

Case Report

Granuloma Annulare, a Possible Paradoxical Reaction of the Adalimumab Treatment in a Severe Case of Psoriasis Vulgaris

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ABSTRACT: Granuloma annulare (GA) is a benign chronic inflammatory dermatosis, self-limited, slightly pruritic or asymptomatic in the majority of the cases, with specific clinically and histologically features, that occurs in all age groups, but it is rare in infancy. GA is associated to five clinical variants: localized, generalized, perforating, subcutaneous and arcuate dermal erythema. The etiology of GA is usually unknown, but in 60-75% of the cases it is associated with metabolic disorders (diabetes mellitus, dyslipidemia), thyroid disorders, neoplasms, infections or drug induced. We present a psoriasis case treated with anti TNF α agents, Adalimumab, that after three and a half years of treatment developed GA.

KEYWORDS: Psoriasis, granuloma annulare, anti TNF α agents, paradoxical reaction.

Introduction

Granuloma annulare (GA) is a benign chronic inflammatory dermatosis, with specific clinically and histologically features, that occurs in all age groups, but it is rare in infancy.

GA recognizes five clinical variants: localized, generalized, perforating, subcutaneous and arcuate dermal erythema.

The etiology of granuloma annulare is usually unknown, but in 60-75% of the cases is associated with metabolic disorders (diabetes mellitus, dyslipidemia), thyroid disorders, neoplasms, infections [1,2].

GA can be also induced by drugs such as: allopurinol, diclofenac, calcium channel blockers, antidepressants, anticonvulsants, interferon, etc.

Paradoxically, GA can be triggered by anti TNF α agents, used for GA refractory cases [3].

For over 17 years, anti TNF α agents are being used to treat a variety of systemic and cutaneous inflammatory conditions (rheumatoid arthritis, psoriatic arthritis, spondyloarthropathy, Crohn disease).

Nonetheless, in rare cases, anti TNF α agents can induce some autoimmune conditions including granulomatous diseases (GA,

sarcoidosis, interstitial granulomatous dermatitis, rheumatoid nodules, etc.).

Therefore, the patients undergoing anti TNF α therapy must be closely monitored to determine a potential overactivation of the cytokines responsible for inducing granulomatous reactions [4].

We present the case of a patient with severe psoriasis treated with Adalimumab for 3 and a half years, who developed GA and also a review of the most recent cases described in the specialized literature regarding the side effects of the anti TNF α therapy with a special focus on GA.

Clinical Case

The 66 year-old male patient, from rural area, was consulted for an eruption formed by multiple arcuate lesions, 1.5-2.5cm diameter, pruritic, erythematous with hypopigmented center, located on the dorsal of the hands with a 2 months onset. (Figure 1).

The patient was known with psoriasis vulgaris for 4 years and for 3 and a half years under treatment with Adalimumab.

He was also diagnosed with stage III hypertension, duodenal ulcer, cervical spondylitis at the age of 62.



Figure 1. Skin lesions in Granuloma annulare.

The clinical examination showed: class I obesity (BMI: 30,8), erythematous patches covered by silvery white scales, easily detachable located on the scalp, pain and craquemets at the cervical spine.

To determine the severity of the psoriasis were done the PASI [5] (Psoriasis Area and Severity Index) score that was currently 1.8 and initially 16.4, and for the impact of the disease on the quality of the patient's life, DLQI [6] (Dermatology Life Quality Index) score that was currently 1 and at the initiation 21.

Laboratory tests showed: red blood cells = $4.800.000/\text{mm}^3$, Hemoglobin = $15,4\text{mg/dL}$, Red blood cells volume = 44,2%, VEM = 92,1fL, HEM = $32,1\text{mg/dL}$, CHEM = 34,8%, platelets = $241.000/\text{mm}^3$, white blood cells = $7.160/\text{mm}^3$, Neutrophils = 56.4%, Creatinine = $0,92\text{mg/dL}$, Glucose = 113.37mg/dL , TGO = 26.1U/L , TGP = 25.3U/L , Triglycerides = 66.70mg/dL , Cholesterol = 32.26mg/dL , Urea = 20.03mg/dL , uric acid = 5.14mg/dL , ESR = 2/h. Pulmonary X-ray, Quantiferon TB Gold, TPHA, HBsAg, anti HCV antibodies were negative.

A biopsy from a lesion located on the dorsal right hand was harvested under local anesthesia with 1% xyline.

Tissue was routinely processed for fixation in neutral buffered formalin and for paraffin embedding, and histopathology investigation was performed in Department of Pathology from the Emergency County Hospital of Craiova.

Histological evaluation (hematoxylin-eosin staining) showed an epidermis with orthokeratosis, atrophy of the epithelial crests, collagen degeneration surrounded by epithelioid cells and fibroblasts, dissected by an inflammatory infiltrate of mostly lymphocytes, few giant cells and mononuclear cells, in the mid and deep dermis (Figure 2), features compatible with the diagnosis of granuloma annulare.

The differential histopathology diagnosis was done with granulomatous dermatoses like: sarcoidosis (pathology shows dermal granuloma formed by epithelioid histiocytes, giant cells with intracytoplasmic inclusions Schaumann bodies and asteroid bodies); lipoidic necrobiosis (pathology shows in dermis and subcutaneous tissue, interstitial granulomas arranged in palisades, perivascular infiltrate formed by lymphocytes Th, histiocytes, plasma cells and eosinophils, reduced lumen of the dermal vessels due to granulomatous infiltrate and sclerosis and extracellular lipids in the superficial dermis) [7].

In rheumatoid nodules the histopathological exam shows granulomatous tissue reaction pattern with central necrosis surrounded by histiocytes and lymphocytes that form a granulation tissue and occasional macrophages.

