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Case Report

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Alopecia Areata Universalis Elicited during Treatment with Adalimumab

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Key Words
Alopecia areata · Adalimumab · Tumour necrosis factor α · Tumour necrosis factor inhibitors · Side effects

Abstract
Adalimumab is a fully humanized recombinant anti-tumour-necrosis-factor (TNF-α) monoclonal antibody which has been approved for rheumatoid arthritis, active ankylosing spondylitis, psoriatic arthritis and Crohn's disease. We report a case of alopecia areata (AA) universalis occurring 6 months after administration of adalimumab monotherapy in a patient with a long-standing history of psoriatic arthritis and psoriasis. The diagnosis was confirmed by a scalp biopsy which showed a peribulbar infiltrate of both CD4+ and CD8+ T cells, CD1a+ dendritic cells as well as CD68+ and CD163+ macrophages. In addition, immunofluorescence staining for TNF-α was found in the mononuclear cell infiltrate. This case suggests a complex role of TNF-α in the induction of AA.

Introduction

In recent years, a growing number of biological agents have been introduced for the treatment of various auto-immune, allergic, neoplastic and other diseases. Adalimumab is a fully humanized recombinant anti-tumour-necrosis-factor (TNF-α) monoclonal antibody. It has previously been approved for the treatment of rheumatoid arthritis, active ankylosing spondylitis, psoriatic arthritis and Crohn's disease [1]. Despite the proven efficacy of anti-TNF-α in certain diseases, the neutralization of TNF-α by anti-TNF-α treatments has led to the development of auto-immune phenomena and rarely even to auto-immune diseases [2]. We report a

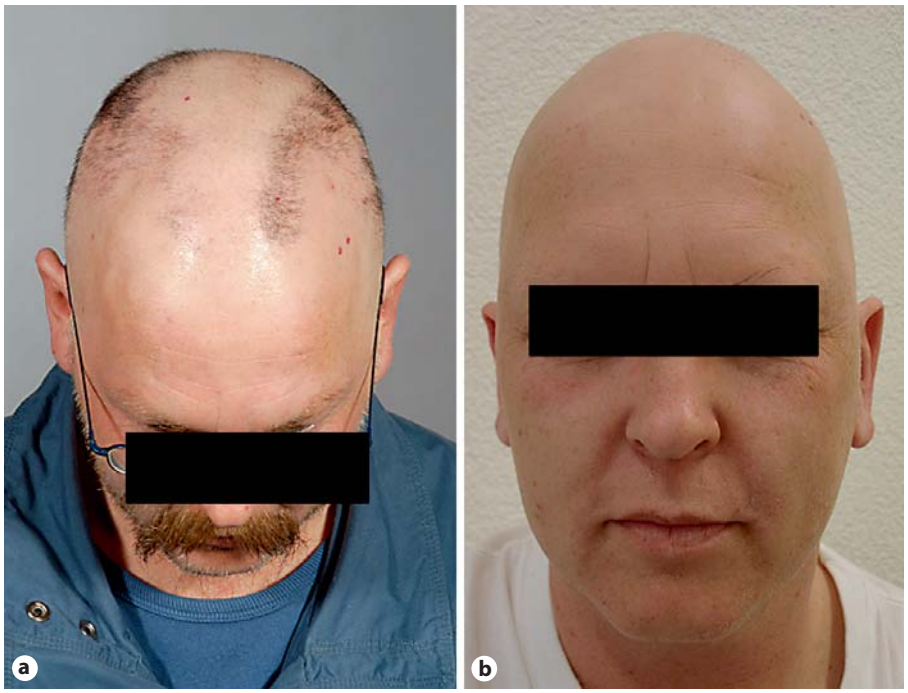

Fig. 1. AA 6 (**a**) and 8 months (**b**) after starting adalimumab therapy.

