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Single Case

Tocilizumab-Induced Erythema Annulare Centrifugum

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Keywords
Tocilizumab · Erythema annulare centrifugum · Rheumatoid arthritis · Adverse drug reaction

Abstract
We report the case of a 42-year-old woman with rheumatoid arthritis undergoing treatment with subcutaneous tocilizumab for the past 6 months. Three days after the administration, an asymptomatic inflammatory annular plaque of 4 cm with discrete whitish scales at the inner border margin developed at the injection site in the left iliac fossa. A smaller plaque in the left groin appeared soon after. The mycological exam was negative. Histology showed a lymphoplasmacytic superficial and deep perivascular, and periadnexal, dermal infiltrate, without epidermal changes. Lesions spontaneously regressed in 4 months. The diagnosis was clinically and histologically consistent with erythema annulare centrifugum, following the exclusion of other differential diagnoses. Erythema annulare centrifugum represents a delayed-type hypersensitivity reaction generally considered idiopathic or otherwise related to numerous triggers, including drugs such as biologics. We describe the first reported case of tocilizumab-induced erythema annulare centrifugum. This case should alert dermatologists to this relatively rare and complex entity and should raise awareness to cutaneous biologic drug reactions.

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Introduction

Erythema annulare centrifugum (EAC) is a type of figurate erythema in which inflammatory, annular, erythematous papules, or plaques expand centrifugally, displaying central clearing. Lesions are mostly found on the hips and legs, naturally healing in variable timing (days to decades), albeit post-inflammatory hyperpigmentation might be observed. Two clinical variants are recognized – superficial and deep – with corresponding histopathological features. The former presents with a trailing scale, reflecting epidermal changes, while mid and lower dermis alterations occur in the latter, giving rise to non-scaly, more elevated, lesions [1, 2].

Pathogenesis remains incompletely understood. EAC has been suggested to represent a type IV or delayed-type hypersensitivity reaction, generally considered idiopathic or otherwise associated with cutaneous or systemic infection, malignancies, autoimmune diseases, and various drugs, including biologics [1, 2].

Case Report

A 42-year-old Caucasian female with a history of rheumatoid arthritis (RA) and under treatment with subcutaneous tocilizumab for 6 months, presented with a painless non-pruritic annular plaque in the left iliac fossa. The plaque had an individualized erythematous border, discrete whitish scales at its inner margin, and central clearing (Fig. 1). The lesion developed at the site of tocilizumab administration 3 days after an injection and progressively increased in size to reach 4 cm in diameter. One smaller lesion with similar features further appeared in the left groin (Fig. 1). A KOH test and fungal culture were negative, and skin biopsy revealed a lymphoplasmacytic superficial and deep perivascular, and periadnexal, dermal infiltrate, without epidermal changes (Fig. 2, 3). Tocilizumab was suspended, and lesions underwent spontaneous regression in approximately 4 months, currently exhibiting residual hyperpigmentation at a 21-month follow-up.

Previous RA treatment included monotherapy with oral methotrexate and sulfasalazine. Her past medical history was also significant for polycystic ovary syndrome and normocytic normochromic anemia related to RA. Her other regular medication included analgesic drugs as required. She denied any other extra-articular symptoms, and any recent traveling, or relevant environmental exposures.

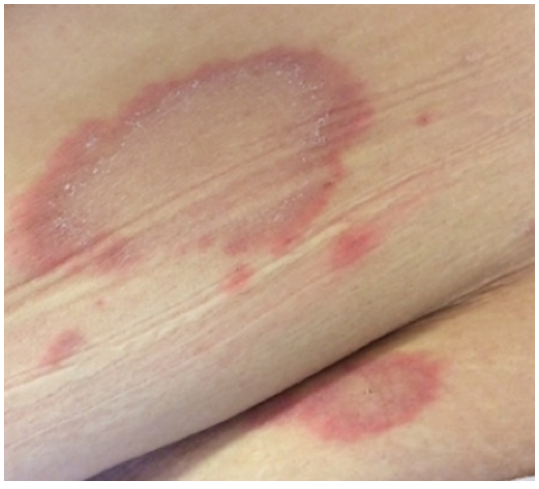

Fig. 1. Annular plaque with discrete whitish scales at the inner margin, located in the left iliac fossa. A smaller plaque is visible in the left groin.