Based on clinical appearance, laboratory investigation and histopathological examination, the diagnosis were: granuloma annulare, type II

psoriasis vulgaris, stage III hypertension, class I obesity.

The patient received systemic treatment for GA with Pentoxifyllin 400mg 3 times per day and Levocetirizine 5mg/day and topically Tacrolimus 0.1% once every evening and

mometasone furoate ointment once every morning.

The evolution was favorable without stopping the Adalimumab treatment that proved efficient for psoriasis.

The patient gave a written informed consent regarding the publication of these data.

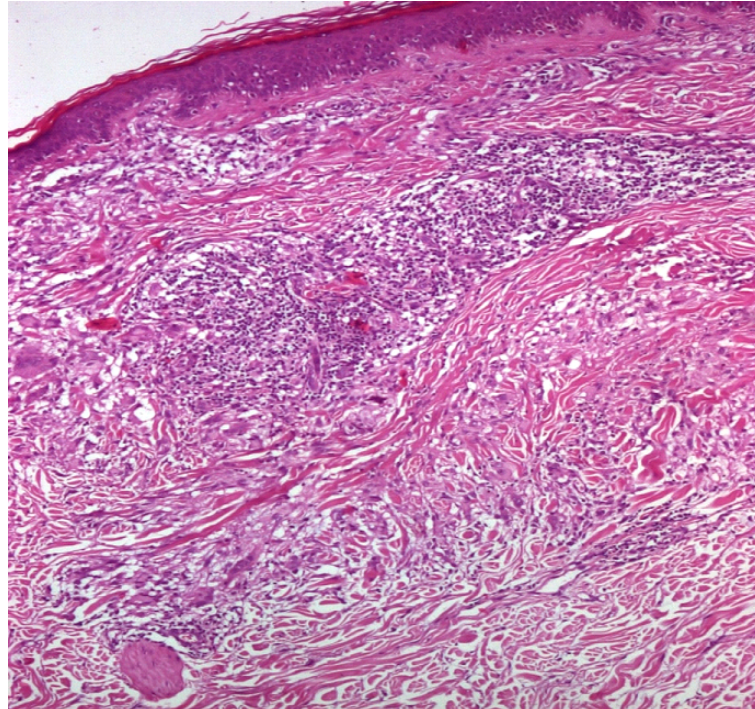


Figure 2. Histopathology of the skin lesions showed collagen degeneration surrounded by epithelioid cells, fibroblasts and mononuclear inflammatory infiltrate in the dermis; hematoxylin-eosin, Ob 5x.

Discussions

Granuloma annulare (GA) is a benign inflammatory dermatosis, first described by T. Colcott Fox and later by Radcliffe-Crocker [8,9], characterized clinically by multiple oval or annular plaques with borders composed of numerous dermal skin colored or erythematous papules [2].

The pathogenesis is not precisely known.

The condition is more commonly associated with diabetes mellitus [10], but also with dyslipidemia [11], thyroid disorders (autoimmune thyroiditis), malignancies (Hodgkin disease, pulmonary adenocarcinoma, breast carcinoma, mycosis fungoides, ovarian neoplasm) [2], sun exposure and tuberculosis [8].

Post vaccinations or secondary to viral infections (HIV, Epstein-Barr virus, hepatitis B virus, hepatitis C virus and herpes zoster virus) granuloma annulare has been reported.

GA can be also induced by drugs such as: allopurinol, diclofenac, quinidine, calcitonin, amlodipine, ACE inhibitors, and calcium channel blockers.

Recently, proposed pathogenic mechanisms for granuloma annulare include overexpression of TNF α and MMP induced by macrophages that determines degradation of collagen [12].

A 56 year-old patient diagnosed with rheumatoid arthritis, developed an eruption compatible with GA after 22 months from the initiation of Adalimumab treatment has been described in the literature.

The lesions disappeared after stopping the biological therapy but a similar eruption occurred when Etanercept drug was introduced.

So, the development of GA secondary to anti TNF α agents seems to be a mass effect and demonstrates the correlation between these drugs and the occurrences of this benign chronic dermatosis [11].

A true paradoxical reaction is a reaction that occurs during the treatment with biological agents.

The paradox refers about the fact the clinical manifestations seen in this type of reaction are, most of the times, the same reason for which the biological treatment is introduced (for example: worsening of the psoriatic lesions after biologic therapy).

The borderline paradoxical reactions encompass the clinical manifestations that appear after the biologic therapy, without that agent being used to specifically treat those conditions (for instance: sarcoidosis occurred after treatment with biologic agents of ankylosing spondylitis, this drug not being useful in treating sarcoidosis). This type of reactions can occur after anti TNF α therapy [13].

Adalimumab is a human monoclonal antibody IgG₁ against TNF α blocking its interaction with the p55 (TNFR1) and p75 (TNFR2) cell surface TNF receptors.

The mechanism of action is based on TNF α neutralization and inducing the apoptosis of TNF α expressing mononuclear cells [2,14,15].

Voulgari et al. conducted a study on 199 patients diagnosed with rheumatoid arthritis and 127 with spondyloarthritis undergoing anti TNF α therapy.

The aim of this study was to determine the number of patients that develops GA during the biologic treatment.

Among the rheumatoid arthritis patients treated with anti TNF α therapy, 9 (4,5%) were diagnosed with GA while none of the spondyloarthritis patients had this condition.

All patients presented the generalized type of GA, seven during the first year after the initiation of the biologic therapy and two in the following year.

In 2 cases, the authors considered mandatory to stop the biologic therapy due to extensions of the eruption, still all the patients responded to topical treatment with corticosteroids [16].

Conclusion

In the presented case, granuloma annulare might be considered a paradoxical reaction of the Adalimumab treatment since the other etiologies described in the database were excluded.

Conflict of interests

None to declare.

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