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Case report

Anemia and lower limbs edemas in a patient with HIV infection

Anemia y edemas de miembros inferiores en un paciente con infección por VIH

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Sir,

In the Mediterranean area, leishmaniasis is caused by *Leishmania infantum*. Visceral leishmaniasis (VL) is the most severe systemic form caused by this potentially fatal organism in the absence of treatment [1,2]. The classic clinical form is characterized by intermittent febrile episodes, hepatosplenomegaly, and pancytopenia secondary to bone marrow invasion, leading to anemia, hemorrhages and concurrent infections [3]. Atypical VL such as cases with renal involvement, occurs in human immunodeficiency virus (HIV) infection with low CD4+ T lymphocyte counts [1]. These patients may also be affected by other opportunistic infections, making diagnosis even more challenging [4]. We present this case because atypical forms in immunocompromised patients represent a major diagnostic challenge, and we have reviewed the few cases of membranoproliferative glomerulonephritis (MPGN) associated with this infection in the literature.

The patient was a 49-year-old man of Portuguese origin who had been living in northern Spain for two years, after previously residing on the Mediterranean coast. Notably, he had been diagnosed with HIV infection 25 years earlier and, at the time of hospital admission, was receiving treatment with tenofovir, emtricitabine, darunavir and ritonavir. His HIV viral load was suppressed, and his CD4+ T lymphocytes count was 519 cells/mm^3. He also had a chronic liver disease secondary to hepatitis C virus infection, with undetectable RNA levels. Additionally, he had a history of giant condylomata acuminata in the anal region, requiring surgical resection in 2015. In June 2017, he was diagnosed with anal carcinoma, requiring colostomy. The patient had also undergone splenectomy following polytrauma 20 years ago.

The patient presented to the emergency department due to progressive edema of the lower limbs, refractory to diuretic treatment. Physical examination on admission revealed low-grade fever (37.8ºC) and

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edema with fovea of the lower limbs up to the knees. There were no abnormalities in cardiopulmonary auscultation or increment in jugular venous pressure. Laboratory tests revealed anemia of 7 g/dl and a thrombocytopenia of 41,000 platelets/ml. In addition, it highlighted an albumin of 2.3 mg/dl, with urea 41 mg/dl and creatinine 0.91 mg/dl and a 24-hour proteinuria of 3,024 mg. Bence-Jones proteinuria was negative, and no monoclonal gammopathies were observed in the proteinogram.

The patient was diagnosed with nephrotic syndrome, and tenofovir was discontinued. Combination therapy with lamivudine and darunavir / cobicistat was started. A complete immunological study, including antinuclear antibodies, antineutrophil cytoplasmic autoantibodies, and anti-glomerular basement membrane antibodies, was requested and returned negative results. Complement levels, rheumatoid factor, and cryocyte levels remained in the normal range. An abdominal computed tomography (CT) scan was performed and showed chronic liver disease and a polylobulated formation measuring approximately 8 cm, compatible with splenosis following splenectomy, as previously observed in imaging studies. This had previously been associated with portal hypertension.

A renal biopsy was performed and reported as follows: kidney cylinders with an MPGN pattern, identifying numerous intracellular parasitic forms at glomerular level (in tendocapillary cells) and at interstitial level associated with lymphohistiocytic inflammatory infiltrates. The morphological image was compatible with *Leishmania* infection. The immunofluorescence study showed diffuse and intense deposits of IgG, IgM, C1q at endocapillary level and weak and segmental deposits of IgA, C4 and C3. PCR for *Leishmania* in the renal biopsy was positive. The study was completed with bone marrow biopsy at sternal level, showing parasites compatible with intracellular Leishmania (**Figure 1**).

