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CASE REPORT

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

Ki-Hun Kim, Woo-Young Sim, Bark-Lynn Lew

Department of Dermatology, Kyung Hee University School of Medicine, Seoul, Korea

Nivolumab (anti-PD-1) currently used in many cancers. With the usage of nivolumab increased, many cutaneous side effects were reported including maculopapular rash, lichenoid reactions, vitiligo, bullous disorders, psoriasis exacerbation, and alopecia areata (AA). Here, we report AA after nivolumab for treatment of hepatocellular carcinomas (HCC). A 55-year-old male presented with multiple hairless patch from 1 month ago. He suffered HCC and treated with nivolumab for 6 months after hepatectomy. He treated for hair loss with triamcinolone intra-lesional injection without improvement. We performed skin biopsy on the scalp. Histopathologic findings revealed decreased of hair follicles on the horizontal section with lymphocyte infiltration on the perifollicular area on the vertical section. Clinicopathologic findings were agreed with AA. Considering lack of previous history of AA and hairless patches with 6 months after nivolumab injection, we diagnosed him as nivolumab induced AA. Treatment included topical steroid, and minoxidil. No regrowth of hair was noted after 4 months of follow-up. Nivolimumab induced AA is rare side effect. Pathogenesis of nivolumab induced AA remain unclear. But our case is likely related to nivolumab, known to induce immune related adverse events, and given in the delay of a few months between introduction and the occurrence of the hair loss. Here, we reports nivolmumab induced AA; rare side effect. **(Ann Dermatol 33(3) 284～288, 2021)**

-Keywords-
Alopecia areata, Nivolumab

INTRODUCTION

Immune checkpoint inhibitors (ICI) are new therapies used for solid and hematologic cancers. These novel agents consist of monoclonal antibodies that target immune check points, including the cytotoxic T-lymphocyte associated protein-4 (CTLA-4), and the programmed cell death protein-1 (PD-1) receptors and its ligand (PD-L1)[1,2]. They induce activation of CD4 and CD8 cells that target tumor cells and may target unidentified cutaneous antigens resulting in an inflammatory process after cross-reaction with normal antigens, and in immune-related adverse events (irAEs)[3]. IrAEs include endocrinopathies, pneumonitis, colitis, hepatitis, and dermatological events. Dermatological side effects include maculopapular rashes, lichenoid reactions, pruritus, vitiligo, bullous disorders, and psoriasis exacerbations[3]. 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%[3]. However, there have been only a few reports regarding AA that have been diagnosed with clinico-histological correlations[4].

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 re-

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Corresponding author: Bark-Lynn Lew, Department of Dermatology, Kyung Hee University Hospital at Gangdong, 892 Dongnam-ro, Gangdong-gu, Seoul 05278, Korea. Tel: 82-2-440-7329, Fax: 82-2-440-7336, E-mail: bellotte@hanmail.net
ORCID: https://orcid.org/0000-0003-4443-4161

garding AA induced by nivolumab[5], 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

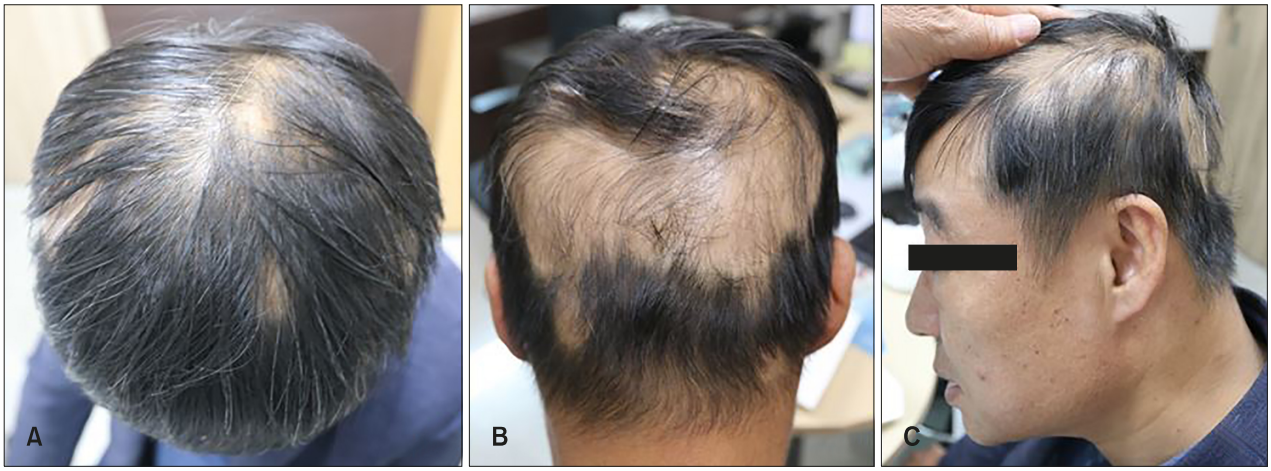

Fig. 1. Multiple hairless patches on the vertex without eyebrow, eyelash, or other body hair involvement (A: vertex; B: occiput; C: left temporal area of the scalp). We received the patient's consent form about publishing all photographic materials.

