

Granuloma annulare after infliximab treatment for rheumatoid arthritis

KOUTROUMPAS A¹
ZAFIRIOU E²
TERZIS A³
SAKKAS LI¹

A 72-year-old male presented with painful swelling of hands, feet, knees, ankles and shoulders in April 2006. His medical history was remarkable for coronary artery disease with myocardial infarction in 1987, and he was on isosorbide mononitrate, metoprolol, losartan, and aspirin. He was diagnosed with rheumatoid arthritis (RA) and received leflunomide and hydroxychloroquine. Due to inadequate response, oral methotrexate (7.5mg/week) was added, but leucopenia and elevated liver enzymes led to discontinuation of treatment. The patient was scheduled for infliximab treatment. Since he had a positive PPD skin reaction (12mm) and clear chest x-rays, the patient started on isoniazid (INZ) prophylaxis for 9 months. After one month of INZ prophylaxis, the patient was started on infliximab (3.5mg/Kg). Three months later, the dose of infliximab increased to 4mg/Kg for inadequate response. In July 2007, the patient reported a rash which was persistent. The rash consisted of ring-like firm, flesh-colored papules with mild pruritus on torso and lower extremities. Biopsy showed granuloma annulare (GA). Infliximab was discontinued. A search for malignancy, lymphoma and tuberculosis, including bone marrow biopsy, bone marrow and gastric lavage culture for *M.tuberculosis* and detection of *M.tuberculosis* by DNA hybridization methods, serological test for HIV, HBV, HCV, and *Borrelia* infection were all negative. The patient was put on dapsone that resulted in slow resolution of the rash. Interestingly, RA remained quiescent, despite discontinuation of all medications for over 8 months.

GA is a granulomatous skin lesion of unknown aetiology. It affects patients of all ages but usually patients before 30 years of age. It has been reported in patients with lymphoma, solid tumors, viral infections (HIV, EBV and HZV), insect bites, and tuberculosis. Five clinical variants of GA are recognised: localized, generalized,

¹Rheumatology Department, University Hospital of Larissa, Larissa, Greece

²Dermatology Department, University Hospital of Larissa, Larissa, Greece

³Department of Morbid Anatomy, University Hospital of Larissa, Larissa, Greece

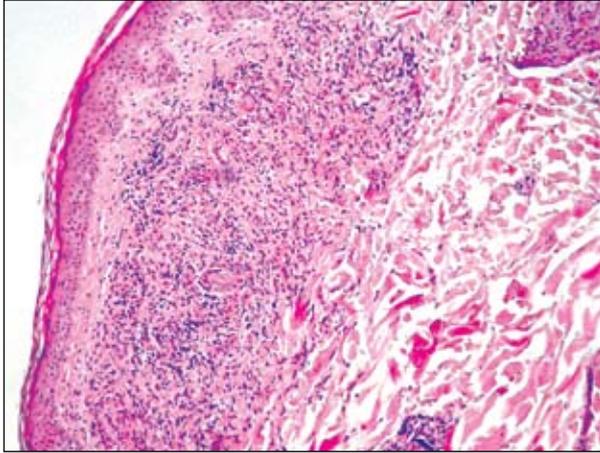


Figure 1. Histology appearance of GA.

subcutaneous, perforating, and patch. Localized GA is the most common variant and appears as annular pink papule, usually on an extremity. The subcutaneous variant appears as subcutaneous nodule on an extremity, whereas the perforating variant appears as a crusted, umbilicated papule or plaque. Patch GA appears as a pink macule¹. Our patient had the generalized form in his torso and lower extremities. Histologically, GA consists of a central acellular area of degenerating (necrobiotic) collagen fibers that contains mucin (stained bluish with colloidal iron). This necrobiotic area is surrounded by histiocytes (macrophages) that form palisade and express TNF α and metalloproteases, and perivascular T lymphocytes mainly of CD4 type that express IFN- γ ². In the mycobacterial granuloma paradigm, TNF- α and IFN- γ are essential for the efficient activation of cells and maintenance of granuloma structure. The GA structure suggests a delayed-type, cell-mediated, hypersensitivity reaction of TH1 type, but the inciting agent, infectious or not, is not known. Recently, *Borrelia* was detected in GA by immunohistochemistry using floating-focus microscopy³.

