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Letter to the Editor

Two difficult management autoimmune diseases☆

Dos enfermedades autoinmunes de difícil manejo

Dear Editor:

We present the case of a 56-year-old male patient, allergic to penicillin, with a history of hypercholesterolaemia, diabetes mellitus and seropositive, nodular, and erosive rheumatoid arthritis, diagnosed in 2009. He had received several biological treatments (etanercept, adalimumab, tocilizumab, rituximab, abatacept, which were withdrawn due to inefficacy or adverse effects) and was currently being treated with 25 mg methotrexate weekly, 5 mg of celecoxib and tofacitinib every 12 h, without incident and with the rheumatic disease in remission.

He presented at the emergency department on 3 occasions due to the presentation of a generalized, very itchy, wheal-like rash of more than 24 h onset, which left hyperpigmentation and on occasions purpura where the wheals were located (Fig. 1). The rash was accompanied by a general feeling of malaise, a tightening of the chest, glottic and uvula labial edema. The patient was administered with intravenous glucocorticoids and antihistamines in the emergency department, with rapid improvement of symptoms. During one visit adrenaline was required. Despite the treatment with high doses of systemic glucocorticoids, maximum doses of second-generation antihistamines, sedating antihistamines and ranitidine, the patient continued having extremely itchy general lesions.

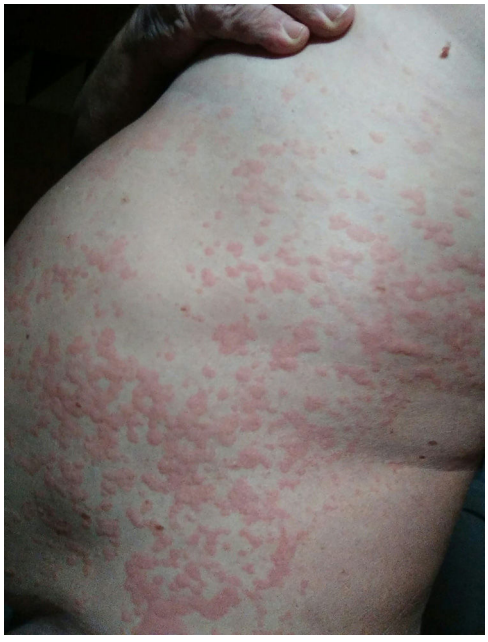

Fig. 1. General outbreak.

Analysis revealed high acute phase reactants, leucocytosis with neutrophilia, D-dimer of 1080 ng/ml, normal complement, negative antinuclear antibodies and IgE 383 KU/l with specific IgE negative to *Anisakis* and *Ascaris*. A punch skin biopsy was performed on an acute lesion which showed mild neutrophilic vasculitis in the superficial and deep dermis with an absence of eosinophils, compatible with urticarial vasculitis (UV). Computerized tomography of the chest was performed, together with an echocardiogram, which were both normal.

- Once the diagnosis of normocomplementemic UV (NUV) had been established we considered whether the cutaneous symptoms were toxicoderma from the new immunosuppressants (Janus kinase inhibitor) or some other autoimmune process associated with the patient's rheumatoid arthritis. We ruled out the first option because the patient had been treated with tofacitinib for months without complications and because although the treatment was temporarily suspended, the skin lesions persisted. Symptoms were not controlled, and we therefore considered treatment with omalizumab. Other therapeutic options were ruled out (colchicine, sulphone or cyclosporine) due to the patient's immunosuppression. Several published cases have reported on the use of omalizumab in UV[1–5] aside from specification sheet usage. The article by De Brito et al.[3] reviewed cases published until 2018 in patients with UV and comparing the efficacy of omalizumab, observed that the NUV responded better to omalizumab than the hypocomplementemics (HUV). This led them to believe that there could be 2 diseases with different physio pathological mechanisms. In NUV the IgE and mastocytary cells would play a more important role whilst the endothelial damage from immunocomplex deposits would be more involved in the HUV, which would therefore not respond so well to omalizumab.

