in the literature on the use of imiquimod in EMPD, found complete remission of the disease in 21 of the 27 reported cases (78%). The factors that influence the success or failure of imiquimod therapy in this setting have not yet been clearly established. Factors that might explain the variability of response to treatment include the size of the lesion, its variable thickness in different areas, and the presence of extensive adnexal involvement.

We agree with Hiraldo-Gamero that the small number of published cases makes it difficult to draw conclusions concerning the efficacy and safety of 5% imiquimod cream in selected cases of EMPD. Our report provides additional evidence on the medium-term safety of this treatment and represents the longest follow-up period free of disease reported in the dermatologic literature.

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P. Herranz, E. Sendagorta,* M. Feito, C. Gómez-Fernandez

Servicio de Dermatología, Hospital Universitario La Paz, Madrid, Spain

*Corresponding author.
E-mail address: elenasendagorta@hotmail.com (E. Sendagorta).

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Exacerbation of Atopic Dermatitis in a Patient Treated With Infliximab☆

Exacerbación de dermatitis atópica en paciente tratado con infliximab

To the Editor:

Biologic agents are now being used to treat chronic inflammatory diseases, mainly those of rheumatic, dermatologic, or gastrointestinal origin. This development has led to a reassessment of the diagnosis and therapeutic management of their associated adverse effects, which can include relapses of certain pre-existing diseases that a patient may have; although these relapses have been successfully treated in some cases, they have been difficult to control in others.[1] We present the case of a patient with infliximab-treated ulcerative colitis who developed a relapse of atopic dermatitis, and we review the cases reported in the literature.

The patient was a 30-year-old man with a past history of ulcerative colitis on treatment with infliximab; the disease had been refractory to treatment with mesalazine and azathioprine. After the fifth infusion he developed widespread, intensely pruritic eczema that did not respond to topical corticosteroids or oral antihistamines.

The patient had a history of atopic dermatitis (AD) since childhood, but denied rhinitis or extrinsic asthma. The AD lesions had always developed in flexures (cubital and popliteal fossae) and had responded to corticosteroids and topical calcineurin inhibitors, without requiring systemic treatment or phototherapy.

On physical examination, erythema and fine desquamation were observed on the face, trunk, and in the limb flexures; almost 50% of the body surface area was affected (Fig. 1). There were no alterations of vital signs and respiratory function was not affected.

Additional tests did not reveal eosinophilia or elevation of immunoglobulin (Ig) E or acute phase reactants (C-reactive protein, erythrocyte sedimentation rate). Moderate spongiosis and a predominantly lymphocytic perivascular infiltrate were observed on histology. The absence of necrotic keratinocytes, the minimal damage to the basal layer, and the deep lymphocytic infiltrate with no eosinophils, together with the clinical manifestations, were more suggestive of a relapse of his AD than of a toxic dermatitis.

As a precaution it was decided to interrupt treatment with infliximab and start prednisone 0.5 mg/kg/d in a slowly tapering regimen. Control of the skin condition was achieved in 3 weeks (Fig. 2).

The etiology and pathogenesis of AD is characterized by an acute phase with an inflammatory pattern involving type 2 helper T (T_H2) cells (often with elevated IgE levels and eosinophil counts), and a chronic phase with a T_H1 inflammatory pattern. It is therefore to be expected that the anti-tumor necrosis factor (TNF) agents used in psoriasis would improve the chronic forms of AD but that there would be no clear response in the acute phase.[3]

In the chronic phase of AD there is elevation of serum TNF-α, which is released initially by mast cells and subsequently by the T_H lymphocytes and keratinocytes. The release of the cytokine further stimulates the inflammatory

