

Eruptive Lentiginos after Adalimumab Therapy

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Abstract

Adalimumab, a TNF-alpha antagonist, is the first fully humanized recombinant immunoglobulin G1 (IgG1) monoclonal antibody. It is presently widely used in the systemic treatment of rheumatoid arthritis, inflammatory bowel disease, moderate and severe psoriasis and hidradenitis suppurativa. However, its administration is associated with a two-fold risk of severe and possibly fatal infections and in some rare cases with congestive heart failure, lymphoma, lupus-like syndrome, cytopenias, hepatotoxicity and development of demyelinating neurological disorders. Furthermore, the occurrence of various types of melanocytic skin lesions has been reported during treatment with adalimumab. In the present paper we report the case of a female psoriatic patient who developed eruptive lentiginos following treatment with this compound.

Keywords

Lentiginos, Melanocytes, TNF- α , Adalimumab, Psoriasis

1. Introduction

Emerging biologic agents target specific key mediators in the immunopathogenesis of various immune and inflammatory diseases [1] and presently include three distinct classes of compounds: The inhibitors of interleukin-12 (IL-12)/interleukin-23 (IL-23), interleukin-17 (IL-17) and the inhibitors of tumor necrosis factor-alpha (TNF-alpha). The members of the latter class (etanercept, infliximab, adalimumab) are widely used in the systemic treatment of various autoimmune and inflammatory diseases, including moderate to severe plaque psoriasis. Recently, the occurrence of various types of melanocytic lesions has been reported during treatment with TNF-alpha inhibitors [2]-[4]. In the present paper we report the case of a psoriatic female patient who developed eruptive lentiginos, subsequent to treatment with adalimumab.

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2. Case Report

In January 2010 the dermatologist of a 75-year-old woman with a 35-year history of chronic plaque psoriasis with arthropathy initiated a subcutaneous treatment with 40 mg adalimumab (Humira, Abbott Laboratories Ltd, Athens, Greece) every second week. Pre-treatment assessment for tuberculosis with tuberculin test was negative and chest radiograph was normal.

In February 2013, after three years of continuous treatment with adalimumab, she was admitted to the Department of Internal Medicine with a tuberculous peritonitis which was successfully treated with rifampicin, isoniazid and ethambutol (to be reported elsewhere).

Because of a relapse of her chronic plaque psoriasis due to the discontinuation of adalimumab, the patient (Fitzpatrick skin type IV) presented to the Department of Dermatology, University of Patras, Greece in September 2013. Apart from the psoriatic lesions, physical investigation revealed the presence of numerous and disseminated asymptomatic brown macular lesions (**Figure 1**), that developed in a short span of time 2 months after onset of adalimumab therapy, on both the apparently normal skin and the resolving psoriatic plaques. Her family history for lentiginos and melanoma was negative.

She had previously been treated by her home town dermatologists with different topical (corticosteroids, dithranol, emollients) and systemic regimens (cyclosporine, acitretin, leflunomide). However, she had received no phototherapy or photochemotherapy. Her past medical history was remarkable for coronary heart disease, paroxysmal atrial fibrillation and cataract.

Routine laboratory tests including a complete blood count, blood chemistry, urinalysis, immunological and serological investigations (tests for syphilis, HSV 1 & 2, HIV 1 & 2, hepatitis A, B and C and CMV) were performed. Their results were either negative or within normal limits and chest X-ray and electrocardiogram were unremarkable. An informed consent was obtained from her to perform the biopsies, take photographs and report her case.

Histological examination of the brown macular lesions obtained from various sites showed distinct prolongation of rete ridges and increased numbers of uniformly dispersed melanocytes in the basal layer with variable hyperpigmentation (**Figure 2**). Occasionally, a sparse lymphohistiocytic infiltrate and considerable numbers of melanophages could be seen in the papillary dermis. Thus, the diagnosis of eruptive lentiginos was established. Biopsy specimens of adjacent clinically unaffected skin were essentially normal (**Figure 3**). The patient was instructed to topically apply anthralin ointment 2% once daily (short contact therapy) on her psoriatic plaques. However, she was lost to follow-up.

3. Discussion

TNF-alpha is a cytokine known to play a significant role in the surveillance of infectious and neoplastic disorders [3]. Adalimumab, a TNF-alpha antagonist, is the first fully humanized recombinant immunoglobulin G1



Figure 1. Eruptive lentiginos in the resolving psoriatic plaques of a patient treated with adalimumab.

