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CASES WITH A MESSAGE

Granuloma annulare development in a patient with rheumatoid arthritis treated with tocilizumab: case-based review

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Abstract

Granuloma annulare (GA) is the most common non-infectious disease. Despite the fact that it is a benign disease, it can be associated with a variety of disorders and certain drugs including biological disease-modifying anti-rheumatic drugs (bDMARDs). A 50-year-old man with a history of rheumatoid arthritis refractory to methotrexate, hydroxychloroquine and infliximab was treated with tocilizumab (TCZ), an interleukin-6 receptor antagonist, 162 mg subcutaneously every week. The patient responded very well to TCZ treatment with a decrease of acute phase reactants and reduction of disease activity score for 28-joints count. However, 3 months later he developed erythematous polycyclic eruptions affecting the lower extremities consistent with a diagnosis of GA which was confirmed by a skin biopsy. TCZ has been discontinued and the patient was treated with prednisone presenting complete resolution of skin manifestations after 4 weeks. This is the first case of GA development during TCZ treatment. Thus, we review the literature and discuss the relevant cases of GA development in patients treated with bDMARDs. When dealing with patients treated with these agents, all physicians should be aware of possible adverse events and the potential development of such complications.

Keywords Granuloma annulare · Rheumatoid arthritis · Interleukin-6 inhibitors · Tocilizumab

Introduction

In the last 2 decades, the use of biological disease-modifying anti-rheumatic drugs (bDMARDs) has revolutionized the treatment of rheumatoid arthritis (RA) and spondyloarthropathies (SpA) [1, 2]. Despite a good overall efficacy profile and acceptable toxicity profile they can induce a number of adverse events including autoimmune phenomena [3–6]. Various autoimmune disorders have been reported after bDMARD treatment, among them granuloma annulare (GA) development [7].

Because the use of bDMARDs is becoming more widespread, a greater understanding of possible side effects is being recognized. When dealing with patients treated with these agents all physicians should be aware of possible adverse events and the potential development of such complications. Thus, we describe here, for the first time, a patient with RA who developed GA skin lesions during administration of TCZ and discuss the relevant literature.

Case presentation

A 60-year-old man with a 3-year history of RA involving primarily the small joints of the hands and wrists bilaterally visited our rheumatology clinic for evaluation. He was refractory to methotrexate, hydroxychloroquine and infliximab. At this time, he was under treatment with leflunomide 20 mg/day and prednisone 5 mg/day. He did not report psoriatic skin lesions, mouth ulcers, Raynaud's phenomenon or uveitis.

Past medical and family history were unremarkable. He did not receive any medications for other pathological conditions except those for RA. Laboratory evaluation showed hemoglobin 9.8 g/dl with features of anemia of chronic disease (low serum iron and normal ferritin levels). The C-reactive protein (CRP) was 60 mg/l (normal values < 6 mg/l) and the erythrocyte sedimentation rate was

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72 mm/h. Serum IgM rheumatoid factor was 1/320 (latex fixation test), while anti-citrullinated peptide antibodies and antinuclear antibodies (ANA) were negative. Hand and wrist X-rays showed periarticular osteopenia and severe erosive changes involving the carpal bones, metacarpophalangeal and proximal interphalangeal joints bilaterally. The disease activity score for 28-joint count (DAS-28) was 6.8. TCZ 162 mg subcutaneously (SC) every week was added to his treatment scheme. He responded very well to TCZ treatment with decrease of CRP and ESR, increase of hemoglobin and a decrease of DAS-28 to 3.7. However, after 3 months he developed erythematous polycyclic skin eruptions covering his lower extremities (Fig. 1). The clinical diagnosis was compatible with generalized GA, which was confirmed with skin biopsy (Fig. 2). Owing to the extent of the skin lesions, TCZ was discontinued and the patient was treated with prednisolone (15 mg/day) with excellent results after 4 weeks of therapy. We searched the PubMed and EMBASE databases [8] using the words "granuloma annulare [AND] infliximab or etanercept or adalimumab or certolizumab or golimumab or secukinumab or tocilizumab". All results with the prior-mentioned terms were included except those where bDMARDs have been used for the treatment of GA.

