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Case Report

Efficacy of Rituximab Combined With Wyclophosphamide in a Patient With Systemic Lupus Erythematosus and Peritoneal Vasculitis Refractory to Conventional Inmunosupressive Therapy

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ABSTRACT

Peritoneal vasculitis is a rare and severe clinical manifestation of systemic lupus erythematosus. We report a patient who presented with ascites due to peritoneal vasculitis and cutaneous, articular, hematological, and renal inflammatory activity. Treatment with glucocorticoids and immunosuppressive drugs was ineffective. In view of the resistance to different therapies, 4 weekly infusions of 375 mg/m^2 of rituximab (RTX) were started, in association with cyclophosphamide pulses during the first and the third weeks. With this treatment strategy, the patient reached a complete response which was achieved in later flares of inflammatory activity (the second and third flares were multisystemic and with ascites again, and the fourth flare with nephritis).

Eficacia de rituximab combinado con ciclofosfamida en una paciente con lupus eritematoso sistémico y vasculitis peritoneal resistente a tratamiento inmunosupresor convencional

Palabras clave:
Lupus eritematoso sistémico
Vasculitis
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RESUMEN

La vasculitis peritoneal es una manifestación clínica infrecuente y grave del lupus eritematoso sistémico. Se presenta el caso de una paciente con ascitis por vasculitis peritoneal y afección cutánea, articular, hemática y renal. El tratamiento con glucocorticoides e inmunosupresores resultó ineficaz para el control de la ascitis. Dada la resistencia al tratamiento convencional, se administró rituximab en cuatro infusiones semanales de 375 mg/m^2, potenciado con pulsos de ciclofosfamida las semanas 1 y 3. Con esta estrategia se consiguió una respuesta completa, que se repitió en brotes posteriores (el segundo y el tercero, multisistémicos y de nuevo con ascitis significativa, y el cuarto con nefritis).

Introduction

Ten percent of patients with systemic lupus erythematosus (SLE) develop ascites, which can be due to multiple causes.[1] It is usually related to nephrotic syndrome, heart failure, constrictive pericarditis, protein-losing enteropathy, or Budd-Chiari syndrome. Gastrointestinal vasculitis affects 1%-2% of all patients with SLE.[2] It can present itself in any of its components, including the peritoneum, and can lead to severe complications. Peritoneal vasculitis is an infrequent cause of ascites. We present the case of a patient with SLE and steroid and other immunosuppressant-resistant peritoneal vasculitis. Peritoneal vasculitis is a frequent cause of ascites.

Case Report

A 28-year-old woman was diagnosed in 2001 with SLE based on skin and joint involvement, sicca syndrome, lymphopenia, and positive antinuclear antibodies. In January 2003 treatment with steroids was started with 3 pulses of 1 g of intravenous (IV)

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methylprednisolone, followed by oral deflazacort and cyclophosphamide (CF) (6 IV pulses at a dose of 15 mg/kg monthly) due to skin manifestations (alopecia and subacute lupus lesions) and steroid, antimalarials, methotrexate, azathioprine, and IV immunoglobulin (Ig)-resistant arthritis. After inducing remission, the dose of steroids was gradually reduced. In 2004 she consulted, 1 month after the administration of a second trimestral pulse of IV CF, presenting skin lesions of an urticarial nature in exposed areas, generalized joint pain, ascites, and abdominal pain. Complementary testing showed: inflammatory anemia (Hb, 7.7 g/L); leukopenia (3.42×10^9/L); lymphopenia (0.3×10^9/L); creatinine, 0.69 mg/dL; hypoproteinemia (6.4 g/dL); hypoalbuminemia (2.9 g/dL); hypocomplementemia; C-reactive protein, 18.2 mg/L; ESR, 55 mm/h; proteinuria (2.2 g in urine de 24 h); altered urinary sediment (238 888 leukocytes/min, 144 444 RBC/min and 8889 casts/min in the Addis recount in 3 h urine); positive antinuclear antibodies (>1/640 on Hep2 with a homogeneous pattern); positive anti-double stranded DNA antibodies (on *Crithidia luciliae*); positive anti-ENA antibodies specific for U3RNP; the chest x-ray showed a left pleural effusion; the echocardiogram evidenced a pericardial effusion; abdominal echography and a tomography with IV contrast showed important ascites, without alterations in the liver parenchyma or the portal, intrahepatic, or suprahepatic vessels, or signs of intestinal vasculitis (as per the criteria proposed by Ko et al[3] an Byun et al[4]). Data of the ascitic fluid were: 3320 cel./µL (85% polymorphonuclears), 41.1 g/L proteins, 0.75 g/L glucose, negative microbiologic tests, and the cytology showed a mixed inflammatory exudate. Due to the important flare of multisystemic activity (skin, serosal, hematological, and renal), treatment with steroids (3 IV boluses of 1 g methylprednisolone followed by deflazacort 60 mg/day) and Ig (400 mg/kg/day for 4 consecutive days). Due to the inefficacy of these interventions, CF was then added (a new 750 mg IV pulse) as well as mycophenolate mofetil (2 g/day). A month later, the skin lesions and joint pain had disappeared and the renal parameters were normal, but voluminous ascites persisted. An exploratory laparotomy was performed where a generalized thickening of the peritoneum, without liver or intestinal alterations, was seen. The peritoneal biopsy confirmed small vessel necrotizing vasculitis (Figure), while the liver biopsy was normal. Faced with a lack of response to treatment, rituximab was administered (RTX), 375 mg/m^2/week for 4 weeks, potentiated on the first and third week with CF (750 mg IV), with an amazing response. Ascites disappeared, as well as the rest of the clinical alterations, anti-DNA antibodies were now negative and complement titers were normalized. The patient presented 3 more flares, 11 (fever, ascites, skin vasculitis, leukopenia, lymphopenia, inflammatory anemia, thrombocytopenia, low complement, and positive anti-DNA antibodies), 20 (fever, arthritis, polyadenopathy, pleuropericarditis, ascites, nephritis, lymphopenia, inflammatory anemia, hypocomplementemia, and positive anti-DNA antibodies) and 26 months later (nephritis, leukopenia, lymphopenia, inflammatory anemia, and positive anti-DNA antibodies). The patient responded satisfactorily once again to the same treatment protocol and 13 months after the last cycle of treatment is in complete remission.