Treatment with liposomal amphotericin B was initiated at a dose of 3 mg/kg daily for the first 5 days, and then on days 10, 17, 24, 31 and 38. Subsequently, the patient received prophylaxis for 6 months with liposomal amphotericin B at a dose of 3mg/kg every 15

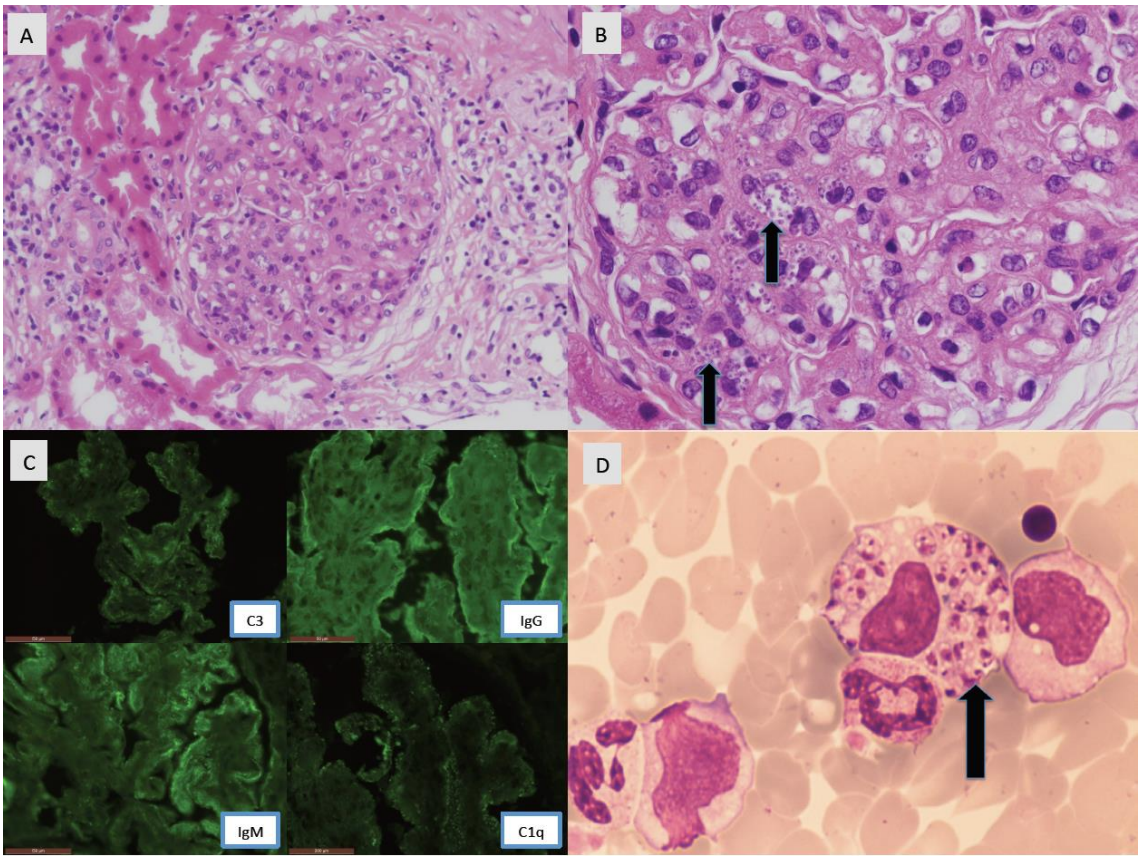

Figure 1. A: Mesangial hypercellularity, endocapillary proliferation, and capillary-wall remodeling (with the formation of double Contours) all of which result in lobular accentuation of the glomerular tufts**. B:** Leishmania amastigotes in the glomerulus **C:** Immunofluorescence showed deposits IgM, IgG, C1q and C3 and lower for C4. **D:** Bone marrow biopsy. Histiocyte with multiple intracellular microorganisms containing a nucleus and a rod-shaped kinetoplast. May-Grünwald-Giemsa stain. Amastigotes were also found in bone marrow and peripheral blood neutrophils.

days, resulting in a progressive decrease in proteinuria, improved serum albumin levels with progressive increase in platelets and without requiring new transfusions of blood products.

HIV induces immunosuppression primarily through the destruction of CD4+ T lymphocytes, which facilitates the dissemination and progression of *Leishmania*, which is normally controlled by cellular immunity. In turn, *Leishmania* chronically activates macrophages and other immune cells, increasing HIV replication. Patients with HIV-*Leishmania* coinfection often present with more aggressive and disseminated forms of the disease, involving unusual organs such as the gastrointestinal tract or bone marrow.

Renal disease is a rare complication of VL that can manifest as acute renal failure, renal amyloidosis, different types of GMN nephritic and nephrotic syndrome [5]. In general, kidney disease associated with leishmaniasis occurs in the immunocompromised host, particularly in the context of HIV infection with low CD4 + T Lymphocyte count [4].

