

## Alopecia Areata Universalis Elicited during Treatment with Adalimumab

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### Key Words

Alopecia areata · Adalimumab · Tumour necrosis factor  $\alpha$  · Tumour necrosis factor inhibitors · Side effects

### Abstract

Adalimumab is a fully humanized recombinant anti-tumour-necrosis-factor (TNF- $\alpha$ ) 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- $\alpha$  was found in the mononuclear cell infiltrate. This case suggests a complex role of TNF- $\alpha$  in the induction of AA.

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### 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- $\alpha$ ) monoclonal antibody. It has previously been approved for the treatment of rheumatoid arthritis, active ankylosing spondylitis, psoriatic arthritis and Crohn's dis-

ease [1]. Despite the proven efficacy of anti-TNF- $\alpha$  in certain diseases, the neutralization of TNF- $\alpha$  by anti-TNF- $\alpha$  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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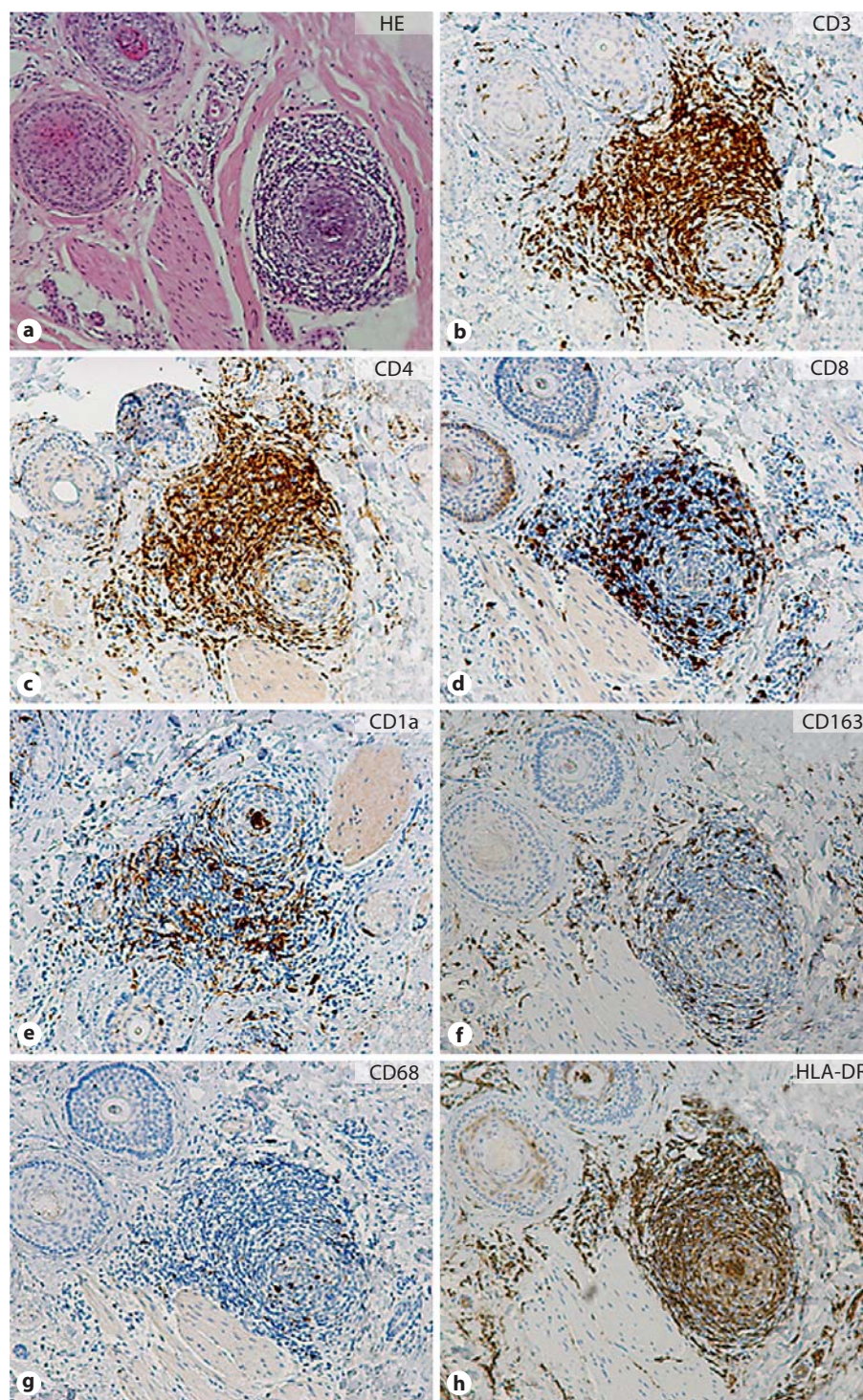
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**Fig. 2.** Histological examination (haematoxylin-eosin, HE) showing a peribulbar lymphocytic infiltrate with a reduced number of diminutive hairs (a) and immunohistochemical findings demonstrating CD3+ (b), CD4+ (c), CD8+ (d) T lymphocytes, CD1a+ 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  $\times 200$ .

