SHORT COMMUNICATION

Scarring Alopecia Under Immune Checkpoint Blockade: a Report of Three Cases

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Immunotherapy with anti-programmed cell death protein 1 (PD-1) and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies is now a standard therapy for many malignancies. The mode of action involves inhibition of negative regulators of T cell activation, which also induces immune-related adverse events (irAE). More than 40% of patients develop cutaneous side-effects, most frequently maculopapular rash, pruritus and vitiligo (1). Alopecia has been observed as a rare adverse event with a prevalence of up to 2% (1). However, the underlying cause of alopecia has not yet been thoroughly studied, either clinically or histologically (2–4). To date, mainly non-scarring alopecia areata has been reported as the causal disease for alopecia associated with checkpoint inhibition (5, 6). We report here 3 patients with scarring alopecia under treatment with anti-PD-1 and anti-CTLA-4 antibodies.

CASE REPORTS

Case 1. A 62-year-old woman with pulmonary metastatic melanoma received combination therapy with nivolumab and ipilimumab. After 3 doses she developed grade 3 autoimmune colitis, which resolved on corticosteroid-tapering. Computed tomography (CT) scans revealed regression of the pulmonary metastases; therefore treatment with nivolumab monotherapy was continued. Two and a half months later she noticed complete hair loss of the eyebrows and frontotemporal recession of the hairline with single hairs in the middle of the forehead ("lonely hair" sign), perifollicular erythema and hyperkeratosis (**Fig. 1**a, b). Scalp punch biopsy revealed perifollicular lichenoid interface dermatitis at the isthmus of the hair shaft surrounded by fibrosis. The clinical presentation and histopathology were consistent with the diagnosis of frontal fibrosing alopecia (FFA). She started treatment with topical clobetasol 0.5 mg/g solution. After 2 months' treatment, inflammation and hair loss improved slightly. The patient refused additional medication with oral hydroxychloroquine due to possible side-effects. Nivolumab was discontinued after 1.5 years. After 3 years she still showed continued remission of the pulmonary metastases. FFA was progressing slowly with further receding hairline.

Case 2. 76-year-old woman with incomplete-resected mucosal melanoma of the paranasal sinus received pembrolizumab for over 2 years. While on treatment, she developed multiple, mild (grade 1–2) cutaneous irAE, such as rash, pruritus and non-segmental vitiligo. After 2 years she presented patchy alopecic areas with loss of follicular ostia on her scalp. The surrounding hair follicles showed perifollicular erythema and follicular hyperkeratosis (Fig. 1c, d). Histopathology revealed interface dermatitis with dense lymphocytic infiltrate around the isthmus and infundibulum and mucinous perifollicular fibrosis (**Fig. 2**) consistent with the diagnosis of lichen planopilaris (LPP). Topical therapy with clobetasol 0.5 mg/g solution was initiated and the inflammation decreased. She stopped pembrolizumab after 2.5 years of treatment due to sustained complete remission.

Case 3. A 63-year-old woman with malignant melanoma received adjuvant therapy with nivolumab after complete resection of a single cutaneous metastasis. Following 16 weeks of therapy, she reported severe pruritus and hair loss from the scalp. On clinical examination perifollicular erythema and collar-like scaling around the hair follicles were found. Histological workup showed interface dermatitis at the isthmus of the hair follicles with incipient fibrosis consistent with the diagnosis of LPP. Topical therapy with clobetasol 0.5 mg/g solution led to a rapid improvement in pruritus and she proceeded with nivolumab.

DISCUSSION

Alopecia has been observed as a side-effect of checkpoint inhibitors, but to the best of our knowledge no comprehensive analysis has been conducted. This case series reports 3 patients who developed scarring alopecia under immune checkpoint inhibitors. In 2 patients the

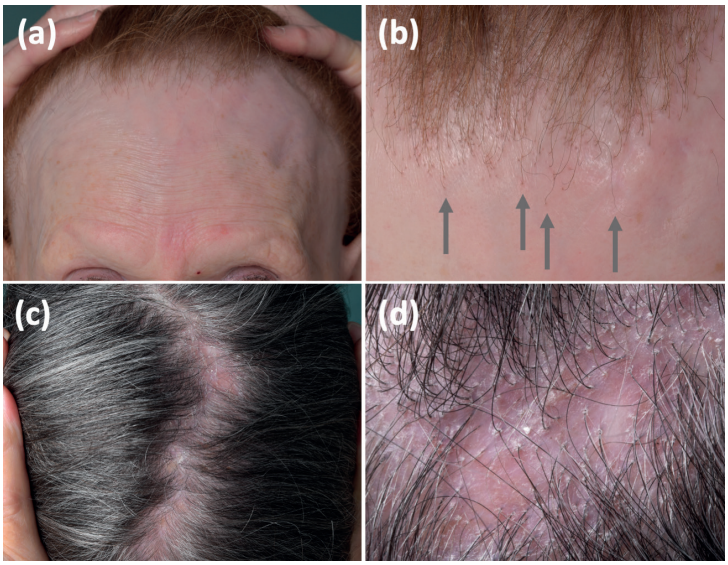

Fig. 1. Clinical images of scarring alopecia under immune checkpoint blockade. (a) Case 1: Complete bilateral hair loss of the eyebrows and recession of the frontotemporal hairline 2.5 months after initiation of combination therapy with ipilimumab and nivolumab. The clinical findings were consistent with frontal fibrosing alopecia (FFA). (b) *Arrows* mark single hairs in the middle of the forehead of the same patient. This so called "lonely hair"-sign is typical for FFA. (c) Case 2: Hairless patches without any follicular openings on the scalp after 2 years of treatment with pembrolizumab. (d) Erythema and collar-like scaling around the surrounding hair follicles are characteristic features of lichen planopilaris.