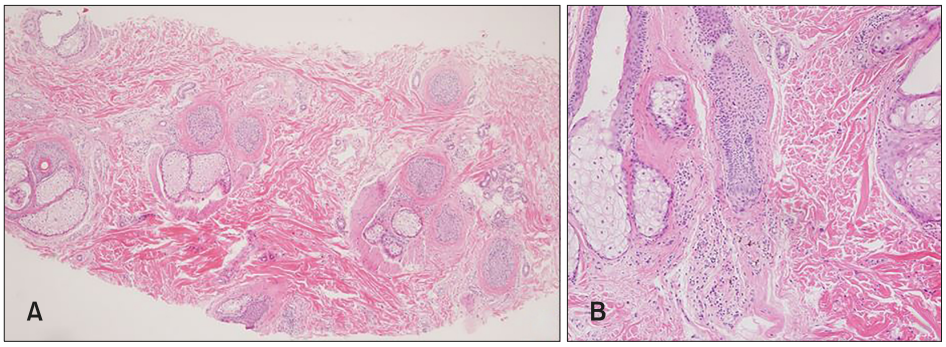

Fig. 2. (A) Decrease of hair follicles with inflammatory cell infiltrations in the perifollicular area. Nearly all follicles were in the telogen stage (H&E, ×40). (B) Mild lymphocyte infiltration in the perifollicular area (H&E, ×100).

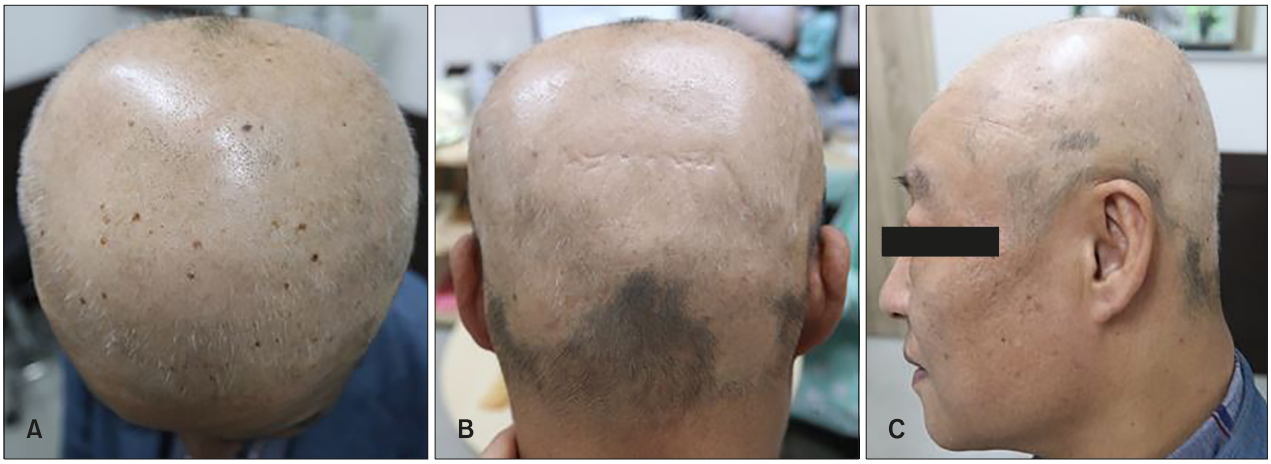

Fig. 3. After 2 months of topical treatment, patient hair loss was aggravated and progressed to alopecia totalis (A: vertex; B: occiput; C: left temporal area of the scalp).

months after a hepatectomy. Five months after taking nivolumab, patient's hair loss started. He was treated for hair loss with triamcinolone intralesional 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 perifollicular 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 that time: 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[5]. 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[5-8].

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[9]. Our patient's clinical and histopathological findings were in agreement with the diagnosis of AA.

However, it is doubtful whether AA was caused by nivolu-

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

Reference journal	No.	Drug	Type	Age (yr)/Sex	Cancer	Onset after anti-PD-1 (mo)	SALT	Prognosis
Lakhmiri et al.[5]	4	Nivolumab	AA	54/Female	Lung	6	S5 (AU)	No regrowth of hair
			AA	64/Female	Lung	15	S2	Partial regrowth
			AA	29/Female	Melanoma	4	S2	Complete regrowth
			AA	33/Female	Melanoma	2	S1	Partial regrowth
Guidry et al.[7]	1	Pembrolizumab	AA	64/Female	Melanoma	9	S1	Complete regrowth
Hofmann et al.[8]	7	Nivolumab	Unclassified	62/Female	Melanoma	19	-	Partial regrowth
		Nivolumab	Unclassified	70/Female	Melanoma	3	-	Partial regrowth
		Nivolumab	Unclassified	59/Female	Melanoma	3	-	Partial regrowth
		Pembrolizumab	Unclassified	52/Male	-	7	-	Partial regrowth
		Pembrolizumab	Unclassified	29/Female	-	3	Only eyelashes	Complete regrowth
		Pembrolizumab	Unclassified	29/Female	-	9	Only eyelashes	Complete regrowth
		Pembrolizumab	Unclassified	29/Female	-	5	Only body hair	No regrowth
Weber et al.[6]	8	Nivolumab	Unclassified				-	

SALT: severity of alopecia tool, AU: alopecia universalis, -: information was not mentioned in reference article.

mab. While several cases have been reported[5], the pathogenesis of nivolumab-induced AA remains unclear. There has been a report discussing nivolumab-induced vitiligo[10], 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[5-8], 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[5]. 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[6]. Similar to this result, some authors suggest that nivolumab-induced AA is also a sign of a good response to cancer treatments[5]. 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[11]. 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[12]. 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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Research data are not shared.

ORCID

Ki-Hun Kim, https://orcid.org/0000-0002-1886-3694
Woo-Young Sim, https://orcid.org/0000-0001-5300-6869
Bark-Lynn Lew, https://orcid.org/0000-0003-4443-4161

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