Nivolumab-Induced Alopecia Areata: A Case Report and Literature Review

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Nivolumab (anti-PD-1) is one of the ICIs currently used in the treatment of many cancers such as hepatocellular carcinomas (HCC), lung cancers, colon cancers, and melanomas. As the usage of nivolumab has increased, so have the reports of many cutaneous side effects including AA. Although worldwide there have been several reports regarding AA that have been diagnosed with clinico-histological correlations. In addition to these cutaneous side effects, alopecia, including alopecia areata (AA), alopecia universalis, and diffuse alopecia, were also known side effects of PD-1 receptor inhibitors and anti-CTLA-4 agents, with a prevalence of 1.0% ~ 2.0%.

However, there have been only a few reports regarding AA that have been diagnosed with clinico-histological correlations.

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Regarding AA induced by nivolumab, this has not yet been reported in Korea. Herein, we report on a case of AA after treatment with nivolumab for an HCC.

**CASE REPORT**

A 55-year-old male presented with multiple hairless patches on his scalp dating back 1 month. He had suffered from an HCC and had been treated with nivolumab for 6

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**Fig. 1.** Multiple hairless patches on the vertex without eyebrow, eyelash, or other body hair involvement (A: vertex; B: occiput; C: left temporal area of the scalp). We received the patient’s consent form about publishing all photographic materials.

**Fig. 2.** (A) Decrease of hair follicles with inflammatory cell infiltrations in the perifollicular area. Nearly all follicles were in the telogen stage (H&E, ×40). (B) Mild lymphocyte infiltration in the perifollicular area (H&E, ×100).

**Fig. 3.** After 2 months of topical treatment, patient hair loss was aggravated and progressed to alopecia totalis (A: vertex; B: occiput; C: left temporal area of the scalp).
months after a hepatectomy. Five months after taking nivolumab, patient’s hair loss started. He was treated for hair loss with triamcinolone intrakleosomal injections at a different hospital without improvement. A physical examination revealed multiple hairless patches on his entire scalp without eyebrow, eyelash, or other body hair involvement (Fig. 1). Nail pitting was not found. The severity of his alopecia tool (SALT) score was evaluated as grade S2. He didn’t have any previous history of AA. We performed skin biopsy on the hairless patches of his scalp. Histopathological findings revealed a decreased number of hair follicles with peripheral lymphocytic infiltration. Most follicles were in the telogen stage, and the telogen/anagen hair ratio was approximately 1 (Fig. 2). Dermoscopic findings revealed lots of broken hairs with black dots. With clinicopathological correlations, we diagnosed him as having AA. Treatment included topical steroids and minoxidil. Despite 2 months of topical treatments the patient’s hair loss was aggravated with resultant alopecia totalis (Fig. 3). His SALT score was upgraded to S4. No hair regrowth was noted after 4 months of follow-up. After his alopecia treatments, the patient was diagnosed with thyroid metastases during his routine follow-ups, and he underwent additional radiotherapy. With this patient’s condition, he didn’t undergo AA treatment.

**DISCUSSION**

AA is a rare side effect of ICI treatments. The first case of alopecia was reported in 2006 with at least 31 cases having been reported since then: 20 cases with anti-PD-1; 2 cases with anti-CTLA-4; 3 cases with both anti-PD-1 and anti-CTLA-4; and 6 cases with monoclonal antibodies targeting the PD-L1. However, almost anti PD-1 cases reported without type classification of alopecia except 5 cases. These anti PD-1 induced alopecia patients’ information were summarized in Table 1.

AA is an acquired autoimmune disease which can be associated with other autoimmune disorders (e.g., vitiligo, thyroiditis, and type 1 diabetes). The diagnosis is clinical with areas of alopecia being well defined, localized, or diffuse, and non-scarring. Numerous and regular yellow dots, black dots, and exclamation mark hairs are evocative on dermoscopy. Histology is necessary in case of doubt, and is characterized by a peribulbar lymphocytic inflammation of variable intensities in the acute stage, and a miniaturization of follicles with an inversion of the telogen/anagen hair ratio during the subacute and chronic stages. Our patient’s clinical and histopathological findings were in agreement with the diagnosis of AA. However, it is doubtful whether AA was caused by nivolumab.

