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BRIEF REPORT

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Urogenital Schistosomiasis Mimicking IgG4-RD in a Patient With HIV

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This article reports a case of urogenital schistosomiasis mimicking IgG4-related disease (IgG4-RD) in a 47-year-old immunocompromised man with HIV. Initially diagnosed with IgG4-RD, further biopsies revealed schistosoma eggs. Elevated IgG4 levels indicated a Th2 immune response, highlighting its complex role in antischistosomal immunity and the need for careful differential diagnosis.

Keywords. HIV; IgG4RD; *Schistosoma haematobium*; Th2 response; urogenital schistosomiasis.

IgG4-related disease (IgG4-RD) is a benign fibroinflammatory disorder of unknown cause. It was initially described in the early 2000s in patients with sclerosing pancreatitis and IgG4 hypergammaglobulinemia [1]. IgG4-RD is characterized by the presence of inflammatory pseudo-tumoral lesions, mostly found in the pancreato-biliary tract, the retroperitoneum, or the head and neck regions, but it may affect all organs [2]. Pathological examination usually reveals a reactive lymphoplasmacytic infiltrate enriched in IgG4 plasma cells, with abundant regulatory and follicular helper T cells, as well as storiform fibrosis and obliterative phlebitis and occasionally increased numbers of eosinophils [3, 4]. An elevated IgG4 serum level is often observed but lacks specificity in the diagnosis of IgG4-RD [5, 6]. IgG4-RD is an exclusion diagnosis and relies on clinical, biological, histopathological, and radiological criteria, so that it is mandatory to exclude numerous differential diagnoses according to the American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) 2019 classification criteria [7]. Many conditions associated with IgG4+ plasma cell infiltration can mimic IgG4-RD, such as plasma cell or mixed-type idiopathic multicentric Castleman disease, rheumatoid arthritis, lymphoid neoplasia, and infectious diseases.

Schistosomiasis is a parasitic infection contracted through skin contact with contaminated water in endemic areas. Different species exist, and *Schistosoma haematobium* is the main causing agent of urogenital schistosomiasis, highly prevalent in Africa.

We report here a case of urogenital schistosomiasis presenting as IgG4-RD in an immunocompromised host with HIV.

CASE REPORT

The patient is a 47-year-old man from Mauritania, living in France since the age of 21. His last journey to Africa was to Mali in February 2019. He has a history of HIV-1 infection, diagnosed in 2004. At that time, antiretroviral therapy was started, but the patient quickly abandoned regular medical follow-up. Complications developed including *Pneumocystis jirovecii* pneumonia in 2010 and a lower urinary tract infection with *Salmonella* paratyphi B in 2017. Antiretroviral therapy (emtricitabine, tenofovir, bictegravir) was re-introduced in July 2019. He was admitted in December 2019 due to weight loss and lower abdominal pain. There was no fever, night sweats, diarrhea, or hematuria. An abdominal computed tomography (CT) scan revealed a voluminous contrast-enhanced prostatic lesion with necrotic appearance and contiguous bladder extension, as well as left latero-aortic enlarged lymph nodes (Figure 1*A*, panels *A* and *B*). The vesico-prostatic lesion was responsible for hydronephrosis requiring emergency urinary bypass with nephrostomy. Biological findings are summarized in Supplementary Table 1 and showed acute renal failure, elevated C-reactive protein, and polyclonal hypergammaglobulinemia (totaI IgG level = 44 g/L including increased IgG4 level to 8.86 g/L). The total IgE level was measured at 1000 IU/mL. Bacterial, fungal, and mycobacterial prolonged urine cultures were negative. Microscopic examination did not reveal any schistosome eggs in the nephrostomy and bladder urine samples. A commercial indirect hemagglutination (IHA; Fumouze Laboratories) test using erythrocytes coated with *Schistosoma mansoni* adult worm antigens (WAs) and an enzyme-linked immunosorbent assay (ELISA) with *S. mansoni*

