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A typical presentation of cutaneous leishmaniasis after renal transplantation

Sir,

Leishmania parasites are transmitted to humans through the bite of sand flies and may cause visceral, cutaneous or mucocutaneous disease, with clinical features ranging from localized ulcers to systemic lethal disease. The mucocutaneous form is mostly found in Latin America and millions of people live in areas of active parasite transmission [1]. A 49-year-old female transplant recipient under immunosuppressive treatment developed multiple erythematous and painful lesions on the legs (Figure 1A). The diagnosis of leishmaniasis was confirmed by enzyme-linked immunosassay, immunofluorescence assay and immunohistochemistry, as well as by multiplex polymerase chain reaction (PCR) analysis as previously described [2]. Leishmania amastigotes were present in the lesions and PCR analyses revealed parasites from the L. braziliensis complex (Figure 1B). By conventional reverse transcriptase-PCR reaction (RT-PCR) [3] expression of IL-4 (Figure 1C) and IL-13 (Figure 1D) mRNA was demonstrated and IFN-gamma mRNA (Figure 1E) was not detected in the wound tissue. After 50 days, the wounds completely healed after treatment with amphotericin B [4]. No relapses were observed after 18 months of maintaining normal renal function. Treatment with amphotericin B was efficient and safe in the case studied, while the patient was taking a calcineurin inhibitor. Thus, in endemic areas for leishmaniasis, atypical skin lesions in immunosuppressed patients should be investigated for the presence of Leishmania parasites.

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Sir,

Idiopathic membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adults.
Corticosteroids, cytotoxic agents and cyclosporine have been largely used in idiopathic MN, but their use may be ineffective or contraindicated in some patients [1]. The pathogenetic potential of B cells in this disease has been employed to explore the therapeutic use of new drugs, such as rituximab, a monoclonal antibody to B-cell antigen CD20. CD20 expression is limited to B cells, begins in humans at the early pre-B-cell stage, and persists until the B cells undergo terminal plasma cell differentiation. The binding of rituximab to the surface receptor of B cells inhibits their activation, proliferation, differentiation and production of immunoglobulins [2].

In the last few years, rituximab has been used in the treatment of type II mixed cryoglobulinaemia (MC), a systemic vasculitis associated in most cases with hepatitis C virus (HCV) infection, and sustained by proliferation of oligoclonal cells. In some categories of patients, anti-viral treatment of active HCV infection may be ineffective or not tolerated, whereas current immunosuppressive treatments may lead to relevant complications and enhance the viral load [3].

**Case report**

A 69-year-old man was admitted to our unit in July 2000 for nephrotic syndrome. In 1998, HCV-related infection and urinary abnormalities had been diagnosed in another hospital. On admission, the physical examination showed peripheral oedema. Blood pressure was 120/80 mmHg, and no clinical chest or abdominal abnormalities were found. Laboratory investigation revealed the following: serum creatinine (sCr) 0.9 mg/dl, proteinuria (Upr) 9.1 g/24 h, serum total proteins 5.1 g/dl, serum albumin 2.4 g/dl, aspartate aminotransferase (AST) 17 IU/l, alanino aminotransferase (ALT) 13 IU/l, gammaglutamyltransferase (GGT) 6 IU/l, alkaline phosphatase (ALP) 91 IU/l. No macroscopic and/or microscopic haematuria were present. Urinary sediment showed granular and epithelial casts. Complement factors, such as C3, C4, circulating immune complexes, serum immunoglobulins and reumathoid factor were in the normal range.

Anti-dsDNA antibodies, anti-nuclear antibodies, anti-neutrophil cytoplasmatic antibodies and cryoglobulins were absent. The amount of HCV RNA was 620 000 IU/ml, using an in-house real-time polymerase chain reaction assay (lower detection cut-off 600 IU/ml); HCV genotype was 2a/2c. The patient underwent ultrasound-guided renal biopsy which revealed, at light microscopy, a diffuse thickening of glomerular basement membrane with granular subepithelial and intramembranous deposits. Parietal IgG and C3 deposits were absent. The amount of HCV RNA was 278 000 IU/ml. Rituximab was started at a dosage of 375 mg/m²/week i.v. for 4 weeks and administration of enalapril was continued regularly. No fever, pain or allergic reaction occurred after every infusion of rituximab. After this short course of therapy, Upr decreased to 1.8 g/24 h and reached levels of complete remission after 6 months; CD20 B lymphocytes decreased from 9.8% to 0.1%; a decrease in HCV RNA levels was also observed (193 574 IU/ml). Kidney oedema disappeared and blood pressure was normal (115/80 mmHg). After 24 months, the patient was in complete remission, with Upr of 0.24 g/24 h and sCr 0.9 mg/dl, AST 36 IU/l, ALT 50 IU/l, GGT 17 IU/l, ALP 631 IU/l; HCV RNA levels further decreased to 8420 IU/ml.