The case was presented and approved by the committee of special hospital uses and the patient signed an informed consent form. Treatment was initiated with omalizumab at a dose of 300 mg/every 4 weeks, maintaining the antihistamines for several weeks and withdrawing the glucocorticoids. The skin lesions disappeared after the first administration of therapy. The patient has to date received 6 cycles of omalizumab at a dose of 300 mg/every 4 weeks and continues to be asymptomatic.

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Both the acute phase reactants and the D-dimer reached normal levels. It was possible to withdraw the glucocorticoids maintaining just 5 mg/day (arthritis control). Treatment with tofacitinib was re-started 2 weeks after treatment with omalizumab, without incident. On re-initiation of methotrexate the patient presented with an episode of transaminitis which was resolved on dose reduction. No interactions or infections occurred during combined treatment.

This is the first case to be described in the literature of a patient with rheumatoid arthritis and NUV, both autoimmune diseases with difficult management. The patient presented with an extremely rapid and effective response to omalizumab with total disappearance of the skin lesions.

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Exposure to belimumab in the first trimester of pregnancy in a young woman with systemic lupus erythematosus

Exposición a belimumab en el primer trimestre de embarazo en una mujer joven con lupus eritematoso sistémico

Sr. Editor:

Mister editor, belimumab is a fully human IgG1-λ monoclonal antibody that binds to soluble human B-cell survival factor (known as BLyS or BAFF) and inhibits its biological activity.[1] Belimumab was approved for treatment of systemic lupus erythematosus (SLE) because it showed superiority to the standard of care, excluding patients with active nephritis or central nervous system disease.[1,2] Here, we report a case of a SLE patient that was incidentally exposed to belimumab during the first trimester of pregnancy.

A 27-year-old Caucasian female with SLE has been followed for this disease for 10 years. She began with arthritis in her hands, malar rash, oral ulcers, and serositis. Her immunology laboratory had ANA 1/1280, homogenous nuclear pattern, positive anti-dsDNA, positive anti Ro and positive lupus anticoagulant, as well as low C3 and C4 complement levels. She followed treatments with corticosteroids, hydroxychloroquine and methotrexate, with a good initial response, but effectiveness decreased over time. She started to be refractory concerning serositis, arthritis, oral ulcers and skin abnormalities related to these medications, and never had lupus nephritis or neurological compromise. Treatment with belimumab began two years before pregnancy. During this time the disease was successfully controlled, with 0 SLEDAI (SLE Disease Activity Index) points and without adverse events.

She discontinued coming to medical controls; and during this time she got pregnant. When controls were resumed, at week twelve of pregnancy, belimumab was stopped. Her pregnancy was

Table 1
Cumulative pregnancy outcomes for belimumab from clinical trials, spontaneous reports, post-marketing surveillance reports, and the Belimumab Pregnancy Registry (BPR) through 08 March 2016.[7]

Outcomes	Non-BPR[a]	BPR	Total pregnancies
Total pregnancies	275	24	299
Lost to follow up or unknown	45	1	46
Pregnancy ongoing	36	2	38
Total pregnancies with known outcomes	194	21	215
Elective termination with no apparent congenital anomaly	55	1	56
Elective termination with congenital anomaly	0	0	0
Total pregnancies with known outcomes excluding elective terminations	139	20	159
Spontaneous abortion with no apparent congenital anomaly (<22wks)	47	3	50
Spontaneous abortion with apparent congenital anomaly (<22wks)	2	0	2
Still birth with no apparent congenital anomaly (<22wks)	3	0	3
Spontaneous abortion + stillbirth/(total pregnancies with known outcomes excluding elective terminations)	52/139 (37.4%)	3/20 (15.0%)	55/159 (34.6%)
Total live births (infants)	85	17	102
Live births with no apparent congenital anomaly	81	13	94
Live births with apparent congenital anomaly[b]	4/85 (4.7%)	4/17 (23.5%)	8/102 (7.8%)

[a] Non-BPR includes clinical trial outcomes, spontaneous pregnancy reports, and post-marketing surveillance reports outside of the Belimumab Pregnancy Registry.
[b] This does not include pregnancies yet to deliver.