Dermatology Practical & Conceptual

Eosinophilic Annular Erythema due to Certolizumab Pegol Therapy for Rheumatoid Arthritis Post-COVID-19 Vaccine

Andrea Bassi[1], Vincenzo Piccolo[2], Alessandro Ginori[3], Grazia Galippi[3], Carlo Mazzatenta[1]

1 Division of Dermatology, Azienda USL Toscana Nord Ovest, Lucca, Italy
2 Dermatology Unit, University of Campania Luigi Vanvitelli, Naples, Italy
3 Pathology Unit, "Monterosso Polyspecialistic Center", Azienda USL Toscana Nord Ovest, Lucca, Italy

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Corresponding Author: Andrea Bassi, MD, Division of Dermatology, Azienda Toscana Nord Ovest, Lucca, Italy. Tel: +393389340371 Email: bassiderma@gmail.com

Introduction

Certolizumab pegol (CP) is a PEGylated, humanized antibody which binds to and neutralizes TNF-α, a key pro-inflammatory cytokine that plays a central role in inflammatory processes in immune-mediated inflammatory diseases. It is usually well-tolerated and rarely reported as a cause of skin reactions, except for the paradoxical worsening of psoriasis during treatment [1,2];

Here we report a unique case of possible drug-induced diffuse eosinophilic annular erythema.

Case Presentation

A 22-year-old girl presented to our dermatologic department with a diffuse itchy dermatitis involving the trunk, arms and legs. Medical history revealed that after the first dose of BNT162b2 mRNA Covid-19 vaccine in January 2021 she developed persistent joint pain on the hands and knees for which she had a diagnosis of vaccine induced reactive arthritis and started therapy with courses of NSAIDs. In April, due to worsening of the arthritis, hydroxychloroquine and prednisone were added. In July, on the basis of the clinical features and serologic tests, she received a conclusive diagnosis of rheumatoid arthritis. Hence treatment with CP 200 mg/eow was added to therapy. Three weeks after, ie after the second dose of CP, the patient noticed the appearance of isolated, mildly itchy annular lesions on the upper arms and on the back, which were initially diagnosed as annular granuloma (Figure 1A) and treated with topical steroids.

At the end of October, the patient was referred to our department for the rapid worsening of the cutaneous lesions which spread on the trunk, arms and legs in association with increasing itch. On clinical examination we observed diffuse erythematous lesions with annular conformation, most of them with a polycyclic figurate aspect. The edge of