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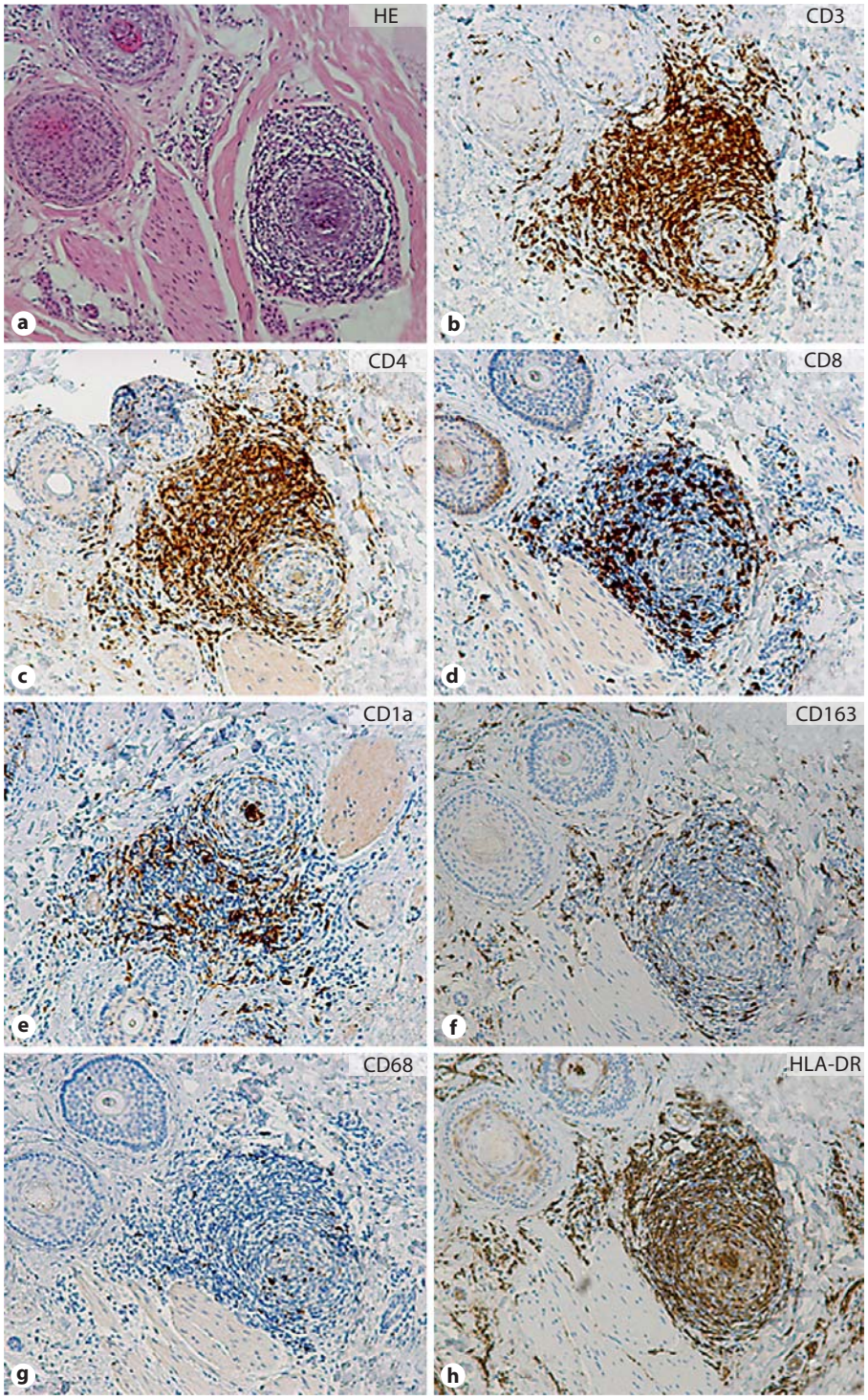

Fig. 2. Histological examination (haematoxylin-eosin, HE) showing a peribulbar lymphocytic infiltrate with a reduced number of diminutive hairs (**a**) and immunohistochemical findings demonstrating CD3+ (**b**), CD4+ (**c**), CD8+ (**d**) T lymphocytes, CD1a+ dendritic cells (**e**) and CD163+ (**f**) and CD68+ (**g**) macrophages around a hair follicle as well as the activation marker HLA-DR (**h**). Original magnification ×200.

case of alopecia areata (AA) universalis occurring 6 months after administration of adalimumab monotherapy in a patient with a long-standing history of psoriatic arthritis and psoriasis.

Case Report

A 43-year-old man was referred to our outpatient clinic due to the sudden onset of patchy hair loss during treatment with adalimumab. The patient had had psoriasis and psoriatic arthritis for 10 years and had been receiving subcutaneous adalimumab monotherapy at a dose of 40 mg every 2 weeks during the past 6 months. Clinical examination revealed non-scarring patchy alopecia affecting 75% of his

scalp (fig. 1a). Despite discontinuation of adalimumab therapy and application of potent topical corticosteroids, the hair loss progressed to 100% scalp involvement and eventually to alopecia universalis over a period of 2 months (fig. 1b). The patient reported no personal or family history of alopecia. Two years prior to his presentation, the patient had been diagnosed as having non-alcoholic fatty liver disease and had stopped taking systemic medications including methotrexate. Antinuclear antibodies were negative. Other laboratory tests were within normal ranges except for alanine aminotransferase 63 IU/l (normal values ≤40 IU/l) and ferritin 728 μg/l (normal values 30–400 μg/l), both of which were reported to be elevated prior to adalimumab therapy due to the underlying liver disorder.

A biopsy specimen of the scalp (haematoxylin-eosin staining) showed a peribulbar lymphocytic infiltrate with a reduced number of diminutive hairs most consistent with AA (fig. 2a). The scalp biopsy specimen was also processed for immunohistochemical analysis with primary antibodies against CD3 (clone: PS1, Novocastra, Newcastle-upon-Tyne, UK), CD4 (clone: 1F6, Novocastra), CD8 (clone: C8/144B, Dako Cytomation, Glostrup, Denmark), CD1a (clone: O10, Dako Cytomation), CD68 (clone: PG-M1, Dako Cytomation), CD163 (clone: 10D6, Novocastra) and HLA-DR (clone: CR3/43, Dako Cytomation) as well as for TNF-α (clone: 28401, R & D Systems, Minneapolis, Minn., USA) immunofluorescence staining as described previously in detail [3, 4].