GA in our patient appears to be an adverse reaction to infliximab. Of 11 GA cases reported thus far after TNF-inhibitor treatment, 10 cases occurred with anti-TNF- α antibodies (infliximab,

adalimumab), and one case with soluble TNF receptor (etanercept)^{4,5,6}. There are differences between anti-TNF- α antibodies compared to etanercept. In contrast to etanercept, anti-TNF- α antibodies bind membrane TNF and cause apoptosis of T cells and suppression of IFN- γ production⁷. In addition, anti-TNF- α antibodies bind to soluble TNF and form large complexes that activate complement, whereas etanercept forms with soluble TNF small complexes that do not activate complement.

Most cases of TNF inhibitor-associated GA occurred during the first year of treatment. It should be reminded that most cases of tuberculosis associated with anti-TNF- α antibodies (Ab) occur early after the initiation of treatment, whereas etanercept-associated tuberculosis cases are much fewer and evenly distributed over long periods, which suggests a dissolution of granulomata and reactivation of latent tuberculosis in anti-TNF- α Ab-associated tuberculosis⁸. It is not far-fetched to speculate that dissolution of granulomata and liberation of modified antigens in a suitable genetic background underlies the pathogenesis of anti-TNF- α Ab-associated GA. Other immune adverse reactions after anti-TNF treatment have been reported, including psoriasiform lesions, drug-induced lupus, ANA induction and vasculitis.

Interestingly, infliximab demonstrated effectiveness in a patient with recalcitrant generalized GA⁹, whereas etanercept has shown conflicting results in two case reports, showing effectiveness in one case and failure in another case of generalized GA^{10,11}. The differential effect of the two anti-TNF blockers on IFN- γ production could explain both the effectiveness of infliximab but not etanercept in granulomatous conditions, such as Wegener's granulomatosis, spondyloarthropathy related uveitis, Crohn's disease and the higher risk of infliximab reactivating latent tuberculosis infection compared with etanercept⁸. Therefore, GA as a side-effect to infliximab seems to be a paradoxical reaction.

Hellenic Rheumatology 2008, 20(2-3):103-105

REFERENCES

1. Alexander JS, Paniker PU. A ring-shaped eruption. *Am J Med* 2006; 119:125-7.
2. Fayyazi A, Schweyer S, Eichmeyer B, Herms J, Hemmerlein B, Radzun HJ et al. Expression of IFN- γ , coexpression of TNF α and matrix metalloproteinases and apoptosis of T lymphocytes and macrophages in granuloma annulare. *Arch Dermatol Res* 2000; 292:384-90.
3. Ziemer M, Grabner T, Eisendle K, Baltaci M, Zegler B. Granuloma annulare—a manifestation of infection with *Borrelia*? *J Cut Pathol* 2008; 35:1050-7.
4. Voulgari PV, Markatseli TE, Exarchou SA, Zioga A and Drosos AA. Granuloma annulare induced by anti-tumour necrosis factor therapy. *Ann Rheum Dis* 2008; 67:567-70.
5. Devos SA, van den Bossche N, De Vos M, Naeyaert JM. Adverse Skin Reactions to Anti-TNF-Alpha Monoclonal Antibody Therapy. *Dermatology* 2003; 206:388-90.
6. Deng A, Harvey V, Sina B, Strobel D, Badros A, Junkins-Hopkins JM et al. Interstitial Granulomatous Dermatitis Associated With the Use of Tumor Necrosis Factor- α Inhibitors. *Arch Dermatol* 2006; 142:198-202.
7. Saliu O, Sofer C, Stein DS, Schwander SK, Wallis RS. Tumor necrosis factor blockers: differential effects on mycobacterial immunity. *J Infect Dis* 2006; 194:486-92.
8. Wallis RS, Broder M, Wong J, Lee A, Hoq L. Reactivation of latent granulomatous infections by infliximab. *Clin Infect Dis* 2005; 41:S194-8.
9. Hertl MS, Haendle I, Schuler G, Hertl M. Rapid improvement of recalcitrant disseminated granuloma annulare upon treatment with the tumour necrosis factor-alpha inhibitor, infliximab. *Br J Dermatol* 2005; 152:552-5.
10. Shupack J and Siu K. Resolving Granuloma Annulare With Etanercept. *Arch Dermatol*. 2006; 142:394-5.
11. Kreuter A, Altmeyer P and Gambichler T. Failure of Etanercept Therapy in Disseminated Granuloma Annulare. *Arch Dermatol*. 2006; 142:1236-7.