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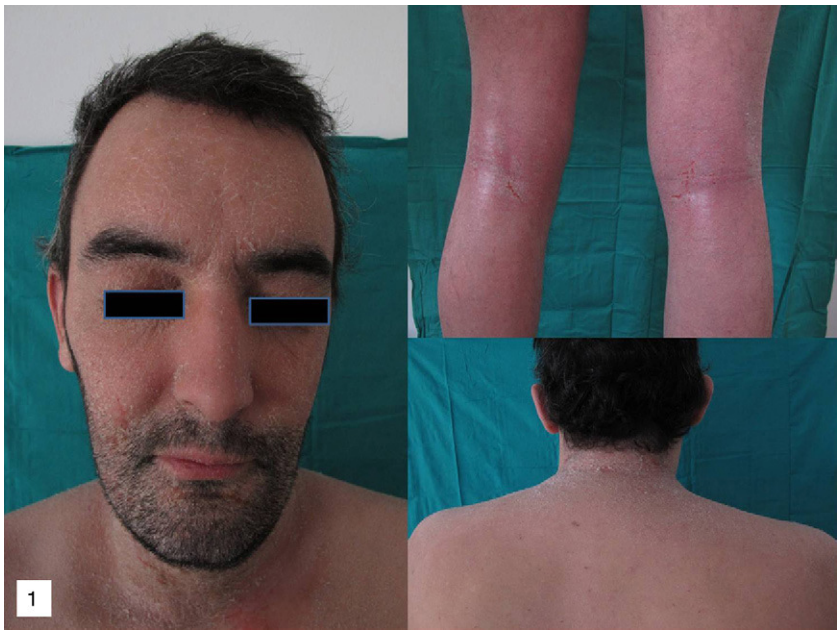

Figure 1 Relapse of atopic dermatitis. State of the patient after the fifth infusion of infliximab.

cascade, leading to higher levels of interleukins 1, 6, and 8, intercellular adhesion molecule 1, and vascular cell adhesion molecule. The clinical and pathological progression of a T_H2 inflammatory pattern to a T_H1 pattern could explain the successful response to therapy in some series of atopic patients.[2] However, it would appear likely that additional, unidentified etiological and pathogenic factors are involved as, in the majority of reported cases, the response is limited to the induction phase.[3]

In our review of the literature we were interested to find 7 well-documented cases of relapses of AD or AD-like disease precipitated by infliximab.[4–7] It is possible that more have not been reported because some relapses of AD may have been categorized as nonspe-

Table 1 Patient and Clinical Characteristics and Course of Relapses of Atopic Dermatitis Precipitated by Infliximab.

	Age, y	Sex	Underlying Disease	History of Atopy	Dosage	Timing of the Relapse of AD	Management
1 (Wright RC[4])	83	Male	Psoriasis	+	5 mg/kg/d	1st infusion	IFX continued. AD controlled with topical therapy
2 (Wright RC[4])	68	Female	Rheumatoid arthritis	+/-	5 mg/kg/d	Not specified	IFX continued. AD controlled with topical therapy
3 (Vestergaard C et al.[5])	46	Male	Suberythrodermic psoriasis + psoriatic arthropathy	+	5 mg/kg/d	7th infusion	IFX discontinued. AD controlled with ciclosporin
4 (Vestergaard C et al.[5])	68	Male	Pustular psoriasis	+	5 mg/kg/d	8th infusion	IFX discontinued. AD controlled with ciclosporin
5 (Chan JL et al.[6])	45	Male	Psoriasis	+	3 mg/kg/d	2nd infusion	IFX continued. AD controlled with topical therapy
6 (Chan JL et al.[6])	62	Female	Rheumatoid arthritis	+	5 mg/kg/d	7th infusion	IFX continued. AD controlled with topical therapy
7 (Chan JL et al.[6])	15	Male	Crohn disease	+	5 mg/kg/d	3rd infusion	IFX discontinued. AD controlled with topical therapy
8 (Ruiz-Villaverde et al.)	30	Male	Ulcerative colitis	+	5 mg/kg/d	5th infusion	IFX discontinued. AD controlled with oral + topical corticosteroids

Abbreviations: AD: atopic dermatitis; IFX, infliximab.

