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Apparent safe use of single dose rituximab for recalcitrant atopic dermatitis in the first trimester of a twin pregnancy

To the Editor: Rituximab, a chimeric monoclonal anti-CD20 antibody originally developed for the therapy of B-cell malignancies, has recently been suggested as an option for severe atopic dermatitis (AD),[1] particularly in patients with elevated levels of total immunoglobulin E (IgE) and/or specific IgE to environmental allergens.

We report a 30-year-old woman with allergic rhinitis, asthma, and AD since childhood, which was resistant to intensive topical therapy with steroids and tacrolimus and oral antihistamines. She had documented allergies to *Dermatophagoides* spp., latex, cow's milk proteins, egg proteins, and peaches. Serial total IgE levels in blood were consistently > 20000 kU/L (normal IgE range < 100 kU/L). She had been previously treated with systemic corticosteroids, cyclosporine, mycophenolate mofetil, and psoralen plus ultraviolet A light phototherapy (PUVA), with inconsistent and temporary results, and she continued to have persistent severe disease. The physical examination revealed lesions involving 80% of her total body surface area (TBSA). Rituximab was then proposed to the patient, after complement deficiency, immunoglobulin deficiencies, and severe infection had been ruled out; pregnancy was excluded by a negative immunologic human chorionic gonadotropin test in urine 1 week before the infusion, because her last menstruation had occurred 4 weeks earlier. A baseline complete blood cell count, total IgE level, and B lymphocyte count were obtained. Written informed consent was signed by the patient. The treatment schedule consisted of two intravenous infusions of rituximab 1000 mg 2 weeks apart.[1] However, before the second infusion, a second pregnancy test was performed, which was positive. The infusion was canceled and the pregnancy was closely monitored in a high-risk pregnancy unit. Obstetric ultrasonographies placed the date of conception 13 days before the first infusion. At week 36 of an uncomplicated pregnancy, two healthy monozygotic twins were delivered via cesarean section. Our patient had a significant decrease in her IgE levels (4000 kU/L) and TBSA decreased to 5% after the single rituximab infusion; during the 17-month follow-up period she did not experience new flares of her dermatitis and no adverse events occurred. Her closely monitored 8-month-old boys are growing and developing normally; careful hematologic and immunologic monitoring has revealed no adverse effects resulting from exposure to rituximab (B lymphocyte levels of 1250/μL and 1050/μL for each twin, respectively; IgA, IgM, IgG, and IgE levels are normal in both twins).

Data regarding the use of rituximab during pregnancy are scarce and have been limited to patients with hematologic disease: non-Hodgkin lymphoma,[2] B-cell lymphoma,[3] Burkitt lymphoma,[4] acute thrombotic thrombocytopenic purpura,[5] autoimmune hemolytic anemia,[6] and idiopathic thrombocytopenic purpura.[7] In all reported cases, no abnormalities have been found in fetal or child development with the weekly regimen of 375 mg/m^2 given as four to six infusions. Furthermore, some have suggested that rituximab therapy for lymphomas is a viable option for deferring cytotoxic therapy early during pregnancy and might help to reduce the risk of fetal malformation or abortion.[4] Because AD is a chronic, nonfatal, inflammatory disease, it is difficult to support its use in pregnant women, regardless of the risk–benefit ratio. Nonetheless, the present case is a valuable contribution in asserting the safety of the drug in this setting.

The significant and long lasting clinical improvement produced in our patient with the single infusion administered suggests that rituximab may be a promising therapy in AD. Its administration during pregnancy appears to be safe for the child, but further studies are warranted.

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Development of pemphigus vulgaris in a patient with psoriasis treated with cyclosporine

To the Editor: In July 2008, a 60-year-old man who had had psoriasis since 28 years of age presented to our department with erosive lesions on the oral and genital mucosa and erosive bullous lesions on the skin, predominantly on the back and chest. The lesions had arisen at a time when his psoriasis had regressed almost completely, with few residual erythematous, finely scaling lesions on scalp and elbows. The patient had been on continuous cyclosporine therapy (initial dosage, 250 mg/day) for his psoriasis for the previous 9 months. When he came to us, the cyclosporine dose had been decreased to 140 mg/day and he was using no topical treatment. The patient also had congenital deaf-mutism and diabetes mellitus, for which he had been taking glimepiride for several years.

A biopsy specimen of an erosive lesion showed suprabasal acantholysis on routine histology, IgG and C3 deposits in intercellular spaces on direct immunofluorescence, and anti−desmoglein 3 antibodies (protein index value: 68 IU) found after an enzyme-linked immunosorbent assay led to a diagnosis of pemphigus vulgaris. The patient was started on prednisone 60 mg/day; the cyclosporine was tapered over 2 weeks and was replaced with azathioprine (100 mg/day). Rapid clearing of the erosive bullous lesions enabled gradual tapering of the steroid. Eight months later, the patient continues on prednisone 15 mg/day and azathioprine 50 mg/day. Two mild episodes of pemphigus exacerbation have been treated with higher steroid doses. Slight worsening of the psoriasis related to steroid tapering has been controlled with topical treatment.

Reports of bullous disorders arising in psoriatic patients are numerous and include predominantly bullous pemphigoid[1] and, among the intraepithelial forms, pemphigus foliaceus.[2] Various mechanisms have been invoked to explain these associations. An independent trigger of the bullous disease has been identified in some cases (eg, ultraviolet irradiation from phototherapy and photochemotherapy[3]), including drugs—particularly penicillamine[2] and enalapril[4]—and even irritant topical antipsoriatic treatment, such as dithranol and salicylic acid.[3] However, removal of the suspicious triggering agent in such cases rarely resolves the bullous disease, especially when systemic drugs are implicated.[4] In the other cases, the trigger tends to be the promoter of the bullous disease, which then develops autonomously. Another mechanism invoked to explain these associations is a genetic predisposition.[5] Nonetheless, a number of other cases have no apparent explanation. Several researchers have made reference to the epitope spreading phenomenon,[1] the hyperactivated immunologic status found in psoriatic patients,[1] or the molecular mimicry phenomenon, which may result from acute or chronic infections.[2] However, these authors also suggest that the association of pemphigus and psoriasis may be a coincidence. A meticulous search for a trigger in our patient, including those mentioned above, was negative. A role for the antidiabetic treatment was excluded. Steroid treatment rapidly cleared his pemphigus lesions, although there was a mild exacerbation of his psoriasis associated with tapering of the steroid dose.

The onset of pemphigus vulgaris despite the immunosuppressant regimen was remarkable and might not be a coincidence. It is possible that the bullous disease may have been triggered by the patient's psoriasis and mediated by unknown mechanisms that overcame the effects of his iatrogenic immunosuppressed status.