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Golimumab-associated persistent erythema multiforme in a patient with ulcerative colitis in full remission

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Abstract

Erythema multiforme is an immune-mediated cutaneous disorder that is thought to represent a hypersensitivity reaction to infections, drugs, vaccines, malignancies, autoimmune diseases, radiation, and menstruation. Golimumab is a human IgG1-kappa anti-TNF antibody that has been approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis. We report herein a 41-year-old woman with persistent erythema multiforme, that occurred 18 months after onset of golimumab treatment of her ulcerative colitis; the latter remains in full remission over a period of 36 months.

Keywords: erythema multiforme, golimumab, anti-TNF-alpha, ulcerative colitis

Introduction

Erythema multiforme (EM) is an immune-mediated cutaneous disorder, clinically characterized by targetoid lesions symmetrically distributed on the extremities with a lack of or minor mucosal involvement (minor form) or significantly affecting one or more mucous membranes (major form), [1]. It is usually acute and self-limited but recurrent and chronic persistent clinical types have also been described [2].

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by gastrointestinal and

potentially systemic manifestations and complications that has a devastating impact on the **patients' quality of life** [3]. **Golimumab is a human IgG1-kappa anti-TNF antibody**, produced in multiple glycoforms by a murine hybridoma line, that is FDA-approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis [4].

Case Synopsis

A 41-year-old HIV-negative woman presented with a 23-year-history of histologically confirmed ulcerative colitis, which was unsuccessfully treated with sulfasalazine and corticosteroids over a period of 20 years. Owing to her poor therapeutic response to the conventional therapy, three years prior to presentation systemic treatment with the anti-TNF biologic agent golimumab was initiated and led to a rapid and complete remission of her disorder and to normalization of her quality of life.

After 18 months of successful treatment with golimumab the patient developed non-pruritic skin lesions that affected her extremities. She was initially treated by her gastroenterologist with topical and systemic antibiotics with no response. Clinical examination revealed targetoid papules and plaques located on her knees, wrists, and fingers of both hands. The palms, soles, trunk, and mucosae were spared. The new onset lesions had a diameter of 1-2 cm and a typical targetoid appearance: a central dark

