Alopecia areata after denosumab treatment for osteoporosis

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INTRODUCTION

In the last 2 decades, various biologic agents have been developed to treat autoimmune disorders. Along with their high clinical efficacy, these agents have been associated with several paradoxical proinflammatory or autoimmune reactions, such as autoimmune hepatitis, drug-induced lupus erythematosus, psoriasiform eruptions, and alopecia areata (AA). New cases of AA become more frequent in patients undergoing treatment with biologic therapies, especially anti–tumor necrosis factor (TNF)-alpha agents, including infliximab, adalimumab, and etanercept.[1] Development of AA also has been noted with other biologic agents such as efalizumab, ustekinumab, and daclizumab.[2-4] Denosumab is a new biologic agent that suppresses osteoclast-mediated bone resorption. This agent was recently approved by the US Food and Drug Administration for treatment of osteoporosis in postmenopausal women at high risk of fracture and prevention of skeletal-related events in patients with bone metastases and unresectable giant cell tumors. Denosumab is a fully human monoclonal antibody to receptor activator of nuclear factor kappa β ligand (RANKL) that belongs to a group of anti-TNF agents. We describe a case of extensive AA after treatment with denosumab.

CASE REPORT

A 69-year-old white man was referred for rapidly progressive hair loss of 2 weeks' duration. The patient's medical history included vitamin B12 deficiency, psoriasis with mainly scalp involvement, and severe osteoporosis caused by renal phosphate leak along with the family history of severe osteoporosis.

Abbreviations used:

AA:	alopecia areata
RANK:	receptor activator of nuclear factor kappa
RANKL:	receptor activator of nuclear factor kappa β ligand
TNF:	tumor necrosis factor

Given the lack of response to treatment of osteoporosis with bisphosphonates, calcium, and vitamin D and an increased risk for fractures, subcutaneous injection of denosumab at a dose of 60 mg was administered. About 2 weeks after receiving the denosumab, the patient had rapidly progressive nonscarring patchy hair loss with clinical and dermoscopic features of AA, which resulted within 2 months in alopecia universalis (Fig 1). There was no nail involvement. Simultaneously, scalp psoriasis regressed. The patient denied family or personal history of AA and didn't report any recent infection, vaccination, or stress. Complete blood count and blood chemistry results were normal, and antinuclear antibodies were negative. Histopathology of the scalp found features of AA on the background of psoriasiform epidermal hyperplasia (Fig 2). Treatment was started with a daily application of betamethasone valerate 0.1% solution in combination with topical 5% minoxidil solution. On follow-up after 10 months, the patient had only minimal vellus hair regrowth.

DISCUSSION

The TNF-family molecule RANKL and its receptor RANK (receptor activator of nuclear factor kappa) were originally identified as key regulators of bone remodeling and are essential for the differentiation,

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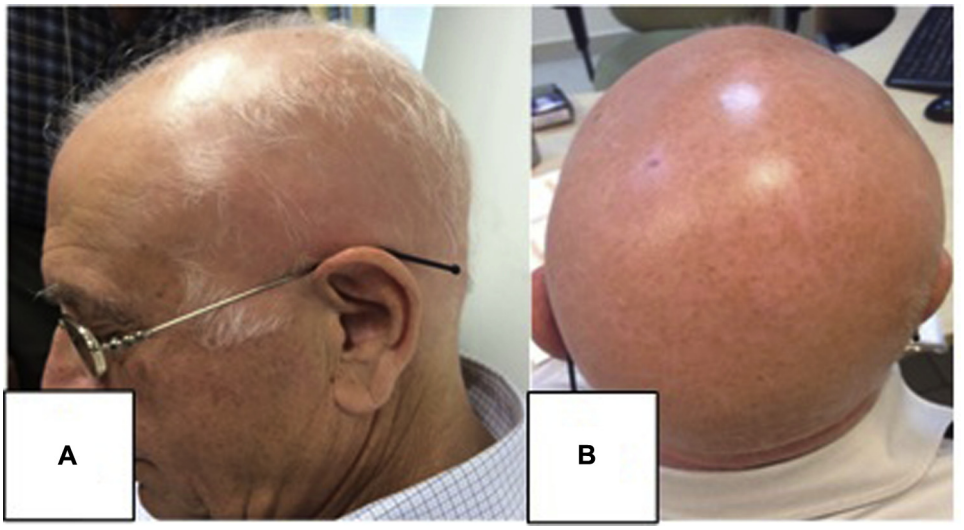

Fig 1. **A**, Extensive AA 2 weeks after denosumab injection. **B**, Two months after denosumab treatment, AA universalis.