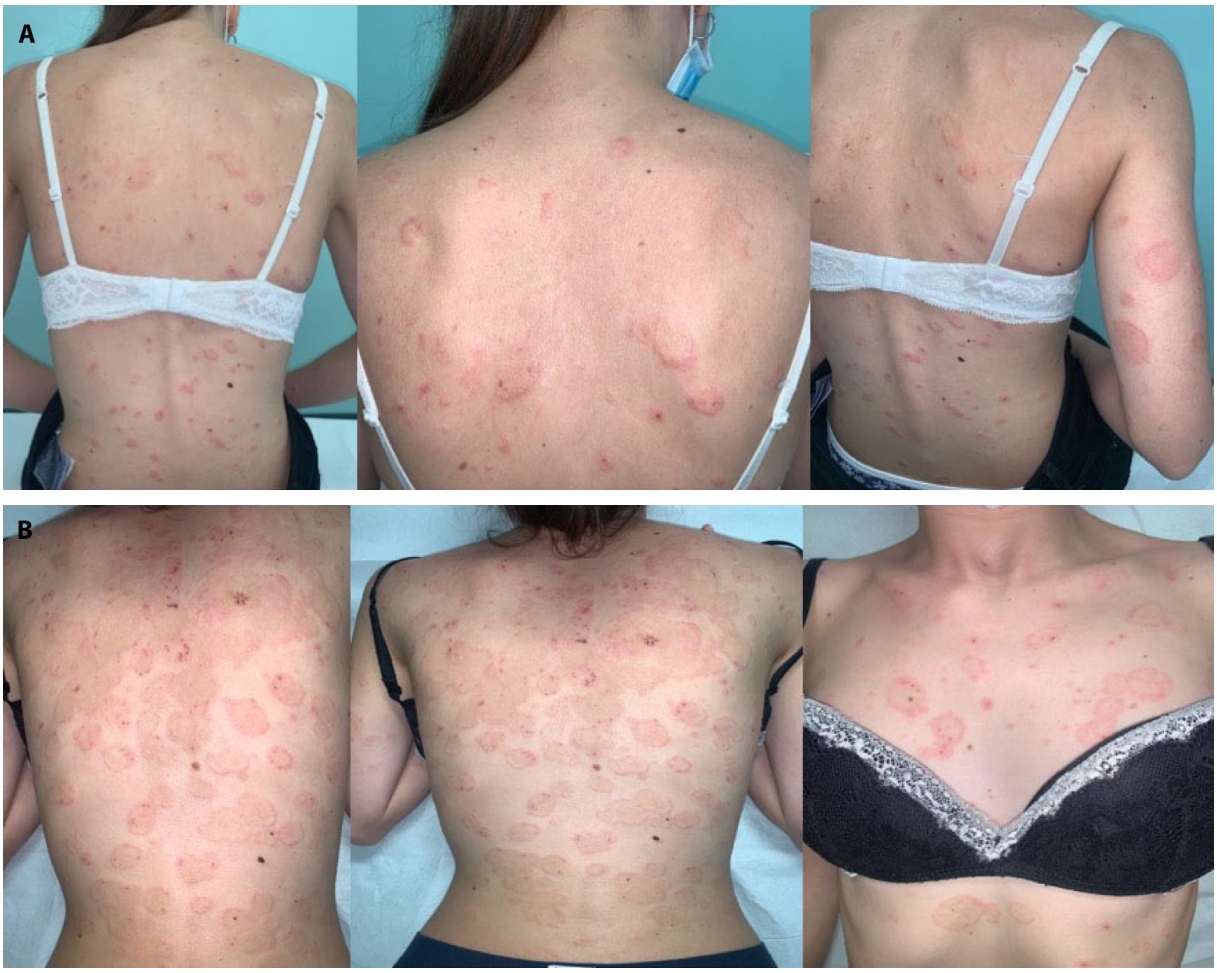

Figure 1. Clinical evolution of the skin lesions from September (A) to the end of October (B).

the lesions appeared slightly infiltrated with sparse vesicles and crusts (Figure 1B). The histologic skin sections showed spongiosis of the epidermis and intraepidermal vesicles. In the superficial and deep dermis, mostly in perivascular areas, there was a dense inflammatory infiltrate constituted by lymphocytes and eosinophils, with intraepidermal eosinophilic exocytosis. There were no mucin deposits in the dermis and the PAS stain to detect fungi was negative. A diagnosis of acute spongiotic dermatitis was made, suggesting a possible drugs etiology due to the clinical findings (Figure 2). Direct immunofluorescence was negative. Blood tests including Indirect Immunofluorescence and antitransglutaminase were negative. Based on clinical pathological correlations, according to Naranjo algorithm [3] we posed a diagnosis of a "possible" drug-induced eosinophilic annular erythema (EAE). Our diagnosis was supported by the improvement of the cutaneous rash and itchy sensation about three weeks after the discontinuation of certolizumab pegol while continuing therapy with hydroxychloroquine and prednisone.

EAE is a chronic, recurrent skin disease of an unknown etiology. It presents as erythematous, usually asymptomatic or mildly pruritic, annular papules and plaques on the trunk and extremities. Annular papules often coalesce into palpable erythematous arches or rings. During resolution, transient pigment changes may be observed, but no atrophy or scarring occurs. It has a variable response to systemic steroids, antimalarial agents, or, as recently reported, to dupilumab [4]. Clinical differential diagnosis is with other figurate erythema such as: Wells syndrome, erythema chronicum migrans, erythema annulare centrifugum, erythema gyratum repens, annular granuloma, subacute cutaneous lupus erythematosus and dermatosis of the pemphigoid group [5,6]. Histologically, EAE is characterized by superficial and deep perivascular lymphocytic infiltrate with a prominent eosinophilic component.