### Table 1. Literature review of anti PD-1 induced alopecia patients’ information

| Reference journal | No. | Drug | Age (y)/Sex | Type | Onset after anti-PD-1 (mo) | SALT | Prognosis |
|------------------|-----|------|-------------|------|--------------------------|------|-----------|
| Lakhmiri et al. 5 | 4   | Nivolumab | 54/Female | AA  | 6                        | S5 (AU) | No regrowth of hair |
| Guidry et al. 7  | 1   | Pembrolizumab | 64/Female | AA  | 15                       | S2    | Partial regrowth |
| Hafmann et al. 6 | 2   | Nivolumab | 29/Female | Unclassified | 4    | S1    | Complete regrowth |
| Weber et al. 6   | 8   | Pembrolizumab | 29/Female | Unclassified | 9    | S1    | Complete regrowth |

SALT: severity of alopecia tool, AU: alopecia universalis, -: information was not mentioned in reference article.
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While several cases have been reported, the pathogenesis of nivolumab-induced AA remains unclear. There has been a report discussing nivolumab-induced vitiligo, and we suggest that nivolumab PD-1/PD-L1 binding may upregulate cytotoxicity of T cells against autoantigens through down regulation of regulatory T cells, which could break immune tolerance. In this inflammatory environment, cytotoxic T cells may easily target autoantigens associated with melanogenesis, and it may potentially play a key role in both AA and vitiligo.

Additionally, as I summarized in Table 1, significant proportion of alopecia was found in melanoma patient. This phenomenon may also associate with mechanism of anti-PD-1 therapy as I suggested above. Melanoma itself activates regulatory T cell to avoid immune response. Target therapy of melanoma focused on down-regulation of regulatory T cell. Inflammatory environment which induced by anti-PD-1 therapy, could easily break immune tolerance and there were possibility of autoimmune reaction like AA. These immune responses may also share common melanocytes associated antigen in pathogenesis of AA, and diminished of melanoma. This common antigen may lead high prevalence of AA in melanoma treating nivolumab.

Our case is likely related to nivolumab since it is known to induce irAEs and given the delay of a few months between its introduction and the occurrence of hair loss. According to previous reports, nivolumab-induced AA occurred 2 to 15 months after nivolumab injections. Our patient also showed hairless patches 5 months after injections. The lack of a previous or familial history of AA increased the possibility of nivolumab-induced AA.

Prior studies have suggested that ICI-induced vitiligo appears after the destruction of melanocytes, and is associated with a good response to treatment in melanomas. Similar to this result, some authors suggest that nivolumab-induced AA is also a sign of a good response to cancer treatments. However, since our patient showed thyroid metastasis, this hypothesis requires additional investigation.

As mentioned above, it appears as if nivolumab-activated autoantibodies are associated with melanogenesis, and therefore with the pathogenesis of vitiligo and AA. However, there have been some case reports regarding hair repigmentation after nivolumab treatments. Similar to vitiligo and AA pathogenesis, hair repigmentation is associated with the immune response, but the mechanism is thought to be completely different. Nevertheless, it is certain that nivolumab influences the melanogenesis pathway to some degree.

There was possibility of association with AA and HCC, so-called paraneoplastic alopecia. However, there was only one report about paraneoplastic alopecia in cat. And no case reported in human associated with HCC. So it seemed poor relationship between the patient’s hair loss and HCC.

Further research is needed to better understand the mechanisms that cause nivolumab side effects. Timely recognition and early dermatological intervention for AA are vital to prevent its progression, minimize additional involvement, and maintain the patient’s quality of life. With the expanding use of nivolumab, physicians must carefully evaluate the state of the patient’s hair which will require a proper dermatological consultation.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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DATA SHARING STATEMENT

Research data are not shared.

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