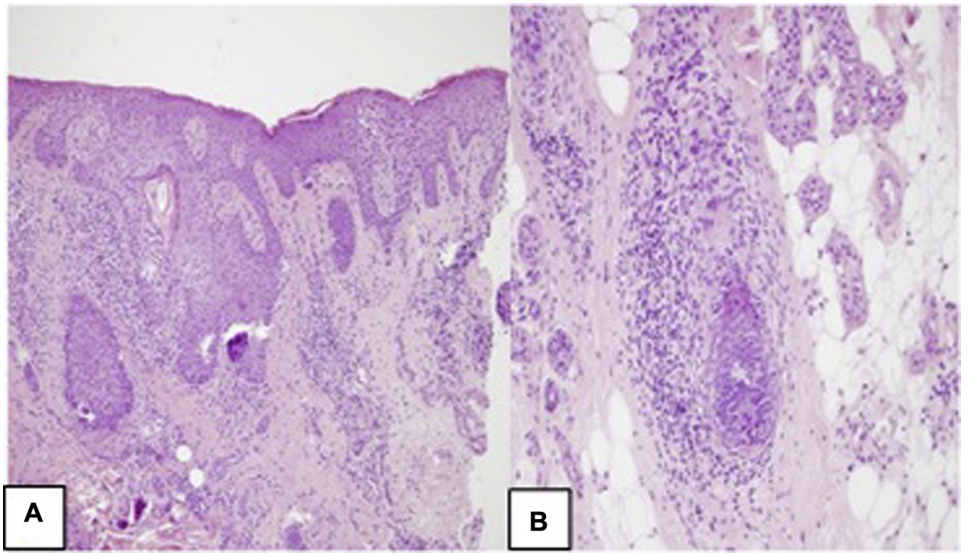

Fig 2. Histopathology of the scalp. **A**, Psoriasiform epidermal hyperplasia, focal thinning of the superpapillary plate, dilated dermal papillae containing tortious blood vessel capillaries, perifollicular and perivascular lymphocytic infiltrate. Most hair follicles are in the catagen/telogen phase and miniaturized. **B**, Peribulbar lymphocytic infiltrate. (**A** and **B**, Hematoxylin-eosin stain.)

activation, and survival of osteoclasts. Mice deficient in RANK or RANKL display increased bone density owing to reduced osteoclast formation, whereas the loss of the RANKL decoy receptor osteoprotegerin results in lower bone mass caused by unchecked RANK activation.[5,6] Denosumab is a fully human monoclonal antibody to RANKL that belongs to a group of anti-TNF agents. Our case describes a patient that had AA shortly after treatment with denosumab and, therefore, raises the possibility of the relationship to this drug. The patient had no previous personal or family history of AA. However, the presence of other autoimmune diseases, such as psoriasis and B12 deficiency, are known to be risk factors for an additional autoimmune disease.

We suggest 2 possible mechanisms of the development of AA after the administration of denosumab. First, as a member of TNF/TNF receptor superfamily, denosumab bears homology to TNF-α and therefore may cause paradoxical autoimmune reaction similar to those reported after using several TNF-α inhibitors. In addition to a role in controlling

bone mass, RANKL/RANK interactions also have been recognized as regulators of T-cell/dendritic cell communications, lymph node formation, and epithelial cell growth and differentiation.[7] The interaction between the RANKL, RANK, and osteoprotegerin plays a crucial role in the formation of medullary thymic epithelial cells containing nuclear molecules called *autoimmune regulators* and establishing self-tolerance. It was found that lymphocytes generated without RANKL fail to establish self-tolerance and cause severe autoimmune phenotypes.[8] A second possible mechanism that could explain the development of alopecia may be related to the impact of RANK on epithelial cell growth and hair cycling. It was found that RANK is expressed by the hair follicle germ, bulge stem cells, and the epidermal basal cells and has been recognized for its role in the renewal of the epidermo-pilosebaceous unit.[9] RANKL is actively transcribed by the hair follicle at initiation of its anagen, thus, providing a mechanism for stem cell RANK engagement and hair-cycle entry. It was found that mice deficient in RANKL are unable to initiate a new anagen, whereas transgenic mice overexpressing RANK in the hair follicle or administration of recombinant RANKL both trigger epidermal growth and anagen entry.

Perhaps both mechanisms suggested participate in our case; the autoimmune mechanism led to AA and the absence of RANK stimulation prevented new anagen initiation leading to the persistent disease course. Complete clinical remission of scalp psoriasis observed in our case raises a thought about testing the effect of RANK inhibitors on psoriasis. According to published records, side effects associated with denosumab include musculoskeletal pain, arthralgia, cystitis, and nasopharyngitis. Regarding the impact of denosumab on hair, in the phase 1 trial hair loss was observed in 11% of Japanese women treated for breast cancer–related bone metastases.[10] However, the study does not specify the type of hair loss, and all participants received concurrent chemotherapy or hormonal therapy. Therefore, hair loss may not have been related to treatment with denosumab. So far, we did not find previous reports of AA after treatment with denosumab. Physicians treating their patients with different biologic medications should be aware of potential paradoxical autoimmune side effects including the development of AA.

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