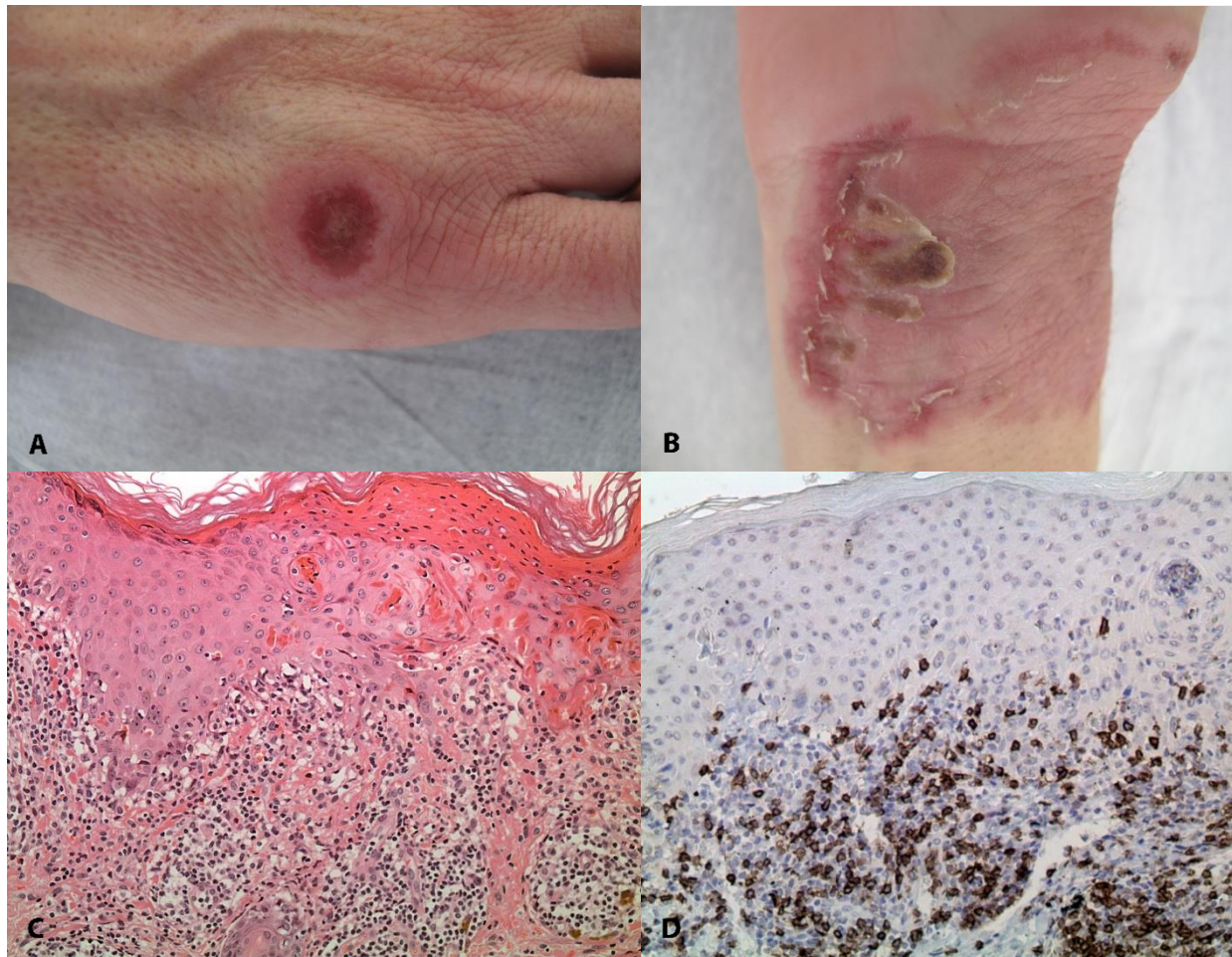


Figure 1. *Clinical images and histology. A) Typical targetoid lesion on the right hand of the patient. B) Atypical annular lesion on the right wrist of the patient, characterized by a pink central zone and a raised erythematous border with sparse necrotic areas covered by scabs. C) Histological examination of skin biopsy obtained from an older lesion shows a dense dermal lymphocytic infiltration along the dermoepidermal junction, vacuolar changes and dyskeratosis of basal epidermal cells. H&E, × 40. D) Immunohistochemistry reveals CD8+ T-lymphocytes in the dermal infiltrate and in the epidermis, × 40.*

red zone that in some cases was necrotic, an intermediate pink and edematous zone with external erythema (Figure 1A). The older lesions were larger (up to 5cm in diameter) and had an arcuate or annular configuration with a pink central zone and raised erythematous border, which focally exhibited small necrotic areas covered by crusts (Figure 1B). There was no evidence of lymphadenopathy or hepatosplenomegaly. Clinical examination of the extracutaneous organs failed to reveal any findings of active infection.

The patient's medical history was otherwise unremarkable. She had not consumed or been exposed to aspirin, acetaminophen, sulfonamides, antibiotics, or any other drugs including over the counter medications, herbal preparations, contactants, or benzoic acid. Moreover, she had no

signs of active infection prior to the occurrence of the skin lesions.

Routinely performed hematological and biochemical tests revealed normal or negative results. Culture of an exudative lesion was negative for common bacteria, mycobacteria, and fungi. Serological investigations for herpes simplex and zoster virus, Epstein-Barr virus, cytomegalovirus, coxsackie A & B, enterovirus, HIV 1 & 2, *Mycoplasma pneumoniae*, *Toxoplasma gondii* and for hepatitis B & C were negative.

As the clinical features of the new onset lesions were typical for EM, skin biopsy was obtained from a larger older lesion. Histopathologic examination revealed a vacuolar interface dermatitis with a dense, mainly lymphocytic, infiltrate with a small number of

eosinophils. Epidermal basal cells exhibited hydropic changes, whereas dyskeratosis (apoptosis) in small groups or individual epithelial cells was observed (Figure 1C). Immunohistochemical staining showed a T cell-rich lichenoid dermal infiltrate, with CD4/CD8 ratio 60/40 and CD8 T cell predominance in the epidermis (Figure 1D). Based on the clinical, histological, and histopathological findings the diagnosis of erythema multiforme (minor form) was established.

The patient had been pleased on golimumab because she was finally able to enjoy a normal life. She vehemently refused either the discontinuation of golimumab or the systemic administration of corticosteroids, as we suggested, fearing that this could endanger her health and quality of life. However, she agreed to receive topical corticosteroids, which led to a slight improvement of her eruption.

Case Discussion

Although the pathogenetic mechanisms of EM are far from being clearly understood, it is believed that this disorder represents a hypersensitivity reaction to infections, drugs, vaccines, malignancies, autoimmune diseases, radiation, and menstruation (Box 1), [1, 2, 5, 6].

The patient reported here suffered from the relatively rare clinical variant of persistent EM, which is characterized by the continuous occurrence of typical (targetoid) and atypical (papulonecrotic, bullous and/or widespread) lesions, without interruption. In the small number of published case reports this variant has been associated with viral infections, inflammatory bowel disease, and neoplasms [7], but surprisingly not with drugs. This might relate to the fact that the administration of the suspected drug was immediately discontinued upon appearance of the eruption. This did not happen in our case since EM was diagnosed 18 months after the onset of the latter.

