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Membranoproliferative Glomerulonephritis and Mixed Cryoglobulinemia as a Form of Presentation of Visceral Leishmaniasis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Male, 69-year-old
Final Diagnosis: Leishmaniasis
Symptoms: Acute renal failure • purpuric skin lesions
Medication: —
Clinical Procedure: Bone marrow biopsy • renal biopsy • ultrasonography
Specialty: Nephrology

Objective: Rare co-existence of disease or pathology
Background: Visceral leishmaniasis (VL) is an endemic systemic disease in the Mediterranean countries, including Spain. This vector-borne infection can present with several clinical presentations, from asymptomatic to severe forms. Renal impairment is frequently described in VL but is usually mild and related to interstitial nephritis, being that glomerular involvement is rarely found.

Case Report: We describe a case of a 69-year-old Spanish male presenting with subacute renal failure due to membranoproliferative glomerulonephritis and mixed cryoglobulinemia accompanied by other autoimmune features (hypocomplementemia, antinuclear and antiDNA antibodies). No hepatosplenomegaly was found with abdominal ultrasound. Hepatotrophic viruses and human immunodeficiency virus serological markers were negatives. We initially suspect the presence of an autoimmune disease and the patient was treated with steroids without improvement. After an extensive study including renal and bone marrow biopsy, a correct diagnosis of visceral leishmaniasis was made, and treatment with liposomal amphotericin B was initiated, achieving renal function recovery and normalization of immunological manifestations.

Conclusions: Renal involvement can be an important feature of VL and it might be associated with increased morbidity and mortality. The association between mixed cryoglobulinemia and renal involvement in VL have rarely been described. VL is frequently associated with diverse autoimmune manifestations and it can be initially misdiagnosed, which could lead to fatal consequences. The role of the immune system in the formation of cryoglobulins are discussed. In our case, an autoimmune disease was initially suspected, and starting treatment with steroids pulses was initiated. However, the presence of mixed cryoglobulinemia in this patient who was hepatitis C serological marker negative and who had poor renal function recovery after immunosuppressive treatment made us suspect other pathologies. The presence of cryoglobulinemia with renal disease in endemic areas of *Leishmania* should make us exclude this infection before starting immunosuppressive treatment.

MeSH Keywords: Cryoglobulinemia • Glomerulonephritis, Membranoproliferative • Leishmaniasis, Visceral

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Background

Leishmaniasis is a vector-borne infection caused by protozoan parasites transmitted by the infected females of certain species of sand fly (subfamily *Phlebotominae*). More than 20 leishmanial species are responsible for the 3 main clinical syndromes: cutaneous leishmaniasis, mucocutaneous leishmaniasis, and visceral leishmaniasis (VL) [1,2].

VL is a systemic disease caused by *Leishmania donovani* in South Asia and East Africa, and by *Leishmania infantum* in the Mediterranean area. According to the World Health Organization (WHO) over 200 000–400 000 new cases of VL appear every year [3]. Spain, as well as other Mediterranean countries, is an endemic area of leishmaniasis (0.38 cases per 100 000 people in 2013) [4].

VL can present with several clinical pictures, from asymptomatic to severe forms [5]. Classically, it is characterized by intermittent fever, general discomfort, weight loss, and hepatosplenomegaly. Laboratory findings like anemia and hypergammaglobulinemia are common. Autoimmune manifestations are also frequent, as cutaneous vasculitis, high titers of rheumatoid factor, serum cryoglobulins and complement consumption [6,7]. There is therefore a large heterogeneity of clinical manifestations, and occasionally the kidney can also be involved.

Herein we present an interesting case of membranoproliferative glomerulonephritis and mixed cryoglobulinemia in a patient with VL.

Case Report

A 69-year-old Spanish male was referred to our Nephrology Department in December 2014 because of subacute renal failure.

He had been diagnosed of arterial hypertension 20 years earlier and soon after he needed a surgical aortobifemoral bypass due to Leriche syndrome. Four years before the admission he underwent transurethral resection surgery of a bladder cancer followed by intravesical adjuvant chemotherapy. Two months before his presentation his serum creatinine (sCr) was 0.8 mg/dL in a routine medical check-up.

At admission he only described intermittent appearance of purpuric lesions on both legs 5 months ago, he did not describe any other symptom such as arthralgias or other systemic symptoms. Examination at admission revealed no abnormal findings except some small residual macules on both tibial skin areas. A normal blood pressure was found. The patient had not travelled abroad for at least 5 years.

