

Onset of Schamberg's disease and resolution of alopecia areata during treatment of atopic dermatitis with dupilumab

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Atopic dermatitis (AD) is a chronic pruritic immune-mediated inflammatory dermatosis with high prevalence both in children and adults. AD pathogenesis is multifactorial, including genetic, immunological, and environmental factors that cause skin barrier dysfunction, alterations in cell mediated immune responses and IgE mediated hypersensitivity. Dupilumab is an interleukin 4 (IL-4) receptor α -antagonist that inhibits IL-4/IL13 signaling through blockade of the shared receptor subunit for IL-4 α . This leads to a downregulation of the Th2 immune response which is the mechanism responsible for the efficacy of dupilumab in patients with AD [1]. Schamberg's disease (SD), also known as progressive pigmented purpuric dermatitis, is the most common pigmented purpuric dermatosis (PPD); it is a recurrent skin disorder characterized by non-palpable pinpoint symmetrical petechial and pigmented macules, purpura, and sometimes telangiectasia, especially on the extremities [2]. Etiology is unknown, although it is plausible that immune-mediated mechanisms may play a role. Alopecia areata (AA) is an autoimmune non-scarring alopecia with heterogeneous severity and distribution that affects up to 2% of the general

population. Currently, available treatment options for AA are of limited efficacy and can be associated with adverse effects [3].

Here, we describe the case of a man affected by severe AD and scalp AA, that developed a form of PPD and concomitant improvement of AA during treatment with dupilumab for AD.

A 30-year-old man with AD since childhood was referred to our Unit. At physical examination, we observed an involvement of his entire body with severe erythema, thickness and lichenification (Eczema Area and Severity Index – EASI: 36 and Dermatology Life Quality Index – DLQI: 18).

He had previously undergone several conventional treatments for AD, including systemic corticosteroids, phototherapy, methotrexate and cyclosporine which was discontinued for nephrotoxicity. Furthermore, he had a 2-year history of alopecia areata (AA) distributed over the entire surface of the scalp. Eyebrows and beard were spared. He had received topical and systemic corticosteroids without significant improvement.

Due to intolerance and failure of the previous therapies, dupilumab therapy was started as a treatment for AD, with an initial dose of 600 mg and subsequent biweekly 300 mg injections. After 3 months of follow-up, clinical examination revealed improvement of AD (EASI 9,6; DLQI 8) but onset of numerous 2-3 mm red/brown, non-blanching, petechial non-pruritic macules, scattered on bilateral forearms and back of the hands (Fig. 1a). He denied itching and burning. Punch biopsy of a purpuric lesion showed hyperkeratosis and acanthosis of the epidermis, mild dermal perivascular lymphocytic infiltration, with erythrocyte extravasation and hemosiderin deposition consistent with SD. Direct immunofluorescence was negative for perivascular or dermo-epidermal immunoglobulin or

complement deposition. Dupilumab was discontinued because of this adverse effect. There was total regrowth of AA of the scalp after 3 months of therapy. Follow-up visits at 1, 3 and 6 months after discontinuation of dupilumab and any other therapy for AD showed no recurrence of AA and progressively complete remission of SD (Fig. 1b) with absence of AD relapse (EASI 5,2; DLQI 5).

SD is included in the group of PPDs which include a spectrum of vascular diseases with different clinical aspects, but with some common histopathological features, including a few epidermal changes (hyperkeratosis, parakeratosis, or acanthosis), perivascular lymphocytic infiltration, red blood cell extravasation, hemosiderin deposition, endothelial cell swelling, spongiosis, lymphocyte exocytosis and lichenoid lymphocytic infiltration [4]. The vascular damage and erythrocyte leakage are probably secondary to a localized T cell-mediated reaction in the vicinity of dermal capillaries. Venous hypertension, stasis, exercise, trauma, contact allergy, dietary factors, alcohol intake, systemic and focal infections are considered risk factors. Drug-induced SD cases are reported in the literature a like as aspirin, thiamine, acetaminophen and amlodipine [4].

Dupilumab is the first biologic drug approved for the treatment of moderate to severe AD. Inhibition of the release of pro-inflammatory cytokines, chemokines and IgE make this monoclonal antibody suitable for both atopic dermatitis and alopecia areata, that share some Th2 mediated pathogenetic mechanisms [1]. Although it is considered a safe drug, high rates of unspecified conjunctivitis have been reported in patients under treatment with dupilumab [1]. Other adverse effects reported are injection site reactions, exacerbations of AD, headache, skin infections (bacterial and herpetic), nasopharyngitis and headache [1]. Development of Shamberg's disease in association with dupilumab treatment has never been described in previous clinical trials or case reports. On the other hand, we cannot

derive from our case any definitive conclusions concerning the role of dupilumab in SD, given that readministration of the drug was not considered in order to avoid triggering an eventual relapse.

AA can be associated with atopy, but the relationship between dupilumab and AA is controversial: some reports describe dupilumab-induced alopecia [5-7] whereas other reports show improvement of AA related to the treatment [8,9]. AA and AD share similar genetic background with common coexistence of the two diseases, as well as other shared clinical and immunological pathways and features, in particular a strong Th2 component and IL-23 up-regulation [5,10]. Th2-pathway genes upregulation is common in both AD and AA, and consequently downregulation with dupilumab can explain its therapeutic efficacy in AA [10]. On the other hand, other immunological mechanisms might amplify the Th1 pathway and promote the development of alopecia areata after treatment with dupilumab [10]. According to previous reports, dupilumab can induce hair regrowth in AA, usually 3-6 months after initiation of therapy, although it may begin already after the initial doses [8,9]. In our patient, a complete resolution of alopecia areata was observed after 3 months of therapy.

In conclusion, this is the first case of a patient with severe AD and AA treated with a short course of dupilumab showing both the development of SD and the simultaneous complete resolution of AA.

The authors declare no conflicts of interest and no financial sources in this research.

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Legend to figures

Figure 1. (a) Bilateral red/brown, petechial non-pruritic macules scattered on bilateral forearms and back of the hands. The histological examination was consistent with the diagnosis of Schamberg's disease. (b) Almost complete remission of the lesions after discontinuation of dupilumab