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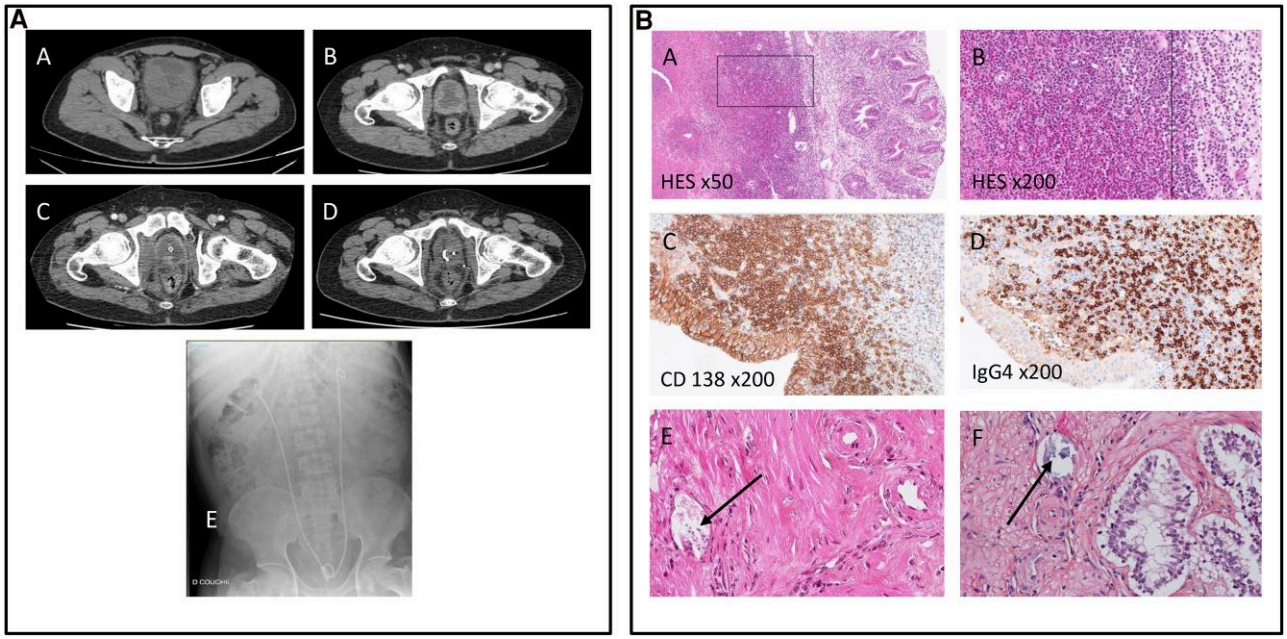

Figure 1. *A* (panels *A*–*D*), Sequential pictures of contrast-enhanced CT scans. Panels *A* and *B*, CT scan at admission showing an important bladder thickening with a vesico-prostatic mass. *C*, CT scan after corticosteroid therapy: partial regression of prostate lesion but persistence of bladder infiltration. *D*, CT scan 2 months after anti-parasitic treatment showing decreased prostate lesion and reduced peri-vesical infiltration. Panel *E*, Plain abdominal x-ray with absent "porcelain bladder" aspect. *B*, Pathological aspects of prostatic biopsies. First biopsy (*A*–*D*). *A* and *B*, Hematoxylin and eosin–stained sections showing an inflammatory infiltrate rich in eosinophils, plasma cells, and neutrophils. *C* and *D*, Immunohistochemical CD138 staining and IgG4 stainings showing increased IgG4+ plasma cells meeting histological criteria for IgG4-RD. Second biopsy (*E* and *F*). Hematoxylin and eosin–stained sections revealing viable schistosome eggs (black arrows). Abbreviations: CT, computed tomography; IgG4-RD, IgG4-related disease.

egg antigens were both negative. CD4+ T-cell count was 304/μL (11%), and HIV viral load was weakly positive (22 copies/mL).

Cystoscopy showed a large vesico-prostatic mass. Transurethral bladder biopsy performed during cystoscopy (Figure 1*B*, panels *A*–*D*) revealed extensive and focally suppurated necrotic remodeling of the bladder mucosa, with a few lesions of vasculitis and no granuloma. A dense mature plasma cell infiltrate, associated with numerous eosinophils, was also noted in the fragments of viable bladder mucosa. No calcified eggs suggestive of schistosomiasis were seen. Plasma cells were polytypic on immunohistochemistry, of predominant IgG isotype, containing a significantly increased number of IgG4+ elements (IgG4/IgG ratio >40%). Epstein-Barr early ribonucleic acid in situ hybridization was negative, as was human herpesvirus-8/Kaposi's sarcoma associated herpesvirus latent nuclear antigen (LNA) staining. There was no pathological evidence for lymphoma or urothelial carcinoma, and the observed intense necrotic changes with deep focal suppuration were more related to an inflammatory process. Periodic acid Schiff (PAS), Ziehl-Neelsen, Grocott stainings were negative. A biopsy of a left external iliac lymph node showed preserved lymph node architecture, with expanded interfollicular zones containing small lymphoid elements and numerous polytypic IgG4+ plasma cells (IgG4/IgG ratio >40%). An undocumented urinary tract infection was suspected, and 3-week ciprofloxacin empirical antibiotic therapy was started, with no improvement. Serum IgG4 levels remained above normal ranges (5.5 g/L). Based on clinical, biological, and pathological data, with no evidence for a malignant or patent infectious process, the patient met diagnosis criteria for IgG4-RD, and oral corticosteroids were initiated (1 mg/kg weight, eg, 60 mg/d), with progressive dose decrease. An evaluation performed 3 months later showed mild improvement of clinical symptoms and decreased CRP (60 mg/L) and IgG4 levels (3.3 g/L). CT pictures showed partial regression of the prostatic lesion but persistence of circumferential bladder thickening and increased perirectal infiltration (Figure 1*A*, panel *C*). A novel bladder biopsy was performed, revealing schistosome eggs in the bladder wall, some of which were viable (Figure 1*B*, panels *E* and *F*). Corticosteroids were stopped, and the final diagnosis of urogenital schistosomiasis was retained. The patient received praziquantel 40 mg as a single dose repeated 14 days later, enabling progressive improvement of all symptoms, with a maximal response observed after 6 weeks of praziquantel treatment (Figure 1*A*, panel *E*; Supplementary Table 1). Praziquantel is highly effective against adult worms, which might explain the delayed efficacy noted in this case, where only eggs were detected at the time of *Schistosoma* diagnosis.