The laboratory examinations disclosed sCr 2.51 mg/dL, proteinuria 1.7 g/24 hours and microhematuria (5–10 red cells per high-power field). He had mild anemia with hemoglobin 10.3 g/dL and mean corpuscular volume (VCM) 92.3 fl. White blood cell (WBC) count 6000 cells/mm³ and platelet count 166 000 cells/mm³ were both normal. Furthermore, he presented hypoalbuminemia 3 g/dL, and polyclonal hypergammaglobulinemia (IgG 2650 mg/dL, IgA 240 mg/dL, IgM 269 mg/dL). Initial immunological study showed high titers of rheumatoid factor (781 U/ml), presence of antinuclear antibodies (1/160, IgG IFI Hep2), positivity of anti DNA antibodies (34 U/ml) and a low serum C4 levels (15 mg/dL), being serum C3 levels normal. Abdominal ultrasound revealed normal sized kidneys, without hepatosplenomegaly. A renal biopsy was performed showing 24 glomeruli, 8% of them were globally sclerosed. The remaining showed mesangial and endocapillary proliferation and the capillary walls appeared staff with double contour images (Figure 1). Epithelial crescents were evident in 3 glomeruli (Figure 2). Interstice had foci of inflammatory infiltrate consisting of lymphomonocytes cells.

Direct immunofluorescence (IF) showed mesangial and sub-endothelial glomerular deposits of IgG and C3 (Figure 3). The picture was classified as type I membranoproliferative glomerulonephritis.

Based on this glomerular picture and renal function impairment, we initially suspect the presence of an autoimmune disease; so, we started treatment with steroids pulses (1 g 6-methylprednisolone \times 3 days) followed by prednisone 1 mg/kg/day. Despite the steroids treatment no renal function improvement was evidenced and sCr reached a maximum of 3.25 mg/dL. Diuresis was always presented, and dialysis was not required. Seven days after starting the treatment, the Laboratory Department was informed about the positivity of mixed cryoglobulins type II [cryocrit 1.35%, IgG 6.2 mg/dL, kappa light chain (LC) 8.2 mg/dL, IgM 4.4 mg/dL, lambda LC 3 mg/dL]. Hepatitis B and hepatitis C serological markers (enzyme-linked immunosorbent assay) and viral genome detection by polymerase chain reaction were negatives, so we excluded these viruses as the cause of cryoglobulinemia. Human immunodeficiency virus serological marker was also negative. To complete the study a bone marrow biopsy was performed showing intracellular *Leishmania* parasites (Figure 4). Detection of *Leishmania* DNA in the urine at that time was also positive. A weekly dose of 4 mg/kg liposomal amphotericin B was promptly started during 5 weeks with subsequent improvement of renal function (sCr 1.2 mg/dL), negativization of serum cryoglobulins and DNA of *Leishmania* in the urine.

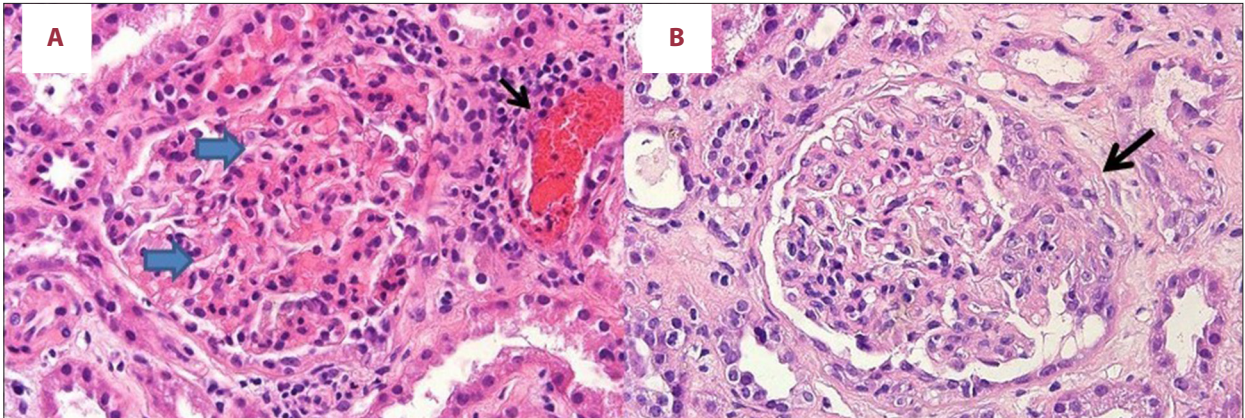


Figure 1. Main histological findings: (A) mesangial hypercellularity and endocapillary proliferation (blue narrow), double-contour lesions of glomerular capillary walls and intratubular red blood cell casts (black narrow), (B) and cellular extra capillary proliferation. Hematoxylin and eosin; original magnification 40x.