Conclusions

In our case the strict temporal association between drug administration and appearance/disappearance of EAE indicate that this reaction should be added to the list of rare adverse events related to certolizumab pegol.

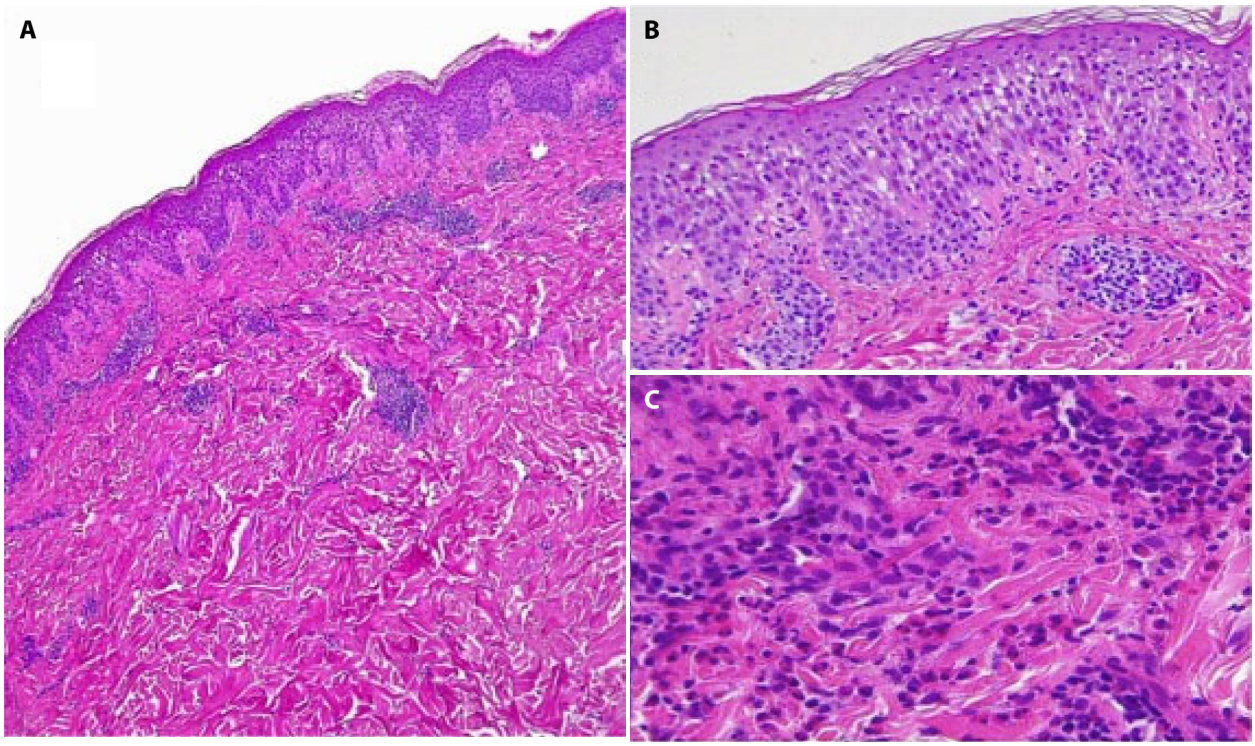

Figure 2. Cutaneous histology showed an inflammatory infiltrate in the superficial and deep dermis, mostly in perivascular areas (A), (40x, H&E stain); there was also spongiosis of the epidermis and the infiltrate was constituted by lymphocytes and eosinophils with eosinophilic exocytosis (B, 200x, H&E stain; C, 400x, H&E stain).

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