Discussion

Granuloma annulare is a skin disorder that occurs in children and adults. An association with a number of different clinical conditions such as diabetes mellitus, thyroid disease, tuberculosis, infections (e.g., hepatitis C virus, Epstein–Barr virus, human immunodeficiency virus), malignancies, trauma as well as the use of various medications has been reported [9, 10]. The first description of GA development in patients while on treatment with bDMARDs was reported by Devos et al. in 2003 who described a patient with psoriatic arthritis (PsA) receiving infliximab (INF) [11]. Two years later, Voulgari et al. reported a case series of nine patients who developed GA during treatment with TNF inhibitors. More specifically, six patients manifested GA during treatment with adalimumab (ADA), two with INF and one after the administration of etanercept (ETN). All patients had RA and presented a complete resolution of skin lesions using prednisone and topical steroids [7]. Exarchou et al. reported immune-mediated skin lesions during TNFi therapy and described one patient with RA who developed GA during TNFi therapy [3]. Other cases of GA have also been described by different investigators in RA patients during TNFi therapy [12, 13]. Recently, Bonomo et al., reported a PsA patient refractory to TNFi therapy and Clark et al., a patient suffering from psoriasis who were both finally treated with secukinumab and developed GA [14, 15] (Table 1). Finally, the development of GA in RA patients is not always related to bDMARD treatment, but the disease in sine could be the inciting factor.

Treatment of GA depends on the extension of skin manifestations and the underlying disease or the causative factor. In most cases, no treatment is necessary rather than discontinuing the possible causative factor. Most lesions disappear within a few months and rarely last more than two years. If the skin lesions are extensive and persist in time, the following treatment options can be applied: (1) topical corticosteroids, tacrolimus or pimecrolimus; (2) topical corticosteroid injections; (3) cryotherapy using liquid nitrogen;

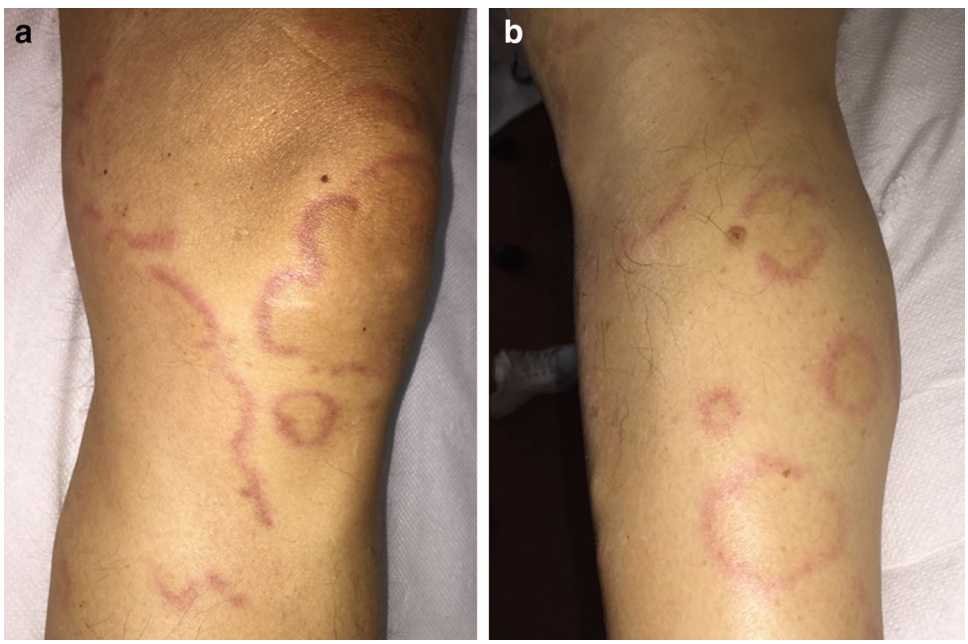

Fig. 1 Erythematous polycyclic skin eruptions covering the anterior (**a**) and medial surface (**b**) of the lower extremities