Patients with chronic VL can have mild proteinuria, microscopic hematuria and leukocyturia [5], but nephrotic syndrome can occur in the presence of AA amyloidosis or a MPGN associated with chronic *Leishmania* infection [7]. Glomerular involvement in VL has been associated with the deposit of immunocomplexes and complement due to polyclonal activation of B lymphocytes by the parasite.

Specifically in the kidney, the activation of macrophages and T cells by *Leishmania* can trigger a chronic inflammatory response with the release of proinflammatory cytokines such as TNF-α, IL-1, and IL-6. These cytokines promote endothelial dysfunction and damage to the glomerular basement membrane. The direct invasion of the parasite could induce glomerular damage through mechanisms such as cell apoptosis and oxidative stress [6].

Only a few cases of MPGN have been described in patients coinfected with VL and HIV [8-16]. In the cases described in the literature, the biopsy findings are similar to those found in our case, except that in our patient, intracellular parasites were observed in the glomeruli in the endocapillary cells. (**Table 1**).

Table 1. Cases described in the literature with nephritic or nephrotic syndrome associated with VL / HIV coinfection.

Authors [reference]	Renal histology	Leishmania present in renal biopsy	Treatment	Outcome
Navarro, et al. [13]	AA amyloidosis	No	l-Ampho B	CRF/HD
de Valliere, et al. [14]	AA amyloidosis	No	Antimony/l-Ampho-B/ Miltefosine	CRF
Suankratay, et al. [8]	MPGN	No. *Leishmania* sp PCR positive in kidney biopsy	Ampho-B / Itraconazole	Improvement
Enriquez, et al. [9]	MPGN	Free *Leishmania* sp in capillary lumen	l-Ampho-B/ Miltefosine	Improvement
Amann, et al. [10]	MPGN	Free *Leishmania* sp in capillary lumen and in tubular epithelial cells	l-Ampho-B/ Miltefosine	Improvement
Tilakaratane, et al. [7]	No renal biopsy	ND	l-Ampho-B	ND
Vasallo, et al. case 1 [11]	MPGN	No	l-Ampho-B	Improvement
Vasallo, et al. case 2 [11]	MPGN	Free *Leishmania* sp in capillary lumen.	l-Ampho-B	Death/AKI
Vasallo, et al. case 4 [11]	MPGN	No	Miltefosine	Death/ Intestinal bleeding
Puerta Carretero, et al. [15]	NGN	No	l-Ampho-B	Improvement

...continuation table 1.

Authors [reference]	Renal histology	Leishmania present in renal biopsy	Treatment	Outcome
Ortiz, et al. case 1[16]	MPGN	*Leishmania* in macrophages, glomeruli, and tubular cells cytoplasm	l-Ampho-B	Improvement
Current case	MPGN	Leishmania in endocapilar glomerular cells	l-Ampho-B	Improvement

MPGN: Membranoproliferative glomerulonephritis; NGN: necrotizing glomerulonephritis;PCR: Polymerase chain reaction; ND: No data; l-Ampho-B: Amphotericin B liposomal; Ampho B Amphotericin B; CRF: Chronic renal failure; HD: Hemodialysis AKI: Acute renal injury.

However, in the described biopsies, free parasites were occasionally found in the capillary lumen [9-11], and in macrophages present at the interstitial level [12], or in tubular cells [10] but within glomerular cells, they have only been observed in one of the cases reported by Ortiz M et al [16]. In other cases, the GMN was related to VL because of immunocomplexes and complement deposit in the glomeruli, while the parasite was identified in other locations, such as the bone marrow [11], or a positive *Leishmania* PCR result was obtained from the kidney biopsy [8].

In conclusion, nephritic and nephrotic syndromes caused by *Leishmania* in patients with HIV infection may not only be related to AA Amyloidosis or MPGN caused by the deposition of immune complexes secondary to systemic infection but may also result from direct glomerular infection by the parasite itself.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Writing—original draft preparation, F.A.R, M.H.V, M.B.B., and R.P.F.; writing—review and editing, P.R.B.; supervision, M.C.F. All authors have read and agreed to the published version of the manuscript.

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