**Comments**

Corticosteroids and cytotoxic agents have been largely used in the treatment of MN. In patients with contraindication to cytotoxic agents or non-responders, new approaches are represented by other agents such as cyclosporine, adrenocorticotropic hormone, tacrolimus and mycophenolate mofetil. No recommendations are provided for the treatment of MN associated with HCV infection.

The rationale for using rituximab in the treatment of glomerulonephritis associated with HCV infection is its action on B lymphocytes. Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody, which binds to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The Fc domain of rituximab recruits immune effector functions to mediate B cell lysis. Possible mechanisms of cytotoxicity include complement-dependent cytotoxicity resulting from Clq binding, and antibody-dependent cellular cytotoxicity, mediated by one or more of the Fcgamma receptors on the surface of granulocytes, macrophages and NK cells and apoptosis [4]. The relation between mixed cryoglobulinaemia and HCV infection shows new links between viral infection, autoimmune phenomena and lymphoproliferative disorders. A monoclonal population may emerge by B-cell polyclonal proliferation stimulated chronically by HCV. In patients with HCV-related MC, the therapeutic strategy should include antiviral therapy. In determining the regression of B-cell lymphoproliferative disorder, rituximab could exert selective B-cell control, modulating and interfering with HCV proliferation.

In preliminary studies, Ruggenenti et al. [2] evaluated the outcome of eight idiopathic MN patients with persistent urinary protein excretion, given four weekly infusions of rituximab (375 mg/m²) in association with a full dose of ACE-inhibitors. At 3 and 12 months, proteinuria decreased by 51% and 66%, respectively; however, proteinuria remained in the nephrotic range in 4/8 patients. On the contrary, our case demonstrates that rituximab induced a complete remission in MN associated with HCV infection and no relapse occurred in the mid term after a short course.

In conclusion, rituximab infusion offers a new alternative approach, with a narrow disease-specific mechanism for the treatment of idiopathic MN, associated with the...
current therapeutic options including non-specific immuno-suppression, conservative treatment with ACE inhibition, blood pressure reduction and lipid control. In MN associated with HCV infection, the rationale is enforced by the selective action of rituximab on B lymphocytes. However, large randomized clinical trials with longer follow-up are needed, to verify the efficacy and the long-term tolerability of rituximab therapy, in both idiopathic and secondary MN.

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Conflict of interest statements. None declared.

Fig. 1. Time course of serum creatinine concentration, 24 h urinary protein excretion rate and HCV RNA in our patient with membranous nephropathy and HCV-related infection treated with interferon and then with rituximab.

Continuous dialysis by gravity through the filter of extracorporeal membrane oxygenation

Sir,

Continuous renal replacement therapies (CRRT) are characterized generally by their good haemodynamic tolerance [1–4]. However, in some critical clinical situations, even CRRT are impracticable.

A 22-year-old man with Marfan syndrome, admitted to the ICU after emergency dissecting aneurysm surgery of the thoracic aorta, presented extreme haemodynamic instability (blood pressure: 46/35 mmHg; Central venous pressure: 9 cmH2O). Despite fluid resuscitation (12 l) including sodium bicarbonate solutions, vasoactive drugs, intraaortic balloon counterpulsation and extracorporeal membrane oxygenation (ECMO) support, he remained unstable. Acute kidney injury developed with anuria, high levels of serum creatinine (3.97 mg/dl), BUN (31 mg/dl), toxic hyperkalemia (8.2 mmol/l), hyperlactactatemia (10.1 mmol/l). Temperature was 36.8°C, arterial pH 7.32; pO2 55.6 mmHg; pCO2 37.7 mmHg and bicarbonate 19.2 mmol/l.