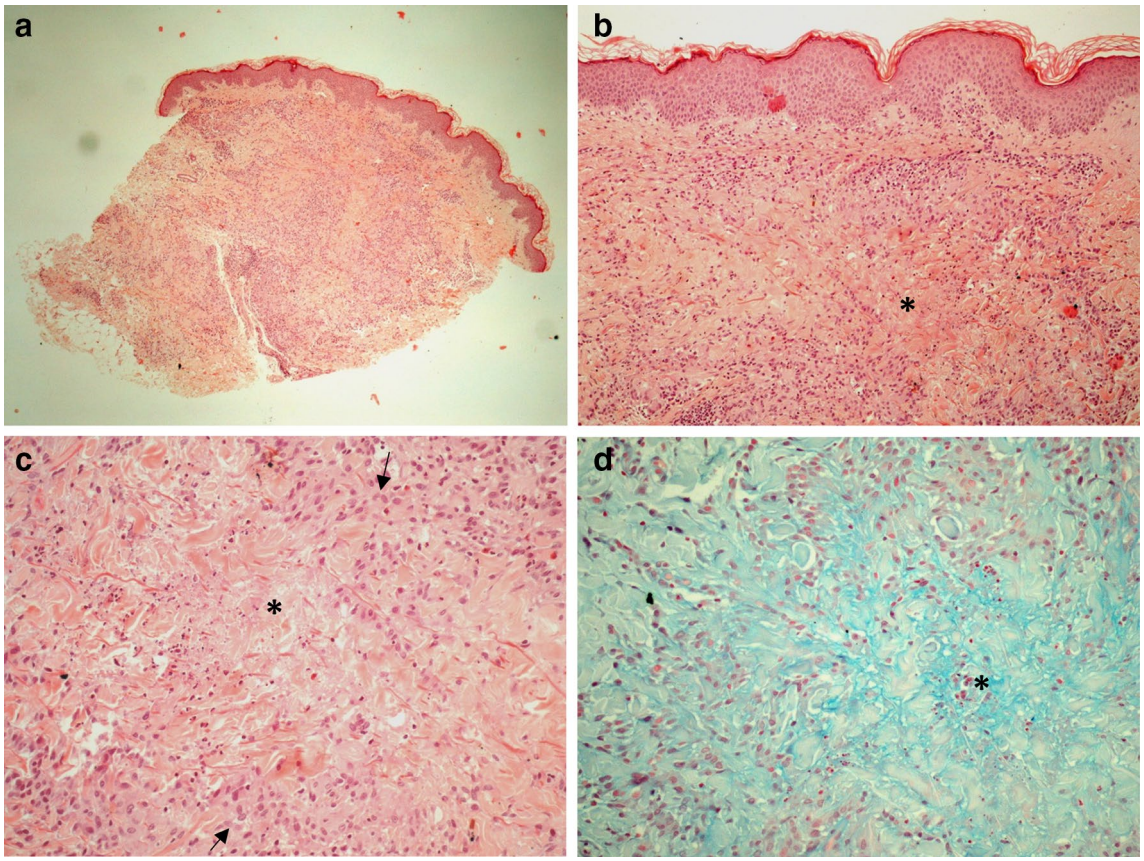

Fig. 2 Granuloma annulare, skin biopsy. Inflammatory infiltration of the dermis consisting of histiocytes and reactive lymphocytes (hematoxylin and eosin stain, **a** X40, **b** X100, **c** X200). The histiocytes (arrows) are clustering around areas of degenerated collagen, extracellular material and cell debris forming a necrobiotic center (asterisk). The latter is highlighted by the special stain Alcian blue (**d** X200)

(4) light therapy using long-wave ultraviolet A radiation (UVA) or psoralen-(P)UVA (photochemotherapy); (5) oral medication which includes corticosteroids, hydroxychloroquine, dapsone, cyclosporine A, pentoxifylline and certain antibiotics; and (6) in some recalcitrant cases infliximab or adalimumab [16].

Tumor necrosis factor inhibitors, IL-6R antagonists and IL-17 inhibitors are bDMARDs with different modes of action for the treatment of inflammatory arthropathies. In the majority of cases, significant clinical efficacy and an acceptable toxicity profile has been reported. However, all of the above-mentioned bDMARDs have been implicated in cases with the development of GA. On the other hand, TNFi were used as off-label therapy in many granulomatous skin lesions including GA and sarcoidosis [17]. Recently, TCZ was approved for the treatment of giant cell arteritis (GCA), which is also a granulomatous disease [18]. These paradoxical effects of TNFi and IL-6R antagonists are difficult to explain. In GCA, the granulomatous lesions contain Th-1 and Th-17 cells which express and produce IL-6, IL-17, IL-1β and TNF while in the GA lesions Th-1 and Th-17 cells express mainly IL-2, TNF and interferon-γ. The latter activate macrophages which act as effector cells causing tissue damage and degeneration through metalloproteinase production [19, 20].