EM has been often reported in patients with UC and in most cases it was related to administered drugs (mainly sulfonamides) for its treatment. However,

sporadic cases of untreated UC associated with EM have also been described and UC is regarded as an independent triggering factor of EM [8, 9]. The possibility that UC could be the causative factor of EM in our patient cannot be definitely ruled-out but it is very unlikely since she was suffering from recalcitrant inflammatory bowel disease for many years without revealing any signs of skin disease. Moreover, UC was in complete remission when the eruption initially appeared, and remained in remission during the next 18 months, whereas the EM was constantly present without interruption.

TNF is a proinflammatory cytokine known to play a pivotal role in the initial host response to infection, the regulation of systemic inflammation, and the pathogenesis of various immune-mediated diseases. Its inhibitors are monoclonal antibodies or fusion proteins specifically designed to block the biologic effects of TNF. Serious cutaneous adverse reactions have been reported during therapy with TNF inhibitors adalimumab, etanercept, and infliximab including EM and Stevens-Johnson syndrome [4, 10-14]. The occurrence of EM in patients treated with diverse TNF inhibitors suggests that EM is a cutaneous side-effect of this class of biologic agents [15].

It is well known that there is presently no test that could reliably prove the causal relationship between EM and a certain drug. Algorithms or probability scales using questionnaires have been developed in order to standardize and improve the assessment of causality of adverse drug reactions in diverse conditions. However, since at least some of the answers to the posed questions depend on clinical judgement and may also be affected by ethical issues **and the patient's right to participate in the** clinical decision process, the quantitative assessment of causality using these algorithms cannot be accurate. For instance, in the algorithm of Naranjo et al. in 1981 [16] different point values (-1, 0, +1 or +2) are given to each answer and the total numerical score corresponds to a certain level of causality. Using this algorithm, the probability of EM being attributable to golimumab in our case is categorized as **"possible," which is rather expected since it is the first** reported case (point value=0), the patient refused

Box 1. Causes of erythema multiforme.

- Infections
 - Common: herpes simplex virus 1 & 2, Mycoplasma pneumoniae
 - Rare: Diverse bacterial, mycobacterial, viral, fungal and parasitic infections
- Drugs
 - Common: sulfonamides, anticonvulsants, antibiotics, antituberculous agents, non-steroidal anti-inflammatory drugs
 - Rare: Reported cases with numerous drugs, causative relation not always confirmed
- Vaccines
 - BCG, diphtheritis-pertussis-tetanus, measles-mumps-rubella, hepatitis B, meningitis, smallpox, human papillomavirus, pneumococcal
- Contactants
 - Nickel, rubber, ammoniated mercury, capsicum, DNCB, disperse blue 124, fire sponge, herbal medicines, poison ivy, resin, rosewood
- Flavorings and preservatives
 - benzoic acid, cinnamon
- Immunologic disorders
 - Inflammatory bowel disease, collagen diseases, vasculitis, sarcoidosis, transient selective C4 deficiency of infancy
- Physical or mechanical factors
 - tattooing, radiotherapy, cold, sunlight
- Foods
 - salmon berries, margarine
- Malignancies
 - Rare: haematologic malignancies
 - Very rare: solid organ malignancies
- Hormonal disorders
 - Menstruation
- Idiopathic (no causative factor identified)

the discontinuation (point value=0) or re-administration of the drug (point value=0), and the dosage was constant (point value=0).

In our patient EM occurred 18 months after the initiation of treatment with golimumab and remains continuously present with no interruption, in spite of the excellent control of UC. These findings taken together with the absence of any other precipitating factors strongly suggest that golimumab is the causative factor of EM in our patient. To the best of our knowledge, this is the first reported case of golimumab-associated EM and additionally the first one of drug-associated persistent EM.

Conclusion

EM is an immune-mediated cutaneous disorder that is believed to represent a hypersensitivity reaction to

infections, drugs, vaccines, malignancies, autoimmune diseases, radiation, and menstruation. It has previously been reported in patients with untreated UC and during treatment with TNF inhibitors (adalimumab, etanercept, and infliximab). In the patient presented herein, EM occurred 18 months after the initiation of treatment with golimumab and remains continuously present until present with no interruption, in spite of the excellent control of UC. These findings taken together with the absence of any other precipitating factors strongly suggest that golimumab is the causative factor of erythema multiforme in our patient. To the best of our knowledge, this is the first reported case of golimumab-associated EM and additionally the first one of drug-associated persistent EM.

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