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 psoria-

sis 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  $\leq 40$  IU/l) and ferritin 728  $\mu\text{g/l}$  (normal values 30–400  $\mu\text{g/l}$ ), 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- $\alpha$  (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- $\alpha$  in the mononuclear infiltrate could be demonstrated by immunofluorescence staining (fig. 3).

## Discussion

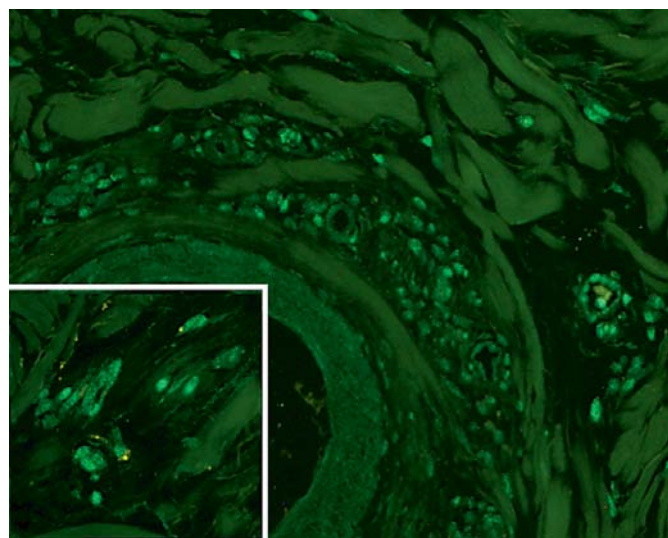
This report suggests that adalimumab can be causally related to the development of AA universalis. AA universalis represents the severest form of AA and mani-

fests 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- $\alpha$  significantly inhibited hair growth in vitro, it was hypothesized that in association with other cytokines, TNF- $\alpha$  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- $\alpha$ . The putative role of TNF- $\alpha$  in the pathogenesis of AA has led to attempts to treat AA with TNF- $\alpha$  antagonists like etanercept. However, previous case reports have failed to show efficacy of anti-TNF- $\alpha$  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- $\alpha$  is a cytokine of the innate immune system with broad pro-inflammatory and immunomodulatory effects [10]. Despite the proven efficacy of TNF- $\alpha$  antagonists in certain pro-inflammatory diseases, the neutralization of TNF- $\alpha$  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<sub>1</sub> 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- $\alpha$  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.  $\alpha$ -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- $\alpha$  therapy [13]. Taken together, both enhanced or reduced levels of TNF- $\alpha$  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- $\alpha$  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)



**Fig. 3.** Immunofluorescence staining showing TNF- $\alpha$ + cells around the hair follicle. Original magnification  $\times 200$ .

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- $\alpha$  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- $\alpha$  in inducing other autoimmune diseases argue against a merely coincidental finding [2, 9].

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

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