputum and bronchoalveolar lavage fluid. The latter showed 160,000 cells/mL with hypereosinophilia (11%) and alveolar hemorrhage. Ziehl and Grocott stainings were negative. Bacteriologic tests were negative. We detected no tumor cell. We resected a nodule during video-assisted thoracoscopy. Anatomopathology revealed Bilharzia eggs with no carcinomatous lesions (Figure, panels F, G). Another nodule showed similar lesions. The eggshells appeared to be Ziehl-Neelson–negative, typical of *S. haematobium*. Echocardiography ruled out pulmonary hypertension.

We confirmed *S. haematobium* by using molecular analysis of mitochondrial cytochrome oxidase subunit I gene. We excluded *S. haematobium–bovis* hybrid species, frequent in Mali, by using internal transcribed spacer region 1 and 2 sequences (*1*).

The patient received 2 courses of praziquantel (40 mg/kg) at 8-week intervals. The tumor was considered free of node involvement and metastases. The patient underwent radical cystectomy with an orthotopic neobladder. Anatomopathology confirmed complete resection of the tumor reaching the muscle layer and the perivesical fat. At 3 months, blood eosinophils were normalized, and chest CT showed complete resolution of all pulmonary nodules. At 6-month follow-up, the patient was still in complete remission.

Schistosomiasis, the second most prevalent endemic parasitic disease, affects ≈230 million persons (2). This helminthic infection is caused by a trematode and is also known as snail fever or Bilharzia. The larvae burrow into human skin after contact with contaminated water and migrate within the vascular system to the lung. Through the portal system, mature forms reach venous plexuses surrounding the bladder, and released eggs enter perivesical venules. Adult lifespan averages 3–5 years and can persist up to 40 years.

Acute schistosomiasis occurs 3–6 weeks after infection. Eosinophilia serves as a diagnostic clue. Acute lung lesions are common (3). *S. haematobium,* found in Africa and the Middle East, induces urinary schistosomiasis with frequent hematuria. The infection causes fibrosis of the bladder, wall calcification, and hydronephrosis. A major complication is the development of SCC. Schistosomiasis-induced SCC is overrepresented in endemic regions, accounting for only 2.5% of bladder cancer in Western countries (4,5); it appears as a unique and voluminous mass with low incidence of lymph node involvement and distant metastases at 8%–10% (4,5). However, the prognosis remains poor, with 90% locoregional recurrence within 3 years. The effective treatment requires radical cystectomy.

Manifestations of chronic disease also involve the lung, and schistosomiasis is the leading cause of pulmonary hypertension, which occurs in 8%–25% of cases (6,7). A less reported aspect of chronic lung involvement is nodular lesions, which are described in 5% of schistosomiasis cases and are often asymptomatic when isolated (8). Belleli was the first to describe *S. haematobium* eggs in the lungs in 1885, stipulating that eggs laying into perivesical plexuses migrate from portal and caval veins to the lungs. Embolized eggs can produce a granulomatous reaction leading to pulmonary fibrosis and obliterative arteriolitis, causing pulmonary hypertension. However, the exact pathophysiology remains unclear and involves different mechanisms. Pulmonary symptoms are more often described with *S. mansoni* and *S. japonicum* than *S. haematobium*, which preferentially transits through the genitourinary rather than the hepatic portal system (9). Radiographic features resemble coins or cavitations, whereas CT shows a ground glass-opacity halo or reticulonodular pattern (8). Nodules, considered to be ectopic sites, remain unspecific and indistinguishable from secondary lesions (6). The diagnosis of chronic lung involvement is oriented by symptoms of associated end-organ. Treatment with praziquantel is efficient on ectopic lesions.

This case is interesting because of the double presentation of schistosomiasis-induced SCC and chronic lung involvement. Although metastases are less frequent than chronic pulmonary nodules, lung metastases were highly expected in the context of invasive SCC. Each diagnosis involves a different therapeutic approach, and delayed diagnosis can affect the patient's prognosis. Lung biopsies might be necessary when severe disorders are suspected and avoided when suspicion for other causes, such as tuberculosis and malignancy, is low (8). In the latter scenario, PCR on bronchoalveolar lavage fluid might be an alternative in the diagnosis of chronic pulmonary schistosomiasis (10).

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Dr. Saade started her work in medicine after she obtained her PhD in molecular biology and is currently a resident in infectious disease and hematology. Her primary research interests include the study of infections in immunosuppressed patients.

References

1. Soentjens P, Cnops L, Huyse T, Yansouni C, De Vos D, Bottieau E, et al. Diagnosis and clinical management of *Schistosoma haematobium–Schistosoma bovis* hybrid infection in a cluster of travelers returning from Mali. Clin Infect Dis. 2016;63:1626–9. http://dx.doi.org/10.1093/cid/ciw493
2. Colley DG, Bustinduy AL, Secor WE, King CH. Human schistosomiasis. Lancet. 2014;383:2253–64. http://dx.doi.org/10.1016/S0140-6736(13)61949-2
3. Ross AG, Vickers D, Olds GR, Shah SM, McManus DP. Katayama syndrome. Lancet Infect Dis. 2007;7:218–24. http://dx.doi.org/10.1016/S1473-3099(07)70053-1
4. Shokeir AA. Squamous cell carcinoma of the bladder: pathology, diagnosis and treatment. BJU Int. 2004;93:216–20. http://dx.doi.org/10.1111/j.1464-410X.2004.04588.x
5. Martin JW, Carballido EM, Ahmed A, Farhan B, Dutta R, Smith C, et al. Squamous cell carcinoma of the urinary bladder: systematic review of clinical characteristics and therapeutic approaches. Arab J Urol. 2016;14:183–91. http://dx.doi.org/10.1016/j.aju.2016.07.001
6. Niemann T, Marti HP, Duhnsen SH, Bongartz G. Pulmonary schistosomiasis—imaging features. J Radiol Case Rep. 2010;4:37–43.

