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Early onset neutropenia after rituximab in lupus nephritis

Sirs,

Rituximab is a mouse/human chimaeric IgG1-k monoclonal antibody that targets the CD20 antigen found on B-lymphocytes. It may be an effective treatment for patients with systemic lupus erythematosus (SLE) (1, 2). In this report we describe a case of early onset neutropenia after rituximab therapy in SLE.

A 48-year-old Caucasian woman was diagnosed, ten years ago, as having SLE and diffuse proliferative glomerulonephritis (class IV) with nephrotic syndrome. Remission of the nephropathy was achieved with steroids and cyclophosphamide.

New onset polyarthritis appeared three months before her current admission. On physical examination the blood pressure was 160/100 mm Hg and mouth ulcers were noted. Laboratory studies: hemoglobin 9.5 g/dl, white blood cell count 5.76 10⁹/l (nv 4.00-11.00), neutrophils 4.45 10⁹/l (nv 2.00-7.20), lymphocytes 0.76 10⁹/l, platelets 118 10⁹/l, creatinine 1.2 mg/dl, C3 52 mg/l, C4 6 mg/dl, ANA 1/640, anti-DNA 1/320; lupus anticoagulant, anticardiolipin antibodies, cryoglobulins and c-reactive protein were negative or normal.

HbsAg was negative and anti-HBsAc was positive. Anti-HBcAc negative for IgM and positive for IgG, anti-HCV negative. 24-h proteinuria was 2.6g /24h, urinary

sediment: microhematuria and red blood cell casts. The urine culture was sterile. The echocardiography and abdominal ultrasound were normal. A lupus flare was diagnosed with probable lupus nephritis relapse. She was treated with three pulses of methylprednisolone (0.5 g each), following prednisone 0.5 mg/kg/day po, and three monthly infusions of cyclophosphamide. However, the serum creatinine worsened to 5 mg/dl. A kidney biopsy had to be cancelled due to prolonged bleeding time not corrected after desmopressin therapy. ANCAs (PR-3, MPO) and anti-glomerular basement membrane antibodies were negative; magnetic resonance imaging of the renal arteries and veins was normal. Rituximab therapy was started at a dose of 700 mg (375 mg/m²); previous white blood cell count and neutrophils were normal. Five days after rituximab therapy, white blood cell count was 3.75 10⁹/l with 3.33 10⁹/l neutrophils. In three days, the white blood cell count normalized. Two weeks later, a second dose of rituximab was administered; 24 hours after it the white blood cell count fell to 2.39 10⁹/l with 1.66 10⁹/l neutrophils; the hemoglobin and platelets did not decrease. One day later, she presented a body temperature of 38°C. Granulocyte colony-stimulating factor (G-CSF), broad-spectrum antibiotics and fluconazole were given. Blood and urine cultures, skin tuberculin test, and serology for infectious agents were negative. Neutrophil-bound antibodies (IgG and IgM, flow cytometry) were negative. The nadir of leukocytes, 1.31 10⁹/l with 0.85 10⁹/l neutrophils, was reached five days after rituximab and three days after starting G-CSF; afterwards they normalized in one week. The patient became afebrile and made an uneventful recovery. Bone marrow aspiration disclosed normal granulopoiesis, no maturation arrest and neutrophil precursors present. Her renal function worsened and hemodialysis was started.

Rituximab may be a valuable treatment for lupus nephritis refractory to cyclophosphamide (3, 4). In the oncological setting, several cases of late-onset neutropenia have been described. It tends to occur 2-6 months after rituximab single therapy and can be associated with serious infections (5). Because CD20 antigen is not present on neutrophils, this complication has been related to autoantibodies against neutrophils during immune reconstitution. Neutropenia resolved spontaneously or responded to G-CSF and/or intravenous immunoglobulin treatment (6).

The incidence of neutropenia appears to be rare in patients with SLE treated with rituximab (2, 7). However, recently two cases of early-onset neutropenia associated with rituximab for SLE have been reported (8).

In our patient, there was a close temporal correlation between drug exposure and the early-onset neutropenia. After the first dose of rituximab, we observed a mild decrease in white blood cell count and neutrophil values. On re-exposure, the patient developed a severe neutropenia. The early-onset of the adverse reaction would suggest an immune mediated mechanism (9). Afterwards, she presented fever; apparently the infection was secondary to neutropenia but the reverse cannot be ruled out.

This case report illustrates the necessity to carry out a close monitoring of neutrophil count during rituximab therapy.

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