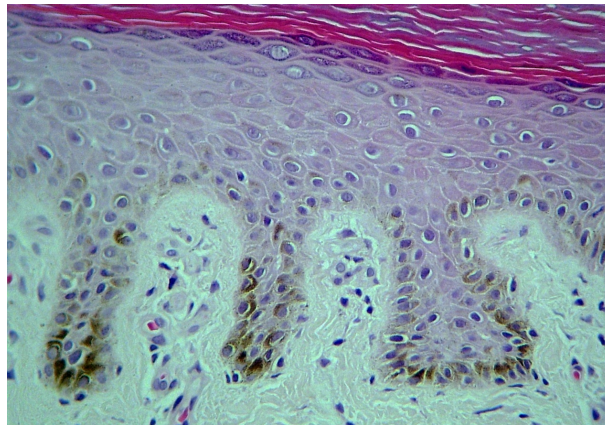


Figure 2. Distinct prolongation of rete ridges and increased numbers of melanocytes in the basal layer ($\times 400$; Hematoxylin-eosin).

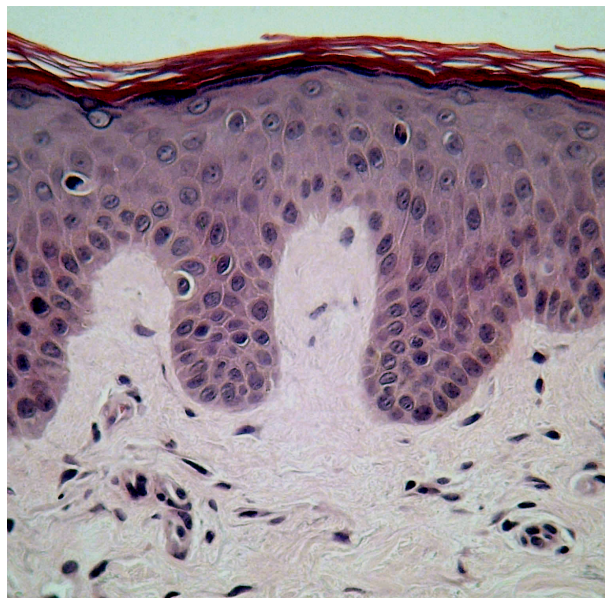


Figure 3. Histological aspects of adjacent clinically unaffected skin of a patient treated with adalimumab ($\times 400$; Hematoxylin-eosin).

(IgG1) monoclonal antibody. It exerts its inhibitory effects on TNF-alpha by occupying the corresponding binding site and competitively inhibiting the binding of this cytokine to its receptor (TNFR) [3] [5].

Adalimumab is presently widely used in the systemic treatment of rheumatoid arthritis, inflammatory bowel disease, moderate and severe psoriasis and hidradenitis suppurativa. However, its administration is associated with a two-fold risk of severe and possibly fatal infections (deep fungal infections, bacterial infections including reactivation of tuberculosis, atypical mycobacterial infections, parasitic infections) [6]. Furthermore, serious but relatively rare side effects of this compound include congestive heart failure, lymphoma (particularly hepatosplenic T-cell lymphoma), lupus-like syndrome, cytopenias, hepatotoxicity and development of demyelinating neurological disorders [6].

Cutaneous side effects of adalimumab include reactions at the injection site, lupus erythematosus, urticaria, pustular dermatoses, leukocytoclastic vasculitis, non-specific rashes and flare of psoriasis [7]. In some rare cases, the use of this compound has been reportedly associated with the occurrence of various types of melanocytic skin lesions, such as melanoma, nevi, hyperpigmentation and lentigines, with the latter representing the simplest

form of them.

Rapid development of hyperpigmented skin lesions is reportedly associated with chemotherapeutic agents and bullous disorders [8]. Phototherapy and photochemotherapy, but also topical corticosteroids and vitamin D derivatives are known to induce the occurrence of lentiginos in treated psoriatic patients [9]. Our patient has never received phototherapy, photochemotherapy or topical vitamin D derivatives. About two decades prior to her presentation to the Department of Dermatology she had been treated with topical steroids; it seems very unlikely, however, that the occurrence of eruptive lentiginos may be attributed to the latter.

To the best of our knowledge, the patient presented here is the second case who developed eruptive lentiginos subsequent to adalimumab therapy. In both, the case reported by Santos-Juanes *et al.* (2008) [10] and in our case, the development of these lesions started two months after the onset of treatment. This chronological association between adalimumab administration and the development of eruptive lentiginos suggests that this drug may be implicated in the etiopathogenetic mechanisms of the latter. Since an intact immune system normally inhibits the proliferation of melanocytic lesions [11], it seems likely that the immunosuppression caused by adalimumab either leads to a dysregulation of melanocytic stem cell division [12] or facilitates the rapid and possibly uncontrolled proliferation of melanocytes in genetically predisposed patients [13] [14].

Furthermore, since the induction of cutaneous benign and malignant melanocytic proliferation seems to be a property shared by adalimumab and all other biologic agents, in patients who are treated with these compounds a close monitoring during treatment and a rigorous follow-up are highly recommended.

4. Conclusion

The results of the present paper taken together with those reported by other groups, clearly indicate that adalimumab and all other biologic agents, apart from their significant and serious side effects, are capable of inducing the cutaneous benign and malignant melanocytic proliferation. Thus, a close monitoring during treatment and a rigorous follow-up of patients treated with these compounds, are of essential importance.

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