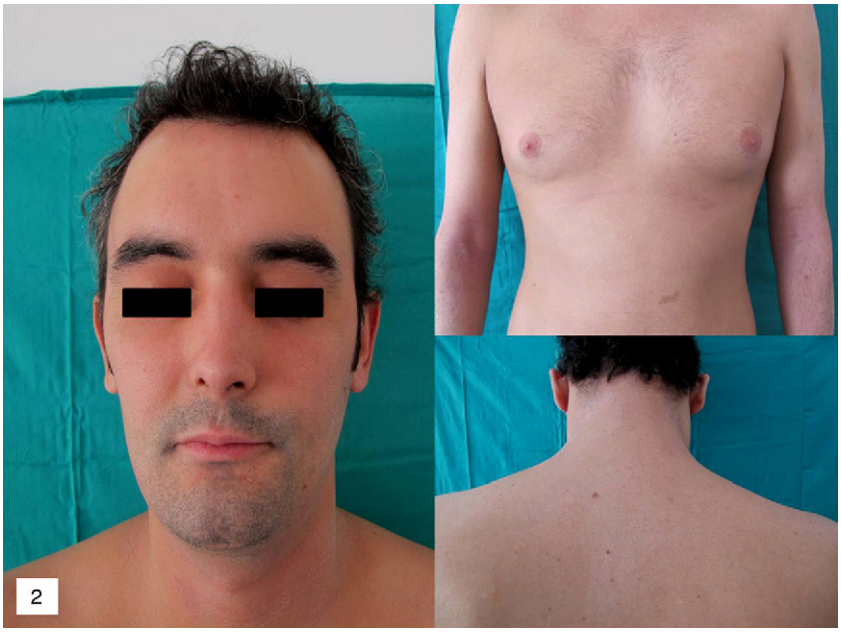

Figure 2 Clinical improvement of our patient after 3 weeks of treatment with oral corticosteroids.

cific eczema (AD has been considered to be a predictive factor for the appearance of eczema-like conditions in patients with psoriasis who receive infliximab),[8] because it is an underdiagnosed adverse effect, or because few cases have required aggressive treatment.[8,9] The details of the cases we found and the case we report are summarized in Table 1.

Almost all patients in the previously published cases had a history of AD and they only differed in the underlying disease for which infliximab had been prescribed. There is no clear pattern that defines the moment at which these reactions may develop, although all occurred within the first 2 years of treatment in these cases. Our patient required systemic treatment and we believe it is important to highlight that, despite the extent of his AD, the changes in laboratory findings in previous reports did not develop in our patient.

Although our understanding of biologic therapies and the etiologic and pathogenic factors of AD increases daily, we are still unable to predict the onset of this type of adverse effect, which is surprising from a pathophysiological point of view. We hope that our presentation of this case will draw attention to the need to take a meticulous dermatology history in patients with AD who are candidates for biologic therapy, particularly in patients with rheumatic diseases or inflammatory bowel disease.

Ethical Responsibilities

Protection of persons and animals: The authors declare that the procedures followed adhere to the ethical guidelines of the responsible committee on human experimentation and comply with the Declaration of Helsinki of the World Medical Association. Data confidentiality: The authors declare that they have followed their hospital's protocol on the publication of data concerning patients and that all patients included in the study have received sufficient information and have given their written informed consent to participate in the study. Right to privacy and informed consent: The authors obtained informed consent from the patients and/or subjects referred to in this article. This document is held by the corresponding author.

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R. Ruiz-Villaverde,* M. Galán-Gutierrez

Unidad de Dermatología, Complejo Hospitalario de Jaén, Jaén, Spain

*Corresponding author.
E-mail address: ismenios@hotmail.com
(R. Ruiz-Villaverde).