As shown in figure 2b–h, a marked infiltration of CD3+ T cells with a predominance of CD4+ T cells was found. In addition, CD1a+ dendritic cells, CD163+ macrophages and to a lesser extent CD68+ macrophages were also observed in the skin sections. HLA-DR was highly expressed in the infiltrate as well as partly on epithelial cells suggesting that these cells are activated. Interestingly, local expression of TNF-α in the mononuclear infiltrate could be demonstrated by immunofluorescence staining (fig. 3).

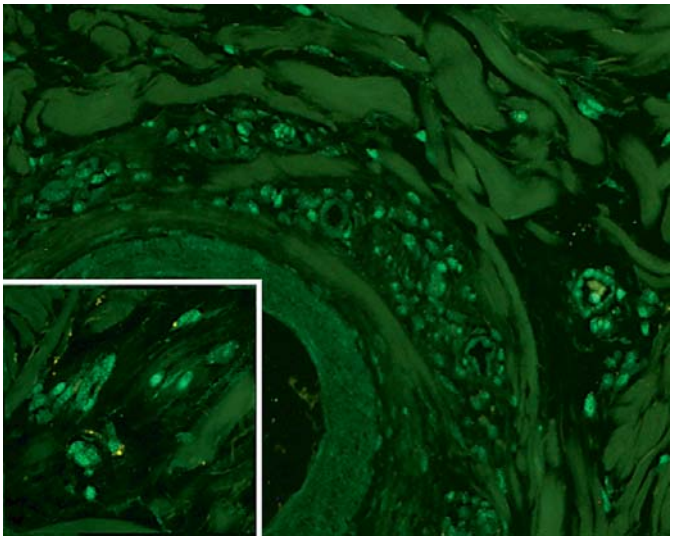

Fig. 3. Immunofluorescence staining showing TNF-α+ cells around the hair follicle. Original magnification ×200.

Discussion

This report suggests that adalimumab can be causally related to the development of AA universalis. AA universalis represents the severest form of AA and manifests itself as a complete loss of all body hair. It is regarded as an auto-immune disorder; nevertheless, its exact pathogenesis is poorly understood. As TNF-α significantly inhibited hair growth in vitro, it was hypothesized that in association with other cytokines, TNF-α may play a role in the pathogenesis of this disease [5]. Indeed, our findings also demonstrate a rich peribulbar infiltrate with pro-inflammatory cells together with expression of TNF-α. The putative role of TNF-α in the pathogenesis of AA has led to attempts to treat AA with TNF-α antagonists like etanercept. However, previous case reports have failed to show efficacy of anti-TNF-α agents in treating AA [6, 7]. Furthermore, even recurrence of AA has been reported with infliximab as well as with adalimumab in a patient with a known history of AA [8, 9].

TNF-α is a cytokine of the innate immune system with broad pro-inflammatory and immunomodulatory effects [10]. Despite the proven efficacy of TNF-α antagonists in certain pro-inflammatory diseases, the neutralization of TNF-α by such treatments has led to the activation of autoreactive T cells with the development of auto-immune phenomena and rarely even to auto-immune diseases such as systemic sclerosis and systemic lupus erythematosus [2]. Notably, F_1 hybrids derived from cross-breeding of NZB mice to TNF knockout mice expressed low levels of TNF and showed evidence of IgG deposits in the kidney that, within 10 months, progressed to overt glomerulonephritis [11]. In addition, previous reports have described the development of psoriasis in patients treated with different TNF-α inhibitors (adalimumab, etanercept and infliximab) for various rheumatological and gastro-enterological diseases. Although the underlying mechanisms are not known factors leading to a dysregulation of further cytokines (i.e. α-interferon), the activation of autoreactive T cells in susceptible individuals might play a role [12]. Furthermore, the immunogenetic background (e.g. certain HLA alleles) or TNF and TNF receptor polymorphisms may be involved in the patients' response to anti-TNF-α therapy [13]. Taken together, both enhanced or reduced levels of TNF-α may be associated with organ-specific or systemic auto-immune diseases. Thus, one may speculate that in our case adalimumab was involved in the induction of AA through modulation of TNF-α production and a subsequent dysregulation of the immune response towards hair follicles.

AA is a rather common disease with an incidence rate of 0.1–0.2% [14]. However, the true incidence of alopecia universalis is not exactly known. The incidence of severe forms of AA (totalis and universalis)

has been reported to range between 3.5 and 30% and is considered to be rarer in adults than in children [15, 16]. In fact, a study performed in a private practice could not find a single AA universalis in 135 patients [17]. Although a random coincidence of AA with TNF-α inhibitors may not completely be ruled out in our adult patient, the report of a previous case of AA universalis with adalimumab therapy as well as the possible pathophysiological role of TNF-α in inducing other auto-immune diseases argue against a merely coincidental finding [2, 9].

In conclusion, although TNF-α is thought to play a role in the pathogenesis of AA, this case together with previous reports, demonstrating the inefficacy of anti-TNF-α in treating AA, hinder the use of TNF antagonists in the treatment of AA.

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