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Biologic Agents and Alopecia Areata

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Alopecia areata (AA) is considered an organ-specific autoimmune inflammatory disease, in which T lymphocytes play a central pathogenetic role [1]. Treatment of AA is often discouraging. The advent of the new biologic medications raised hopes for successful control of many immune-mediated diseases, including AA. Owing to the suspected involvement of tumor necrosis factor- α (TNF- α) in the pathogenesis of AA [2], one might expect that biologic therapies with anti-TNF- α agents might be beneficial.

A 30-year-old Greek woman presented with multiple patches of AA on the parietal and occipital scalp of few weeks duration. She had no personal or family history of AA, but she had experienced a serious psychological stress 1 month before the appearance of hair loss. The patient had a 3-year history of refractory rheumatoid arthritis and she was under treatment with cyclosporine (2.5 mg/kg/day) and leflunomide (20 mg daily). Nine months ago, adalimumab (40 mg s.c. every 2 weeks) was added to the therapeutic regimen. The patient was treated for her alopecia with topical and systemic corticosteroids, without discontinuing any of the prescribed agents for the rheumatoid arthritis. Three months later, the condition remains stable with only minimal hair regrowth.

The pathogenesis of AA remains incompletely understood. AA appears to be precipitated predominantly by CD8 lymphocytes, but the disease mechanism is driven by CD4 cells [1]. Lesional biopsies show a perifollicular lymphocytic infiltrate around anagen hair follicles and the depletion of these T-cell subtypes results in complete or partial regrowth of hair in the Dundee experimental bald rat model [3]. The immune system is likely to play an integral part in hair growth cycle. Philpott et al. [2] showed that IL-1 α , IL-1 β and TNF- α were potent inhibitors of hair follicle growth in vitro. Hoffmann et al. [4] studied the effect of a panel of cytokines and growth factors on hair growth: IL-2, IL-10 and IFN- γ had no effect in this regard, whereas TGF- β ₁ partially in-

hibited hair growth and EGF, TNF- α and IL-1 β completely abrogated it. All these evidences are in favor of an autoimmune phenomenon occurring in AA, with the TNF- α appearing as a potent inhibitor of hair growth.

In the last few years, several biologic agents acting on TNF- α or involving ICAM 1-LFA1 or CD2-LFA3 interactions have been considered as possible treatments for AA. Cases of AA have been described in which etanercept has been proven ineffective, or AA recurred during etanercept therapy for other disease [5]. Strober et al. [6] found that no hair regrowth occurred after treatment of AA with etanercept in 17 otherwise healthy patients. In addition, infliximab did not prevent AA development in a patient with no previous history of this disease [7]. Fabre and Dereure [8] reported worsening of AA in a patient receiving infliximab.

Adalimumab is a fully humanized recombinant anti-TNF- α monoclonal antibody which has been approved for rheumatoid arthritis, active ankylosing spondylitis, psoriatic arthritis and Crohn's disease. To our knowledge, our patient is the third reported case of AA developing during adalimumab therapy. Pelivani et al. [9] described a case of AA universalis elicited after 6 months of adalimumab monotherapy in a patient with a long-standing history of psoriatic arthritis and psoriasis. Garcia Bartels et al. [10] published a case of AA universalis, occurring 4 months after adalimumab was added to a regimen of prednisone and leflunomide. In our patient, apart from the introduction of adalimumab, other factors, namely serious psychological stress, might have played an important part in eliciting AA.

Our patient is the second reported case in which the introduction of adalimumab in a patient already under treatment with leflunomide was followed by AA development. Leflunomide is a new immunomodulatory drug that selectively acts on activated autoimmune lymphocytes by inhibiting dihydroorotate dehydrogenase, an enzyme required for de novo pyrimidine synthesis. These 2 cases suggest that leflunomide has probably no prophylactic or therapeutic effect on AA.

On the other hand, there is evidence suggesting that other biologic therapies that target T cells may represent an effective treatment modality for AA. Heffernan et al. [11] tried alefacept in 4 patients with AA. All 4 patients improved, indicating that alefacept may be effective. A case of AA successfully treated with efalizumab has been reported [12], however subcutaneous injections of efalizumab did not seem to be effective in 62 patients with AA [13]. Furthermore, in one case of AA, efalizumab was proven ineffective [7].

In light of the suggested pathogenetic relationship of AA and TNF- α , it is noteworthy to report cases of AA that occurred and progressed during treatment with TNF- α -blocking agents. The understanding gained from this experience should redirect the therapeutic aims toward alternate interventions.

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