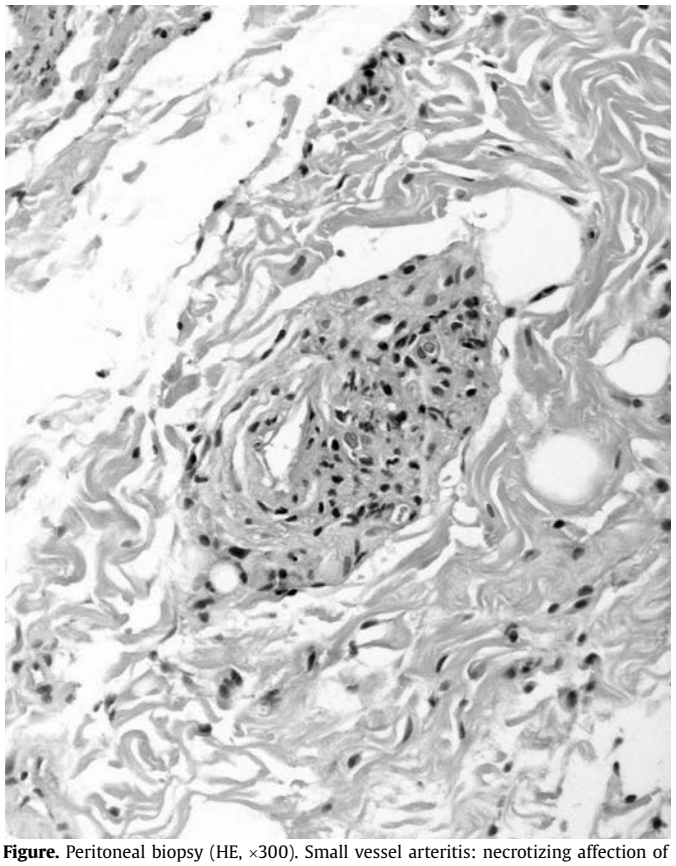

Figure. Peritoneal biopsy (HE, ×300). Small vessel arteritis: necrotizing affection of the complete width of the vessel wall with a polymorphonuclear infiltrate and partial luminal obstruction.

Discussion

Gastrointestinal vasculitis is an infrequent manifestation of SLE (1%-2% of cases with abdominal pain).[2] It can manifest in a diverse manner, from asymptomatic ascites to acute abdominal pain.[5] Mortality is high (53% when the patient has an acute abdomen[5] and up to 50% if the patient has intestinal infarction and perforation[6]). It is manifested as pain, vomit, diarrhea, rectal bleeding, and ascites,[4,7] with orienting radiological signs: thickening of the intestinal wall and dilation of the affected segments, intestinal pneumatosis, and changes in mesenteric vessels (ingurgitation, "comb" sign, attenuation of mesenteric fat).[3,7,8] In this patient, in spite of the demonstration of peritoneal vasculitis, no clinical or radiological signs of intestinal vasculitis were seen. We only found a similar situation described in one other case.[9]

Usual treatment of SLE with severe systemic affection is based on steroids and immunosuppressants. However, mortality in cases of peritoneal vasculitis is very high.[5,6] RTX is a chimeric monoclonal antibody directed versus CD20 which produces a transitory depletion of B lymphocytes. Its binding to ligand affects the activation and differentiation of B lymphocytes. Clearance of B lymphocytes by RTX is produced by several mechanisms: complement dependent cytotoxicity, antibody dependent cytotoxicity, and induction of apoptosis. B lymphocytes have important functions, apart from antibody production: they are antigen presenting cells, regulate the activity of T lymphocytes, and produce cytokines relevant to inflammation.[10] After a literature search on MEDLINE (using the key words lupus, vasculitis, and rituximab; 10 year search), we found the description of one case with diffuse affection of the digestive tract who progressed favorably after the administration of RTX,[11] but we found no reference on its efficacy in patients with severe peritoneal vasculitis. The efficacy of RTX combined with CF could be called into question if the reappearance of clinical activity a few months after the administration of the first 3 cycles of treatment is considered. In our opinion, the benefits of the repeated response to treatment should not be questioned, because in all therapeutic cycles there was a complete remission of activity. Complete remission currently has been maintained for 13 months after the fourth cycle of treatment. We believe this case illustrates the usefulness of RTX combined with CF in SLE and severe visceral affection resistant to other treatment options.

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