American Journal of Internal Medicine
2015; 3(5): 210-212
Published online August 27, 2015 (http://www.sciencepublishinggroup.com/j/ajim)
doi: 10.11648/j.ajim.20150305.13
ISSN: 2330-4316 (Print); ISSN: 2330-4324 (Online)

Erythema Nodosum During Adalimumab Therapy: An Idiopathic Transient Paradoxical Effect

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To cite this article:
Ilker Ilhanli, Yunus Durmaz, Necip Guder, Kıvanc Cengiz. Erythema Nodosum During Adalimumab Therapy: An Idiopathic Transient Paradoxical Effect. *American Journal of Internal Medicine*. Vol. 3, No. 5, 2015, pp. 210-212. doi: 10.11648/j.ajim.20150305.13

Abstract: Contrary to their undoubted efficacy on rheumatologic diseases, potential for developing skin lesions with Tumor necrosis alpha blockers (Anti-TNF alpha) is an important question in our minds. Although we know, most of the studies and case reports in the literature show that adalimumab is an effective treatment agent on erythema nodosum, we should keep in mind this lesion as a rare paradoxical side-effect. Here we present a case of idiopathic transient erythema nodosum during adalimumab therapy.

Keywords: Anti-TNF Alpha, Adalimumab, Rheumatoid Arthritis, Erythema Nodosum

1. Introduction

Biological agents have dramatically changed the prognosis and the therapy of the rheumatic diseases in recent years. Anti-TNF alpha therapy has had a remarkable effect on disease activity in an increasing number of rheumatic diseases, incluiding rheumatoid arthritis [1-3], juvenil idiopathic arthritis [4], ankylosing spondylitis [5-6] and psoriatic arthritis [7].

Many dermatological findings have been reported in clinical trials, including urticaria, rash, and stomatitis like during infliximab therapy [8], and injection-site reactions like during adalimumab therapy [3-9] and etanercept therapy [2].

More severe cutaneous reactions, such as bullous skin lesions, erythema multiforme, discoid and subacute cutaneous lupus erythematosus, atopic dermatitis, and necrotizing vasculitis, have been declared, mostly as single case reports [10-15]. Erythema nodosum due to anti-TNF alpha therapy is one of them [16]. Here we present a case of erythema nodosum during adalimumab therapy of a patient who was diagnosed as rheumatoid arthritis.

2. Case

48 years old female patient who was diagnosed as rheumatoid arthritis 20 years ago, was started to use etanercept 50 mg per week (2 injections per week; trademark had only subcutan 25 mg form of etanercept in the market) 2 years ago, while she was using methotrexate, sulfasalazine, hydroxychloroquine and meloxicam. She also had asthma and was using inhaler steroids.

The clinical and laboratory disease activity was supressed by etanercept. After 1 year of etanercept threapy, she complained from having 2 injections per week, so for patients compliance, 40 mg adalimumab threapy (one injection per week) was started instead of etanercept. After 5th injection (2 months after the switch) of adalimumab the patient admitted to our clinic with painful, red-purple colored cutaneous lesions, especially at lower limbs (Fig 1.). History of infection, drug usage and presence signs and symptoms of Behcet's disease, inflamatory bowel disease and sarcoidosis were asked and she was investigated with chest roentgenogram, endoscopy, patergy test and multiple laboratory tests including hepatitis and tuberculosis. They were all negative. We excluded streptococcal infection, because there was no clinical or laboratory finding (including faucal culture) of any infection and also, we know that erythema nodosum due to streptococcal infections is common in childhood, but in adults main causes are medications, sarcoidosis and inflammatory bowel diseases. Also, we found no evidence for malignancies or other systemic diseases.

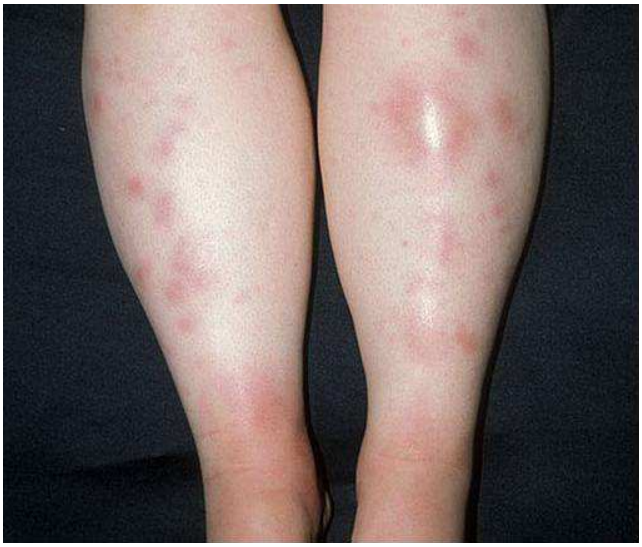

Fig. 1. *Erythema nodosum on lower limbs.*

Adalimumab threapy was stoped and she was observed for a month. Cutaneous lesions disappeared in 1 month. Disease activity was still supressed. Then we started adalimumab threapy again. No new cutaneous lesions appeared during the follow-up period of 5 years.

3. Discussion

Some dermatological manifestations of rheumatoid arthritis are rheumatoid nodules, vasculitis, palmar erythema, purpuric skin lesions, pustuler panniculitis, and livedo reticularis [16, 17].

Adalimumab is a human recombinant immunoglobulin G1 monoclonal antibody specific for human TNF alpha. It has a low immunogenicity potential and it binds to TNF alpha, preventing this cytokine from reaching the p55 and p75 receptors [18].

The most frequent side-effect of adalimumab is cutaneous reaction at the injection site [19]. This has been reported in 20.9% of patients taking 40 mg adalimumab once a week. These are erythema, itching, haemorrhage, pain and swelling. Also patients may present with headache, fever, hypertension and sinusitis at the first hours of adalimumab administration [20]. It has been reported that 0.3% of patients taking adalimumab develop a cutaneous toxicity, the most frequent types are cellulitis, erysipelas or herpes zoster [19]. Other reported side-effects of adalimumab are eczematous reactions, psoriasis and psoriasiform eruption, lymphomatoid papulosis, erythema multiforme, vasculitis, rosacea, folliculitis, fungal infections, actinic keratosis, squamous cell carcinoma, basal cell carcinoma, and low grade basalioma [16,21]. Delle Sedie et al. reported psoriasis, erythema nodosum and nummular eczema in a patient using infliximab [22]. Flendrie et al. reported a case with erythema nodosum under etanercept therapy in their prospective study with 289 rheumatoid arthritis patients using TNF alpha blocking therapy [16]. We should keep in mind these rare paradoxical side-effects [23- 25].

As we know, most of the studies and case reports in the literature show that adalimumab is an effective treatment agent on erythema nodosum [24-29]. Contrary to these findings, we think that our case is the first report of idiopathic transient erythema nodosum during adalimumab therapy. It is a very effective drug, but we consider that all dermatological side-effects should be evaluated to avoid diagnostic delays after excluding the common causes of lesions.

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