Although the prevalence of GA may be high among patients with chronic diseases, its occurrence in patients receiving bDMARDs, especially those receiving TNFi, clearly exceeds the prevalence that might be expected by chance. The exact cause of GA is unknown. Because of the histopathology and T-cell subtypes associated with the lesion, a delayed type of hypersensitivity reaction is suspected, but the inciting antigen has not been recognized yet [21]. The underlying pathophysiological mechanism responsible for the development of GA after TCZ therapy remains elusive. IL-6 is a pleiotropic cytokine acting in many cells and tissues through the IL-6R. It is possible that the inhibition of IL-6R from TCZ may promote the activation of autoreactive T cells leading to tissue damage via an autoimmune mechanism. This is exemplified by the common induction of ANA and anti-double-stranded DNA, anti-cardiolipin antibodies as well as the occurrence

Table 1 Granuloma annulare after treatment with bDMARDs

Author, year [citation]	Number of cases	Disease treated	bDMARD used	Treatment	Outcome
Devos SA et al. 2003 [11]	1	PsA	INF	Cs	Complete resolution
Voulgari PV et al. 2005 [7]	9	RA	2 INF 6 ADA 1 ETN	Prednisone 10 mg/day plus topical Cs (1 patient on INF and 1 on ADA discontinued treatment)	Complete resolution
Exarchou S. 2008 [3]	1	RA	INF	Prednisone 10–15 mg/day plus topical Cs	Complete resolution
Ratnarathorn M et al. 2011 [12]	1	RA	ADA	Discontinuation of ADA	Complete resolution
			ETN	Discontinuation of ETN	Complete resolution
Bonomo et al. 2017 [14]	1	PsA	Secukinumab	Topical Cs (clobetasol propionate) and discontinuation of secukinumab	Marked improvement (within 8 months)
Clark et al. 2018 [15]	1	Psoriasis	Secukinumab	Triple antibiotic therapy (rifampin, levofloxacin, minocycline)	No improvement
				Etanercept	Complete resolution (within 6 weeks)
Pelechas et al. 2018 [current case]	1	RA	TCZ	Discontinuation of TCZ, Cs	Complete resolution (within 4 weeks)

bDMARDs biological disease-modifying anti-rheumatic drugs, *PsA* psoriatic arthritis, *INF* infliximab, *Cs* corticosteroids, *RA* rheumatoid arthritis, *ADA* adalimumab, *ETN* etanercept, *TCZ* tocilizumab

of many autoimmune diseases in patients treated with bDMARDs [5]. Another explanation could be the susceptibility to infections (bacterial, viral) which has been described as a trigger for GA development [7, 9]. It is well known that there is an increase of infection rates in TCZ-treated patients [18]. This report is the first description of GA in a RA patient treated with TCZ. Our observation may add to the discussion about new autoimmune phenomena induced by TCZ therapy. Further studies, in collaboration with other specialties, are needed to identify risk factors of IL-6R antagonists and the development of GA.

Author contributions EP: acquisition and analysis of the data, and manuscript drafting. AP-B: analysis and interpretation of the histological data. PVV: acquisition, analysis and interpretation of the data. AAD: review of the manuscript and final approval.

Compliance with ethical standards

Conflict of interest E. Pelechas, Alexandra Papoudou-Bai, Paraskevi V. Voulgari, and Alexandros A. Drosos declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from our patient included in the study.

