

## Hyperpigmentation of the Face Following Adalimumab Treatment

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Sir,

We report here a case of a patient with chronic psoriatic arthritis affecting multiple joints, in whom an unusual cutaneous reaction with hyperpigmentation of the face developed following treatment with adalimumab.

### CASE REPORT

A 52-year-old man with a 17-year history of chronic psoriatic arthritis affecting multiple joints developed an unusual cutaneous reaction with hyperpigmentation of the face following treatment with adalimumab.

Before treatment he had had only mild psoriasis of the skin, limited to a single lesion located behind one ear. For several years he had been treated with methotrexate (MTX) 12–15 mg weekly (cumulative dose approximately 12,000 mg) and ibuprofen 400 mg daily, but his arthritis deteriorated, resulting in a need for an alternative treatment. He did not have any other diseases and did not smoke tobacco. He had an average daily alcohol consumption of 8 units (1 U equals 33 cl of standard beer or 12 cl of non-fortified wine).

At the beginning of April 2008 he commenced adalimumab 40 mg subcutaneously, every second week, concomitant with his stable dosage of MTX and ibuprofen. Following 2 weeks of adalimumab treatment there was no further need for analgesics, and ibuprofen was henceforward only taken when necessary, approximately twice monthly.

In May 2008, 4–5 weeks after initiating adalimumab treatment, the patient was exposed to a considerable amount of sun during sun-bathing. He developed a reddish colour followed by a darker hyperpigmentation of the face, remarkably with a periorbital zone of apparently normal skin, even though he did not wear sunglasses (Fig. 1). His arms and legs were also heavily exposed to sunlight (not sunburned), but only the face was affected by hyperpigmentation. The patient experienced no other symptoms.

The results of the following tests were either negative or within normal limits: haemoglobin, white blood cell count, se-creatinine, se-iron, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, gamma-glutamyl-transferase, platelets, C-reactive protein level, antinuclear antibodies, DNA-antibodies and urine porphyrins. Se-aspartate aminotransferase (ASAT) was increased to 74 U/l (range 15–45 U/l), but later normalized without effect on the hyperpigmentation. Histopathological examination of a 2 mm punch biopsy from the right chin revealed enlarged epidermal keratinocytes and hyperkeratosis as a result of earlier hydropic basal cell degeneration. Superficially in dermis there were many melanophages and a modest, mainly perivascular, lymphocytic infiltrate, consistent with post-inflammatory hyperpigmentation. The hyperpigmenta-



Fig. 1. Clinical appearance of the hyperpigmentation in the face. Notice the unaffected periorbital skin. Photographs published with permission from the patient.

tion persisted after, firstly, the discontinuation of MTX for 4 months (from July 2008 until November 2008) and, secondly, after the discontinuation of adalimumab for 4 months (from November 2008 until March 2009).

### DISCUSSION

Various types of skin lesions have been associated with the use of TNF- $\alpha$  blockers, most often with etanercept and infliximab (1), but these products have also been on the market longer than adalimumab. The cutaneous reactions in general tend to persist if treatment is continued and if one type of TNF inhibitor is substituted with another. In most patients, there is clinical improvement after discontinuation of therapy (1–3).

Adalimumab is the first fully humanized monoclonal antibody against TNF- $\alpha$ , and was therefore expected to cause little or no significant immune-mediated skin reactions. It is currently registered for the treatment of psoriasis, psoriasis arthritis, rheumatoid arthritis

and Crohn's disease. It seems to share the same severe adverse effects as described for TNF- $\alpha$  inhibitors in general (4). The most common cutaneous side-effect is injection site reactions, seen in 20.9% of patients treated with adalimumab, compared with 13.8% treated with placebo (4). Other adverse skin reactions are less common, and include lupus erythematosus (5), pustular dermatoses (6), leukocytoclastic vasculitis (1), urticaria (7), new onset or worsening of psoriasis (8, 9) and non-specific rashes in 4.5–10.1% (10). No previous studies have reported hyperpigmentation of the normal skin following adalimumab treatment.

The hyperpigmentation in our case remained unchanged following discontinuation of both MTX and adalimumab. Photosensitivity as a complication of MTX is uncommon, but it has been described in combination with ultraviolet phototherapy (11). In 1999 Toussiro & Wendling (12) described similar symptoms in a 40-year-old woman with rheumatoid arthritis following excessive sun-exposure and one year of MTX treatment (cumulative dose of 120 mg). They discontinued the drug, but one year later, the symptoms were unchanged.

Knowing that MTX might affect photosensitivity, it could be argued in the case described here that the combination of MTX and adalimumab increased the patient's sensitivity to the sun, but since MTX had been taken for several years prior to the incident, and since there was a close temporal relationship between exposure to adalimumab and the onset of cutaneous symptoms, we believe that the hyperpigmentation was most likely due to adalimumab. Furthermore, no explanatory abnormal findings were identified on laboratory evaluations. The transiently raised ASAT, representing the only laboratory abnormality, was most likely caused by the chronically large amount of alcohol consumption, and is not believed to be able to influence this skin reaction. Excessive alcohol intake and liver affection are, however, risk factors for porphyria cutanea tarda, but urinary porphyrins were normal, so this diagnosis is unlikely. No physiological factors predisposed this patient to the development of hyperpigmentation, and he had no previous episodes of this kind following sun exposure. Finally, biopsy specimen showing post-inflammatory hyperpigmentation possibly caused by a combination of medication and sun exposure is consistent with an adalimumab-induced hyperpigmentation.

A recently published case report describes the appearance of lentigines confined to resolving psoriatic plaques in a patient treated with adalimumab. A suggested explanation for this is the immunosuppressive action of adalimumab, as systemic immunosuppressants are reported to cause an increase in melanocyte activity (13). This could also be the explanation for the hyperpigmentation in our case. Furthermore, it is possible that the adalimumab-TNF- $\alpha$  complex may form new immunogenic sites, even though adalimumab is

fully humanized. The reason why the periorbital skin is unaffected remains to be elucidated.

Further studies on similar cases and prospective registrations of adverse effects following adalimumab therapy are necessary to obtain an accurate interpretation of the significance of this reaction, induced by as-yet-unknown mechanisms. Until more information is available, practitioners should be aware of this rare adverse effect and advise adalimumab-treated patients to use sun protective measures.

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