Respiratory Medicine Case Reports 30 (2020) 101134

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: http://www.elsevier.com/locate/rmcr

Case report

Nivolumab-induced contact dermatitis in a patient with advanced lung cancer

Shintaro Sato *, Tomohiro Oba, Hiroki Ohta, Yuta Tsukahara, Gen Kida, Emiri Tsumiyama, Kenji Kusano, Tomotaka Nishizawa, Rie Kawabe, Hideaki Yamakawa, Keiichi Akasaka, Masako Amano, Hidekazu Matsushima

Department of Respiratory Medicine, Saitama Red Cross Hospital, Saitama, Japan

ARTICLE INFO

Keywords:
Nivolumab
Contact dermatitis
Lung cancer
Immune-related adverse event

ABSTRACT

An 85-year-old man was being treated for advanced squamous cell lung carcinoma with nivolumab as a second-line treatment. From the beginning of the third course, erythema appeared on his trunk and gradually progressed. Around the start of the fifth course, erythema spread to the proximal part of all limbs in addition to the trunk and was accompanied by a strong itching sensation. He was diagnosed as having contact dermatitis by a dermatologist because his rash was observed only where the moisture-absorbing fiber material of his underwear made contact with the skin surface. After suspending treatment of nivolumab, changing his underwear to a cotton material, and using moisturizers and steroid ointments, his rash disappeared in about a month and the size of his lung tumors remained reduced. The patient developed contact dermatitis despite the use of similar underwear without any skin problems for several years. We speculated that nivolumab-induced T-cell activation may have occurred in his skin, making him more likely to develop contact dermatitis, whose onset is thought to involve T-cell activation. No cases of contact dermatitis have been reported previously although the frequency of eruption as an immune-related adverse event is relatively high. When using immune checkpoint inhibitors including nivolumab, clinicians need to pay attention to the occurrence of skin disorders related to T-cell activation.

1. Introduction

The recent development of immune checkpoint inhibitors (ICIs) has led to promising progress in the treatment of patients with various advanced or metastatic malignancies. In the lung cancer area, the anti-programmed cell death 1 antibodies nivolumab and pembrolizumab or the anti-programmed cell death ligand 1 (PD-L1) antibodies atezolizumab and durvalumab are used as standard therapies for advanced or relapsed lung cancer [1]. However, ICIs may cause immune-related adverse events (irAEs) such as thyroiditis, hypophysitis, interstitial pneumonia, type I diabetes mellitus, adrenal failure, myasthenia gravis, or skin disorders [2]. Despite the relatively high frequency of skin disorders, there has been no report of contact dermatitis to our knowledge. We report a case of contact dermatitis after nivolumab use was begun and caution that ICIs could cause such skin disorders.

2. Case report

An 85-year-old Japanese man was referred to our hospital by nearby general hospital for detailed examination of chest X-ray abnormalities. The patient had a history of aortic aneurysm, hyperthyroidism, and was undergoing hormone therapy for prostate cancer. He had been smoking 10 cigarettes a day from the age of 20 until first visit. He had no special history of allergies. On computed tomography, a tumor 36 mm in diameter was found in the right lower lobe S6 and was diagnosed as squamous cell carcinoma with no EGFR (epidermal growth factor receptor) mutations or the ALK (anaplastic lymphoma kinase) fusion oncogene by bronchoscopic examination (Fig. 1A). The PD-L1 expression was found to be <1%. Stage diagnosis was cT2aN0M1c stage IVB (bone and liver metastasis), and performance status was 0.

He started first-line treatment with carboplatin and nab-paclitaxel,

Abbreviations: ALK, anaplastic lymphoma kinase; CTCAE, Common Terminology Criteria for Adverse Events; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; PD-L1, programmed death-ligand 1.

* Corresponding author. Department of Respiratory Medicine, Saitama Red Cross Hospital, 1-5 Shintoshin, Chuo-ku, Saitama, 330-8553, Japan.
E-mail address: smallerss@hotmail.com (S. Sato).

https://doi.org/10.1016/j.rmcr.2020.101134
Received 7 February 2020; Accepted 14 June 2020
Available online 15 June 2020

after which he was determined to have progressive disease due to the appearance of an intrapulmonary metastasis after four courses of treatment (Fig. 1B). Subsequently, administration of nivolumab as a second-line treatment was started at 240 mg/body every two weeks, and there were no obvious adverse events or changes in X-ray findings through the two courses of treatment. From the beginning of the third course, however, erythema accompanied by itching appeared on his trunk that gradually progressed with repeated exacerbations. Around the start of the fifth course, the erythema spread to the proximal part of his limbs in addition to the trunk and was accompanied by a strong itching sensation, but pustules, blisters, erosion, and epidermal necrosis were not consistently observed (Fig. 1D and E).

A dermatologist was consulted because of no improvement despite the use of antihistamines. As a result, a skin rash was observed only where the moisture-absorbing fiber material of his underwear contacted his skin, leading to a diagnosis of contact dermatitis for this material (CTCAE grade 3). The patient had worn the same moisture-absorbing fiber underwear for the last five years, but this was the first time that a rash had ever appeared. He also had been wearing this underwear since the start of the third course of nivolumab. After suspending treatment with nivolumab, changing his underwear to cotton, and using moisturizers and steroid ointments, the rash disappeared over a month. In addition, his lung tumors have been shrinking and maintaining partial response at 4 months after the last dose of nivolumab (Fig. 1C).