References

1. Kaltsonoudis E, Pelechas E, Voulgari PV, Drosos AA. (2018) Unmet needs in the treatment of rheumatoid arthritis. An observational study and a real-life experience from a single university center. Semin Arthritis Rheum. https://doi.org/10.1016/j.semarthrit.2018.06.003 **(epub ahead of print)**
2. Flouri ID, Markatseli TE, Boki KA et al (2018) Comparative analysis and predictors of 10-year tumor necrosis factor inhibitors drug survival in patients with spondyloarthritis: first-year response predicts longterm drug persistence. J Rheumatol 45(6):785–794
3. Exarchou SA, Voulgari PV, Markatseli TE, Zioga A, Drosos AA (2009) Immune-mediated skin lesions in patients treated with anti-tumour necrosis factor alpha inhibitors. Scand J Rheumatol 38:328–331. https://doi.org/10.1080/03009740902922612
4. Sfikakis PP, Iliopoulos A, Elezoglou A, Kittas C, Stratigos A (2005) Psoriasis induced by anti-tumor necrosis factor therapy: a paradoxical adverse reaction. Arthritis Rheum 52:2513–2518
5. Markatseli TE, Kaltsonoudis ES, Voulgari PV, Zioga A, Drosos AA (2009) Induction of psoriatic skin lesions in a patient with rheumatoid arthritis treated with rituximab. Clin Exp Rheumatol 27:996–998
6. Kaltsonoudis E, Zikou AK, Voulgari PV, Konitsiotis S, Argyropoulou MI, Drosos AA (2014) Neurological adverse events in patients receiving anti-TNF therapy: a prospective imaging and electrophysiological study. Arthritis Res Ther 16:R125. https://doi.org/10.1186/ar4582
7. Voulgari PV, Markatseli TE, Exarchou SA, Zioga A, Drosos AA (2008) Granuloma annulare induced by anti-tumour necrosis factor therapy. Ann Rheum Dis 67:567–570
8. Gasparyan AY, Ayvazyan L, Blackmore H, Kitas GD (2011) Writing a narrative biomedical review: considerations for authors, peer

reviewers, and editors. Rheumatol Int 31:1409–1417. https://doi.org/10.1007/s00296-011-1999-3
9. Alexander JS, Paniker PU (2006) A ring-shaped eruption. Am J Med 119:125–127
10. Keimig EL. Granuloma, Annulare (2015) Granuloma annulare. Dermatol Clin 33:315–29. https://doi.org/10.1016/j.det.2015.03.001
11. Devos SA, Van Den Bossche N, De Vos M, Naeyaert JM (2003) Adverse skin reactions to anti-TNF-alpha monoclonal antibody therapy. Dermatology 206:388–390
12. Ratnarathorn M, Raychaudhuri SP, Naguwa S (2011) Disseminated granuloma annulare: a cutaneous adverse effect of anti-TNF agents. Indian J Dermatol 56:752–754. https://doi.org/10.4103/0019-5154.91847
13. Viguier M, Richette P, Bachelez H, Wendling D, Aubin F (2010) Paradoxical cutaneous manifestations during anti-TNF-alpha therapy. Ann Dermatol Venereol 137:64–71. https://doi.org/10.1016/j.annder.2009.10.003. quiz 63, 78 – 9.
14. Bonomo L, Ghoneim S, Levitt J (2017) A case of granuloma annulare associated with secukinumab use. Case Rep Dermatol Med 2017:5918708. https://doi.org/10.1155/2017/5918708
15. Clark ML, Tobin CA, Sutton A, Missall TA. Granuloma annulare in the setting of secukinumab. Case Rep Dermatol Med 2018:5175319. https://doi.org/10.1155/2018/5175319
16. Piette EW, Rosenbach M (2016) Granuloma annulare: clinical and histologic variants, epidemiology, and genetics. J Am Acad Dermatol 75(3):457–465. https://doi.org/10.1016/j.jaad.2015.03.054
17. Sand FL, Thomsen SF (2015) Off-label use of TNF-alpha inhibitors in a dermatological university department: retrospective evaluation of 118 patients. Dermatol Ther 28:158–165. https://doi.org/10.1111/dth.12222
18. Villiger PM, Adler S, Kuchen S, Wermelinger F, Dan D, Fiege V, Bütikofer L, Seitz M, Reichenbach S (2016) Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet 387:1921–1927. https://doi.org/10.1016/S0140-6736(16)00560-2
19. Samson M, Audia S, Fraszczak J et al (2012) Th1 and Th17 lymphocytes expressing CD161 are implicated in giant cell arteritis and polymyalgia rheumatica pathogenesis. Arthritis Rheum 64(11):3788–3798
20. Martinez-Taboada VM, Alvarez L, RuizSoto M et al (2008) Giant cell arteritis and polymyalgia rheumatica: role of cytokines in the pathogenesis and implications for treatment. Cytokine 44(2):207–220
21. Sfikakis PP, Kollias G (2003) Tumor necrosis factor biology in experimental and clinical arthritis. Curr Opin Rheumatol 15:380–386