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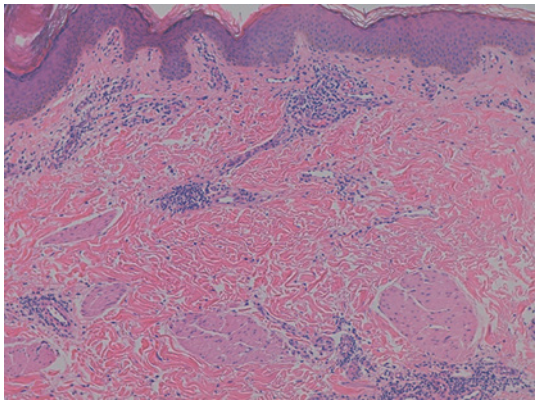

Fig. 2. Histopathological examination shows superficial and deep perivascular, and periadnexal, dermal infiltrate, without epidermal changes (H and E, ×100).

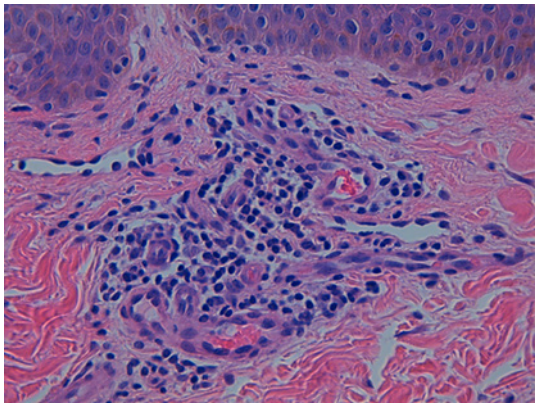

Fig. 3. Close-up of Fig. 2 showing perivascular lymphoplasmacytic infiltrate (H and E, ×400).

Discussion

The aforementioned clinical features imposed three main differential diagnoses. Negative fungal testing excluded a dermatophytosis [1]. Pityriasis rosea (PR) was considered, but its collarette scaling is often peripherally attached beyond the inner border and present in the center of the lesion [3]. PR inversa with isolated lesions could also be assumed [4], but we deemed such an association, a rarity. The PR variant pityriasis circinata et marginata of Vidal could therefore also be considered [5]. Concerning adverse drug reactions, a localized form of pityriasiform type of drug reaction could have been pondered. The timing of onset and subsequent resolution with drug withdrawal would favor this diagnosis, and there are reported cases of PR-like drug eruptions occurring with biologics [6, 7]. However, such reactions tend to be more diffuse and pruritic, with marked inflammation [5, 8]. In any case, histology rendered these and the other previous differentials less likely [1].

Clinicopathological correlation ultimately favored a diagnosis of EAC. In spite of observable desquamation, no corresponding epidermal changes were found on histology. This may merely be due to sampling. Furthermore, a perivascular infiltrate in both superficial and deep dermis would point toward a clinical picture more typical of the deep variant of EAC [2]. Possible explanations for such discordance could include the existence of a mixed pattern, with only 3 cases described in the literature [9], and sampling issues such as biopsy timing or location.

EAC has been described with the use of various drugs, including biologics [2]. Although a fortuitous association cannot be excluded, in the case described herein, tocilizumab would be the most likely trigger. Tocilizumab is a humanized anti-interleukin-6 receptor monoclonal antibody [10]. Interleukin-6 is a cytokine with predominant pro-inflammatory properties,

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playing an important role in the immune response, which underlines the rationale for its receptor inhibition in RA [11]. The fact that EAC occurred after tocilizumab subcutaneous administration might be in accordance with the believed underlying pathomechanisms. Langerhans cells are skin antigen-presenting immune cells that are involved in such hypersensitivity reactions [12], and one could expect their activation following the subcutaneous route.

Conclusion

To our knowledge, this is the first reported case of tocilizumab-induced EAC. EAC remains a diagnosis of exclusion, whose incidence and prevalence are undefined, with information being essentially based on case reports. Dermatologists should be aware of this relatively rare and still puzzling entity. This case specifically sparks further interest in understanding biologic-related cutaneous drug reactions and the complex pathophysiological interplay on their immune-driven origin.

Acknowledgments

Author Dr. André Lencastre was not available to confirm co-authorship, but the corresponding author Dr. Ana Luísa João affirms that author Dr. André Lencastre contributed to the study, had the opportunity to review the final version to be published, and guarantees author Dr. André Lencastre's co-authorship status and the accuracy of the author contribution and conflict of interest statements.

Statement of Ethics

Ethical approval is not required for this study in accordance with local guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Ana Luísa João contributed to data analysis and interpretation and drafting of the manuscript. Dr. Tomás Pessoa e Costa contributed to interpretation of data. Dr. Paulo Barreto contributed to interpretation of data and revision of the article. Dr. André Lencastre contributed to data analysis and interpretation and revision of the article.

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Data Availability Statement

All data that support the findings of this study are included in this article. Further inquiries can be directed to the corresponding author.

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