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Cutaneous B-cell Lymphoma: The Importance of Clinicopathologic Correlation☆

Linfoma de células B cutáneo: relevancia de la correlación clínico-patológica

To the Editor:

Primary cutaneous follicle center lymphoma (FLC) is defined as a malignant proliferation of germinal center cells confined to the skin. It has 3 growth patterns: follicular, diffuse, and mixed. It usually presents clinically as erythematous papules, plaques, and tumors, generally without ulceration, that most often affect the head, the neck, and the trunk. There is, however, a less common variant known as reticulohistiocytoma of the back or Crosti lymphoma that affects the back and consists of plaques and tumors surrounded by macules and papules that extend outward from the tumor.[1]

We present a case with histologic findings that posed a diagnostic challenge and clinical features that were consistent with Crosti lymphoma. The patient was a 53-year-old man who consulted for a back lesion that had grown progressively over the previous 6 years. A previous biopsy performed at another center had shown an infiltrate composed of atypical lymphocytes with positivity for T-cell markers and abundant $CD30^+$ cells. The suspected diagnosis was mycosis fungoides with $CD30^+$ cells. No additional immunohistochemical information was available. A staging study consisting of computed tomography (CT) of the chest and abdomen and routine blood tests was normal.

Physical examination revealed several tumors and plaques surrounded by erythematous macules in the lumbar region and on the left flank (Fig. 1). There were no signs of organomegaly or lymph node enlargement.

A biopsy performed at our center showed a nodular lymphoid proliferation with a tendency to coalesce extending throughout the dermis and into the hypodermis, with no evidence of epidermotropism (Fig. 2). The lesion was composed of medium and large B cells that were positive for CD20 and CD79 and negative for CD3, CD10, CD23, and CD43; there were also, however, abundant $CD3^+$, $CD5^+$, and $CD7^+$ T cells (Fig. 3). Immunostaining was positive for bcl-6 in the large cells and in some of the smaller cells. There was also bcl-2 positivity, but this was difficult to interpret due to the presence of large number of T cells. The cells were negative for CD30, contrasting with the results from the previous biopsy. Approximately 15% of the cells were positive for Ki67. Immunogenotyping revealed clonal rearrangement of immunoglobulin heavy locus (*IHG*) genes and a lack of T-cell receptor gene (*TCR*) rearrangement.

On the basis of these findings, we ordered a staging study consisting of general blood tests (including analysis of lactic acid dehydrogenase and β-2 microglobulin levels), a chest and abdomen CT scan, and a bone marrow biopsy. The results were all normal.

The main entity considered in the differential diagnosis was marginal zone B-cell lymphoma which, unlike cutaneous FCL, tends to be bcl-6-negative. We also considered diffuse large B-cell lymphoma, leg-type, but this is characterized by a diffuse monomorphous infiltrate with large numbers of large $bcl\text{-}2^+$ and $MUM\text{-}1^+$ cells. Because of the large number of T cells observed, we also initially considered mycosis fungoides and pseudolymphoma, but ruled these out on the basis of the clinical presentation, the type of infiltrate, the presence of *IGH* clonal rearrangement, and the lack of *TCR* clonal rearrangement[2] (although it should be noted that *TCR*

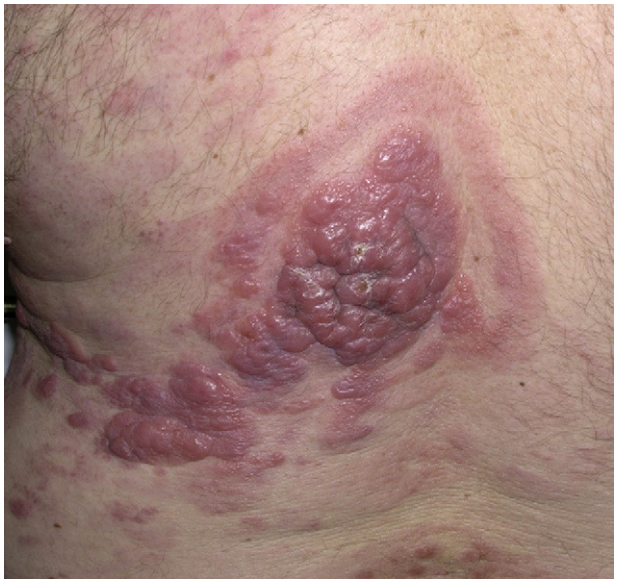

Figure 1 Several tumors and plaques surrounded by erythematous macules in the lumbar region and on the left flank.

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