7. Papamatheakis DG, Mocumbi AOH, Kim NH, Mandel J. Schistosomiasis-associated pulmonary hypertension. Pulm Circ. 2014;4:596–611. http://dx.doi.org/10.1086/678507

8. Gobbi F, Buonfrate D, Angheben A, Beltrame A, Bassetti M, Bertolaccini L, et al. Pulmonary nodules in African migrants caused by chronic schistosomiasis. Lancet Infect Dis. 2017;17:e159–65. http://dx.doi.org/10.1016/S1473-3099(16)30530-8

9. Bethlem EP, Schettino GP, Carvalho CR. Pulmonary schistosomiasis. Curr Opin Pulm Med. 1997;3:361–5. http://dx.doi.org/10.1097/00063198-199709000-00008

10. Gobbi F, Formenti F, Perandin F, Buonfrate D, Angheben A, Paiano S, et al. Real-time polymerase chain reaction assay on bronchoalveolar lavage: an alternative method for diagnosing chronic pulmonary schistosomiasis? Am J Trop Med Hyg. 2017;97:1808–9. http://dx.doi.org/10.4269/ajtmh.17-0499

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Strongyloidiasis and Culture-Negative Suppurative Meningitis, Japan, 1993–2015

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Community-acquired *Enterobacteriaceae* infection and culture-negative meningitis are rare and atypical subtypes of meningitis in adults. Of 37 patients who had atypical suppurative meningitis during 1993–2015 in Okinawa, Japan, 54.5% had strongyloidiasis, of which 9.1% cases were hyperinfections and 3.0% dissemination. Strongyloidiasis should be considered an underlying cause of atypical suppurative meningitis.

Among adults, suppurative meningitis caused by enteric organisms and suppurative meningitis that is culture negative are uncommon (*1*,*2*). These types of meningitis with atypical features (hereafter atypical suppurative meningitis) remain a clinical challenge. The mortality rate among patients with community-acquired suppurative meningitis caused by gram-negative organisms is 52.5% (*1*). Treatment of culture-negative suppurative meningitis requires broad-spectrum antimicrobial drugs; however, the absence of detected pathogens increases the risk for development of antimicrobial drug resistance.

Strongyloidiasis, a nematode infection that occurs in the subtropics and tropics, is associated with *Enterobacteriaceae* meningitis (*3*). Previous reports of strongyloidiasis-associated meningitis also suggested potential links between strongyloidiasis and atypical suppurative meningitis on the basis of 9 cases of *Enterobacteriaceae* meningitis (not consecutive) (*4*) and 17 cases of culture-negative suppurative meningitis (*5*). Our aim was to investigate the association between strongyloidiasis and atypical suppurative meningitis.

We conducted a retrospective chart review of patients who consecutively received a diagnosis of atypical suppurative meningitis during January 1993–December 2015 at Okinawa Chubu Hospital, Okinawa, Japan. This hospital is one of the largest tertiary medical centers in Okinawa. Strongyloidiasis is endemic in Okinawa; reported prevalence is 5.2% (*6*).

We defined atypical suppurative meningitis as suppurative meningitis with positive cerebrospinal fluid (CSF) culture results for enteric organisms or with CSF leukocytosis $\geq$500 cells/mm^3 and negative CSF culture results. We included in the study patients $\geq$18 years of age with CSF that was culture positive for enteric organisms or negative with leukocytosis of $\geq$500 cells/mm^3. Enteric organisms included in this study were *Bacteroides* spp., *Enterococcus* spp., *Escherichia coli*, *Enterobacter* spp., *Klebsiella* spp., *Bifidobacterium bifidum*, *Clostridium perfringens*, *Proteus mirabilis*, *Streptococcus gallolyticus* (*bovis*), and *Campylobacter* spp. (*7*). CSF of patients with bacterial meningitis typically shows leukocytosis of $\geq$1,000 cells/mm^3; CSF of those with nonbacterial meningitis typically shows <250 cells/mm^3 (*8*). Considering the early phase of bacterial meningitis (*9*), the cutoff value (500 cells/mm^3) was defined to include suppurative meningitis and exclude most cases of nonbacterial meningitis. We excluded patients with nosocomial meningitis, prior use of antimicrobial drugs (within 7 days of lumbar puncture), negative CSF culture, and positive blood culture for nonenteric organisms.

We collected information about patient demographic and clinical characteristics, immunocompromised status, type of strongyloidiasis infection, outcomes, CSF analysis results, and culture results. Strongyloidiasis was classified into 3 categories: nonsystemic strongyloidiasis, hyperinfection, and dissemination. We defined these categories according to where larvae were detected: nonsystemic strongyloidiasis in fecal samples only, hyperinfection in sputum, and dissemination in samples other than feces or sputum (*4*). Samples were collected with regard to patients' clinical category. Identifying information was removed before