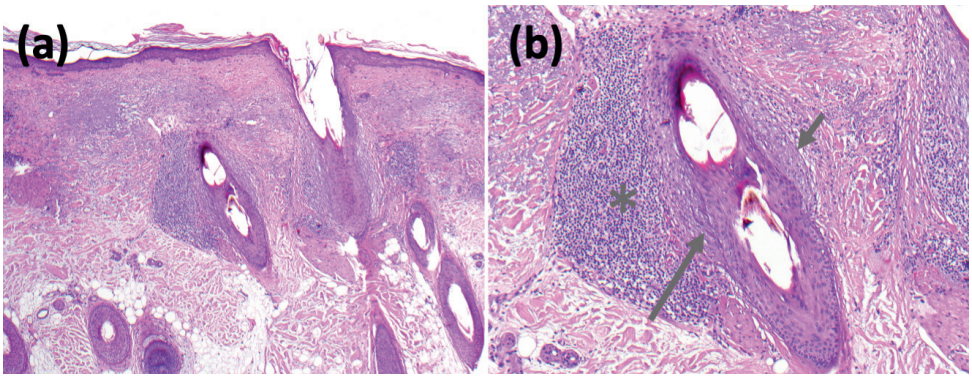

Fig. 2. Histopathology of scarring alopecia under immune checkpoint blockade. (a) Vertical sections of a scalp punch biopsy of case 2 show dense lichenoid interface dermatitis around the infundibulum and isthmus of the hair follicle (Haematoxylin and eosin (H&E) stain ×50). (b) The asterisk marks the lymphocytic infiltrate damaging the hair follicle epithelium (*long arrow*). *Short arrow* marks the perifollicular fibrosis (H&E stain ×200).

clinical presentation was consistent with the diagnosis of LPP. One patient was diagnosed with FFA, which is considered a clinical variant of LPP. We found only one other case of LPP associated with checkpoint inhibition in the literature published in English (7). This was a case of a 47-year-old melanoma patient, who developed oral lichen planus and LPP 2 months after initiation of pembrolizumab therapy (7). We report here the first case of FFA associated with immune checkpoint blockade.

LPP is a rare chronic inflammatory skin disease characterized by an interface dermatitis, which destroys hair follicles and results in irreversible, scarring alopecia (8, 9). Patients with LPP present patchy alopecic areas on the scalp with erythema and hyperkeratosis around the surrounding hair follicles. Accompanying pruritus, burning or pain of the scalp are common. FFA differs from LLP mainly in the clinical picture. It typically occurs in postmenopausal women and is characterized by a recession of the frontotemporal hairline. Eyebrows may also be affected. Histologically, both LPP and FFA present interface dermatitis with a lichenoid lymphocytic infiltrate around the upper part of the hair follicle (Fig. 2). Subsequently, this immune reaction results in irreversible degeneration of the hair follicle epithelia, which are replaced by fibrosis (8, 9).

Lichenoid interface dermatitis reflects T-cell activation leading to T-cell-mediated epidermal damage. This histological inflammatory pattern has been described in numerous cutaneous irAE (1). Interestingly in the context of immune checkpoint blockade, expression of PD-1-PDL(ligand)-1 supports the immune privilege of the bulge region to suppress auto-reactive T cells in the healthy human hair follicle (10). Blocking PD-1 might thus promote an immune privilege collapse, similar to the one proposed for the pathogenesis of alopecia areata (9). These observations suggest that checkpoint inhibitors may induce *de novo* or aggravate pre-existing LPP/FFA, leading to scarring alopecia.

Two of our patients were diagnosed as LPP and FFA a few months after initiation of immunotherapy, suggesting a temporal relationship between the drug and the development of alopecia. However, a late onset after 2 years, as seen in our second patient, does not exclude an association with immunotherapy since late occurrence of cutaneous irAE has been described (1). Although all patients received a complete body examination before the initiation of treatment, mild signs of hair loss could have been missed. Especially in our second patient scarring patches were noticed when already advanced. Pruritus of the scalp or other accompanying symptoms, which could have led to an early detection of alopecia, had not been present. Therefore, aggravation of a pre-existing condition under immune checkpoint blockade is also possible. We can only hypothesize that a potential disposition in the 3 postmenopausal, female patients reported here led to development of LPP rather than alopecia areata after initiation of treatment.

The current series provides further evidence that, besides previously described non-scarring alopecia areata, scarring forms of alopecia are also associated with immune checkpoint blockade. With the increasing use of checkpoint inhibitors in more and more malignancies, healthcare providers are encouraged to thoroughly examine patients regularly for different forms of hair loss. Clinical examination in combination with a skin sample biopsy will lead to the exact diagnosis. Precise diagnoses may also contribute to a better understanding of immunotherapy-associated alopecia, which might currently be an underestimated side-effect.

Therapeutic options for LPP/FFA include not only topical steroids as used for our patients. Intralesional steroid injections, topical tacrolimus, hydroxychloroquine, doxycycline or retinoids represent further therapeutic options (8, 9). In cancer patients with immunotherapy-associated scarring alopecia our first-line treatment would be clobetasol 0.5 mg/g solution (on the affected areas twice daily for 2–3 months) combined with hydroxychloroquine (200 mg twice daily) (8, 9). Early therapeutic intervention may prevent disfiguring alopecia particularly in long-term cancer survivors and makes a decisive contribution to their quality of life.

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