Erythema multiforme after initiation of anti interleukin-12/23 (ustekinumab) treatment for plaque psoriasis

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INTRODUCTION
Psoriasis is a chronic, immune-mediated, inflammatory disease characterized by the presence of indurated erythematous plaques covered by silvery desquamative scales, usually involving knees, elbows, trunk and scalp. Therapeutic options include topical treatments, phototherapy, traditional systemic agents and novel biologic agents. The biologic drug ustekinumab is a fully human monoclonal antibody targeting the pro-inflammatory cytokines interleukin (IL)-12 and IL-23 approved for the treatment of psoriasis and psoriatic arthritis. We report a case of a patient treated with ustekinumab for chronic plaque psoriasis who went on to have erythema multiforme (EM). EM has been reported in connection with tumor necrosis factor α inhibitors, including etanercept, infliximab, and adalimumab. To our knowledge, this is the first case in medical literature reporting EM occurring subsequently to ustekinumab treatment for psoriasis.

CASE REPORT
A 44 year-old white woman with a history of plaque psoriasis since 2014 had several round, concentric, erythematous lesions with targetoid appearance distributed at the extensor surface of her arms and the trunk 4 days after the first administration of a 90-mg dose of ustekinumab (Fig 1).

The patient was treated previously with topical agents and cycles of narrowband ultraviolet B phototherapy, without significant benefit. Cyclical treatment with cyclosporine at 2.5 mg/kg/d was administered for 2 years with an improvement in her psoriasis; however, an increase in serum creatinine made the treatment unsustainable in the long term. Among biologics, ustekinumab was chosen for its favorable administration regimen, as the patient expressed her preference for a treatment characterized by as few injections as possible. The patient’s medical history was remarkable only for obesity (body mass index, 42.52), hypothyroidism, and depressive disorder for which she was taking levothyroxine, 100 mg/d, and venlafaxine, 75 mg/d.

The patient’s skin reaction was clinically consistent with EM. To confirm the diagnosis, blood tests and a skin biopsy were performed. Serology for herpes simplex virus (HSV) IgM was negative, whereas high HSV-1 and varicella zoster virus IgG titers were found.

The histopathologic examination reported the presence of vacuolated basal epidermal cells with some necrotic keratinocytes and a mixed dermal infiltrate composed of lymphocytes, eosinophils, and neutrophils (Fig 2). Perilesional direct and indirect immunofluorescence were negative. The Naranjo scale was assessed with a score of 6 (probable association).

These findings confirmed the diagnosis of EM so her ustekinumab treatment was discontinued.
short taper of prednisolone was administered, which led to a complete resolution of the eruption. The patient is currently receiving a new course of cyclosporine in anticipation of beginning treatment with a different biologic agent.

**DISCUSSION**

EM is an acute, immune-mediated reaction characterized by the presence of typical targetoid lesions constituted by papules and vesicles with concentric color variation and potential mucosal involvement.

Numerous factors have been linked to the development of EM, including infections (responsible for 90% of the cases) and medication use. The most frequent infectious agent involved is HSV. Drugs are responsible for less than 10% of cases, and the most implicated ones are nonsteroidal anti-inflammatory drugs, sulfonamides, antiepileptics, and antibiotics. In the medical literature, the development of EM has been described in association with a specific class of biologic agents, the tumor necrosis factor α inhibitors such as infliximab, etanercept, and adalimumab.

Ustekinumab is a fully human monoclonal antibody targeting the p40 subunit shared by IL-12 and IL-23, shown to exert its therapeutic effects in psoriatic disease via the IL-23 cascade. The most frequent adverse events of ustekinumab treatment are upper respiratory tract infections, dizziness, back pain, myalgia, injection site erythema, ecchymosis, diarrhea, and pharyngolaryngeal pain. Rare serious adverse events reported in literature include major adverse cardiovascular events, such as cardiovascular death, myocardial infarction, or stroke. To our knowledge, EM has never been reported before in association with ustekinumab treatment for psoriasis; therefore, it should be included among those biologic agents that may elicit this condition.

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