No aspect of porcelain bladder was seen on plain radiography (Figure 1*A*, panel *F*).

DISCUSSION

Here we report a case of urogenital schistosomiasis mimicking IgG4-RD. This observation underlines the fact that IgG4-RD should remain a diagnosis of exclusion, especially in immunocompromised contexts such as those with HIV infection. First, the cooccurrence of HIV and IgG4-RD appears to be rare, with only a few reported cases [8]. Reported patients had variable immuno-virological status, and IgG4-RD diagnosis was made before or after HIV diagnosis. All patients had polyclonal IgG hypergammaglobulinemia. The role of HIV in the development or expression of IgG4-RD was not discussed, but HIV-related hypergammaglobulinemia is usually found to be restricted to IgG1 subclass and not IgG4 [9]. Second, the patient had isolated vesico-prostatic involvement, a pattern rarely seen in IgG4-RD. IgG4-RD is well known for its renal tropism with tubulo-interstitial involvement. Only 10 cases reporting bladder localization of IgG4-RD have been published to date, half of which have isolated vesico-prostatic involvement [10]. This aspect was considered in the recent ACR/EULAR 2019 classification, in which such unusual mono-organ infiltration was defined as a Step 1 exclusion criterion [7]. Third, absence of corticosteroid response is another unusual feature in IgG4-RD. Corticosteroids remain the gold standard treatment for IgG4-RD, with high overall response rates. Nearly all patients described in the case reports reporting bladder involvement were treated with corticosteroids and achieved complete remission. In our case, the patient had partial response to corticosteroids, which led us to further question the diagnosis. Finally, the marked inflammatory syndrome with weight loss in our patient is not a classic feature of IgG4-RD.

From a pathological point of view, bladder and lymph node biopsies met IgG4-RD criteria with a dense IgG4+ lymphoplasmacytic infiltrate and elevated IgG4/IgG ratio associated with venular lesions, but absence of storiform fibrosis and presence of neutrophilic inflammation and necrosis also suggested an alternative diagnosis such as an infectious process. All noninvasive samples were repeatedly negative and failed to identify any pathogen. Due to clinical presentation in a patient frequently traveling to Africa, urogenital schistosomiasis was early and strongly suspected, but no ova were seen on urine microscopic examination or on the first bladder biopsy. IHA and ELISA were also negative. All these tests have variable sensitivity, which depends on the type of parasite, the parasite burden, and immunological status [11, 12]. IHA and ELISA were set up using *S. mansoni* antigens, with a variable degree of cross-reactivity with *S. haematobium*. Moreover, ELISA was designed to measure whole antischistosoma IgG antibodies, and a dedicated IgG4 ELISA might have increased diagnostic yield in this case. Finally, HIV infection has been linked to impaired B-cell responses, including IgG subclass deficiency and defective B-cell memory generation [13–15]. This weakened humoral immunity may have played a role in the negativity of ELISA.

ART was initiated 3 months before the beginning of symptoms, and this observation is reminiscent of IRIS reactions observed during HIV infection. Th2 responses with predominant IgG4 synthesis have been shown to be involved in delayed immune responses against *S. haematobium,* and this is in line with the disease course observed in our patient [16]. Microbiological diagnosis was made after corticosteroid exposure, which might have decreased immunological reaction against *S. haematobium,* allowing parasite multiplication and increasing pathogen burden. IgG4-RD is also considered a Th2/Treg driven pathology, which led to this first diagnosis hypothesis. As part of Th2-skewed T-cell responses, IgE levels are typically increased in IgG4-RD and therefore lack specificity in distinguishing IgG4-RD from helminth infections such as schistosomiasis [17, 18]. Morevover, some self-antigens reported as autoantigens may be involved in the pathogenesis of IgG4-RD. This supports the idea that our patient's IRIS related to the parasitic infection could mimic IgG4-RD.

IgG4-RD should remain an exclusion diagnosis, with early recognition of red flags indicating an alternative diagnosis, such as an infectious process in an immunocompromised host. Repeated and comprehensive microbiological workup is warranted, in association with sequential histological examination of the involved sites. This observation also underlines the host–pathogen determinants of urogenital schistosomiasis, with an important role of IgG4 humoral immunity in the control of the infection.

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.

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Author contributions. G.G. and D.B. wrote the manuscript. C.R., F.M., L.G., E.O., R.B., and D.B. contributed to the patient management. J.V. and E.P. performed pathological studies. All the authors critically reviewed the manuscript.

Ethical approval. The study was reviewed and approved by our local ethics committee, and the patient gave his consent for the case report publication.

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