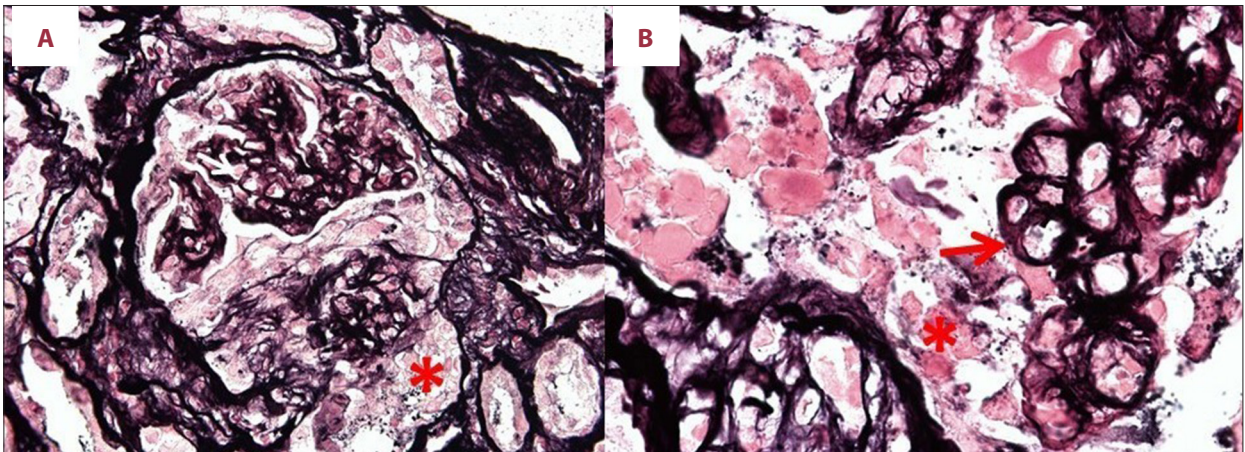


Figure 2. Glomerulus showing double-contour lesions (narrow) and epithelial crescents (*). Methenamine silver stain. Original magnification 40x (A) and 100x (B).

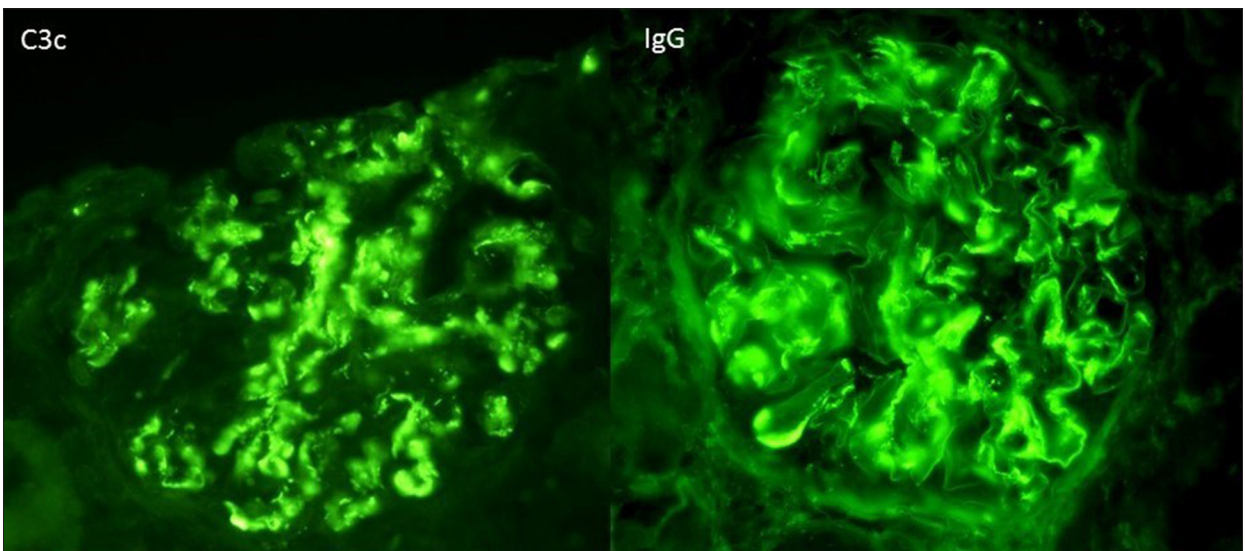


Figure 3. Direct immunofluorescence techniques showing a granular deposit of IgG and C3. Antibodies anti-IgG and C3c marked with fluorescein. Original magnification 40x.

