

Treatment of Pemphigus Vegetans to Rituximab Refractory to Conventional Therapy

Dear Editor,

An otherwise healthy 53-year-old woman was admitted to our Dermatologic Clinic for evaluation of two erythematous plaques on the front and back of both her thighs, which had developed over the previous ten months (Figure 1A). These plaques showed vegetative or hypertrophic elements, and were occasionally pruritic. The rest of her skin and mucosal surfaces were normal, the patient being in good health.

A complete workup was carried out, including a complete blood count and biochemical profile, C-reactive protein count, erythrocyte sedimentation rate, chest X-ray, purified protein derivative (PPD) test and human immunodeficiency virus (HIV) serology, which showed no abnormalities. Bacterial and fungal cul-

tures were negative as well. Histopathological evaluation of a skin specimen revealed acanthosis and papillomatosis in the epidermis with predominantly eosinophilic microabscesses. Direct immunofluorescence assay showed deposits of immunoglobulin G (IgG) and C3 in the lower part of the epidermis, which was consistent with pemphigus. Thus, based on clinical and pathological findings, the patient was diagnosed with pemphigus vegetans (PV).

Treatment with clobetasol propionate applied in occlusive cures proved ineffective after 2 months. The patient was then placed on oral prednisone at a dose of 1 mg/kg/day for 30 days with posterior tapering. However, in addition to her irresponsiveness to



Figure 1A. Erythematous plaque with vegetating and crusted elements on the front right thigh.

Figure 1B. Residual erythema after 45 days of treatment with Rituximab.

this treatment, the patient developed a cushingoid appearance. Consequently, azathioprine (1.5 mg/kg/day) was added, but to no avail. Likewise, the subsequent use of further medications (cyclosporine 2.5 mg/kg/day; methotrexate 15 mg weekly; mycophenolate mofetil 3 g/day) in three-month intervals did not improve the patient's condition.

Due to the lack of response to the different therapeutic approaches, as well as the need for a more aggressive and successful therapy for our patient, we suggested a trial with rituximab (RTX) based on favorable cases reported in the literature. The dosing regimen was 375 mg/m² in weekly infusions for one month. The hypertrophic plaques resolved in approximately 45 days, leaving only a mild residual post-inflammatory erythema (Figure 1B). After one year of follow-up, the patient remained asymptomatic, not requiring further additional medication ever since.

PV is a rare form of pemphigus vulgaris, which represents only 2% of cases of this disorder (1), and whose pathogenesis remains elusive (2). Some triggering agents have been suggested, such as bacterial superinfections and localized trauma, which would account for its flexural preference. However, the latest hypothesis focuses on the fact that it is a predominantly Th2 immunological response. Its development has also been linked with HIV infection, intranasal heroin abuse, transplants, lymphoproliferative disorders, and solid tumours (3).

As far as treatment is concerned, topical and/or oral corticosteroids are recommended as first-line therapy in current consensus documents and therapeutic guidelines, especially in pemphigus vulgaris, which can be extended to the PV subset (4-6). It is widely accepted that their use has significantly reduced morbidity and mortality in these patients. Nevertheless, the side effects and complications associated with the use of steroids have led to the utilization of immunosuppressive agents such as azathioprine, cyclosporine, methotrexate, cyclophosphamide, and mycophenolate mofetil. Even so, it is not clear whether the expected effect of this add-on therapy is actually achieved (5,7).

The use of intravenous immunoglobulins in refractory cases, especially RTX (8,9), has brought about a complete revolution in the management of this disorder. In spite of this, the dosing regimen of RTX remains controversial. Thus, some clinicians support the lymphoma regimen (375 mg/m² weekly for four weeks), while others prefer the one used in rheumatoid arthritis (1 g in two sessions 15 days apart, or a mixed system of induction which includes the lymphoma protocol for three weeks and a final dose of 2

g at week four). However, despite over 150 reported cases in the literature, there is no agreement concerning autoimmune bullous skin disorders.

For this reason, and in view of our limited experience in the use of RTX, as well as the exhaustive use of clinical practice guidelines, we are of the same opinion as Leventhal and Sanchez (10) on the need to re-evaluate the treatment of pemphigus. In an era when pharmacoeconomics is at the forefront, it is vital to obtain the most effective treatments at the lowest possible price, and always with the most favorable risk-benefit profile. Nevertheless, this will clearly involve ascertaining the predictors of poor response that will make these patients legible for more expensive therapies in advance.

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