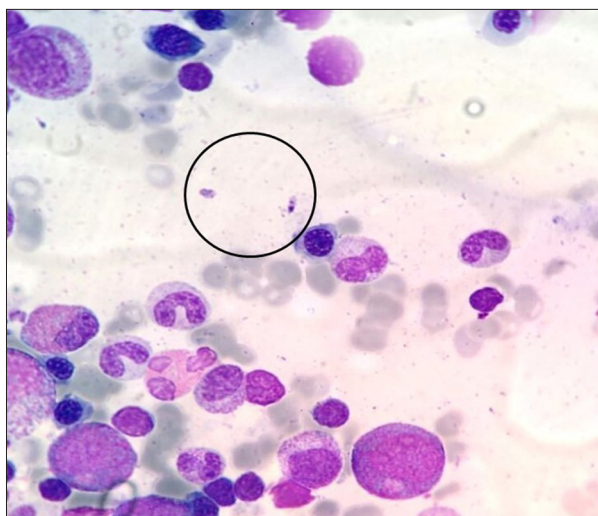


Figure 4. *Leishmania* parasites are observed in a bone marrow aspirate. Original magnification 100x.

Discussion

Renal involvement can be an important feature of VL and it might be associated with increased morbidity and mortality. There are several case reports of renal leishmaniasis both in immunocompetent and immunosuppressed patients [8–14]. Patients can develop proteinuria, hematuria, leukocyturia, and sometimes acute renal dysfunction. Renal involvement is usually mild and improves with the control of the infection. Interstitial nephritis is the most frequent histological finding, sometimes with mesangial glomerular proliferation [15]; however, membranoproliferative glomerulonephritis has rarely been described [6].

Pathogenic mechanisms involved in the renal damage are not well known. Hemodynamics is disturbed in the context of the disease caused by hypovolemia, hypoalbuminemia or anemia, and the different drugs focused on therapy (i.e., amphotericin B) can also be involved in renal damage [16]. A direct invasion of the renal parenchyma by the parasite is also possible, activating a subsequent immune reaction [17]. It has been suggested that VL infection may stimulate T helper 2 lymphocytes, producing interleukins (IL)-4 and IL-10, which activate B cells to produce a wide spectrum of antibodies that are associated with glomerular damage [6,18]. These antibodies might produce glomerular injury through “*in situ*” formation of immune complex or by direct deposition.

VL is frequently associated with diverse autoimmune manifestations. The most frequent findings are high rheumatoid factor titers and antinuclear antibodies (ANAs), although other autoimmune manifestations have also been reported as low complement levels, anti-glomerular basement membrane antibodies (anti-GBM), antineutrophil cytoplasmic autoantibodies (ANCA), anti-Smith (anti-Sm), anti-ribonucleoprotein

(anti-RNP), anti-Sjögren’s-syndrome-related antigen A, (anti-SSA), and anti-SSB antibodies [19]. It could lead to suspect the presence of an autoimmune disease, such as systemic lupus erythematosus, and it could favor using immunosuppressive drugs, with all the negative consequences that could entail.

The presence of cryoglobulins has also been described in VL. Cryoglobulins are immunoglobulins which precipitate at temperatures lower than 37°C; cryoglobulinemia are usually classified according to Brouet et al. [20]. Type II or mixed cryoglobulinemia has a polyclonal Ig, typically IgG, with a monoclonal Ig generally IgM with rheumatoid factor activity [21]. Actual prevalence of cryoglobulinemia in endemic areas of leishmaniasis has not yet been studied [22,23]. In a report of 16 patients with VL, at least 50% presented with serum infection related cryoglobulins after eliminating other causes of cryoglobulinemia, and all of them had positive ANAs or other different autoantibodies [6].

The mechanisms that could be involved in the appearance of serum cryoglobulins are not well known. Some explanations include genetic factors, activation of proto-oncogenes, and leishmania infection itself that could induce the production of cryoglobulins [24]. A common mechanism between hepatitis C and VL has been proposed, based on the phenomenon of molecular mimicry. Patients with cryoglobulinemia secondary to VL or hepatitis C virus have high titers of autoantibodies against a common epitope of gene 3, which participates in lymphocyte activation (LAG-3.1), whereas patients with hepatitis C virus without cryoglobulin present do not have any autoantibodies against this epitope [6,25]. This suggests that the same mechanism can be involved in both hepatitis C virus and *Leishmania* infection to produce mixed cryoglobulinemia.

In our case, an autoimmune disease was initially suspected starting treatment with steroids pulses. However, the presence of mixed cryoglobulinemia in a patient who was hepatitis C serological marker negative and who had poor renal function recovery after immunosuppressive treatment made us suspect other pathologies.

Conclusions

Patients with renal injury secondary to VL can be initially misdiagnosed due to the similarity of this picture with some types of glomerulonephritis, which in turn could favor the use of steroids or other immunosuppressive drugs to try to stop a rapid decline in renal function. This certainly could lead to fatal consequences in an infectious process [24]. Therefore, we recommend that in endemic areas, the possibility of VL should be always be considered in patients with unclarified cause of mixed cryoglobulinemia with glomerulonephritis before starting immunosuppressive treatment.

Conflict of interest

None.

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