3. Discussion

We experienced a case of contact dermatitis that developed during the use of nivolumab for advanced lung cancer. Skin toxicities appear to be one of the most frequent irAEs that occur during the use of ICIs [3]. Their frequency has been reported to range between 35 and 50% [4], and the types of skin rash reported include maculopapular rash, pruritus, lichenoid reactions, psoriasis, acneiform rashes, vitiligo-like lesions, and autoimmune skin diseases [3]. However, there has been no report of a skin eruption diagnosed as contact dermatitis so far, and to our knowledge, this is the first report of contact dermatitis whose suspected cause was nivolumab treatment.

As a treatment method when skin rash appears during ICIs treatment, for CTCAE grade 1–2 eruptions, topical steroids should be used instead of discontinuing ICIs. However, for moderate to severe grade 3–4 rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis, ICIs should be discontinued and consultation with a dermatologist for the indication of systemic steroid administration is required [5]. Antigen avoidance is required when the rash is presumed to be contact dermatitis. Therefore, accurate diagnosis of the etiology of the rash is clinically important in the treatment of irAEs.

ICIs exerts an antitumor effect by blocking the negative regulators of T-cell function. However, it has been pointed out that enhanced T-cell activity may be involved in the development of irAEs, and there have been several reports of patients with irAEs exhibiting robust infiltration of T cells [6]. It is noteworthy that T cells have been reported to be critical regulators in the pathophysiology of contact dermatitis in recent years [7].

The pathophysiology of contact dermatitis is divided into three phases: sensitization, elicitation, and resolution [8]. In the sensitization phase, haptens are collected by resident dendric cells of the skin. Dendric cells migrate to the lymph nodes and present an antigen to naive cells. In the elicitation phase, presentation of an antigen and costimulation activate antigen-specific $CD4^+$ and $CD8^+$ T cells. Reexposure to the hapten initiates transmigration of the effector memory T cells to the dermis and epidermis, resulting in the clinical manifestations of contact dermatitis. In the resolution phase, inflammation tends to converge by prevention of extravasation of circulating effector T cells. As mentioned above, different populations of T cells are deeply involved in various stages of the development of contact dermatitis.

Our patient developed contact dermatitis despite wearing similar underwear without any skin problems for several years, suggesting that nivolumab-induced T-cell activation may have occurred in the skin, thus making the development of contact dermatitis more likely. The use of nivolumab has reduced the size of the tumor to date in our patient, but it is controversial whether it should be re-administered if the tumors grow in the future. Although it is reported that retreatment with anti-PD-L1 therapy resulted in the recurrence of irAEs in 52% of patients with non-small-cell lung carcinoma [9], we consider re-administration to be

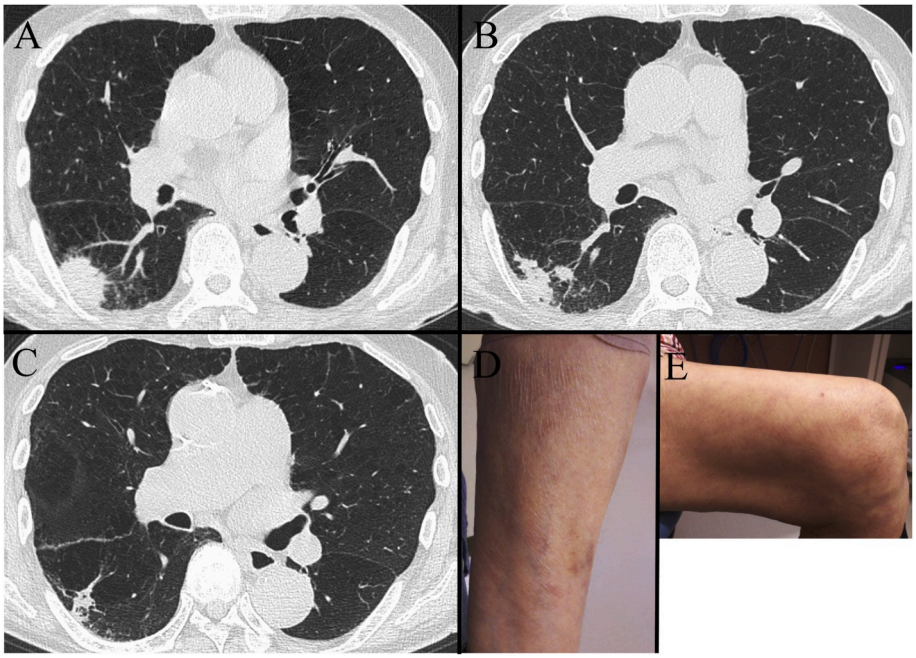

Fig. 1. Chest computed tomography scan images and photographs of the skin rash. At the time of the lung cancer diagnosis, a tumor was found in the right lower lobe (A), and a new central metastasis to the lung was discovered after first-line chemotherapy (B). After the subsequent use of nivolumab, the tumor began to shrink (C), but pruritic eruptions appeared on the patient's extremities and trunk (D, E).

reasonable in this patient because avoiding underwear made of moisture-absorbing fiber material may reduce the recurrence rate of this irAE.

In conclusion, we reported the first case of nivolumab-induced contact dermatitis in a patient with lung cancer. We speculated that the activation of T cells by nivolumab triggered the development of the contact dermatitis. Although the incidence of skin disorders during ICIs treatment is relatively high, clinicians should consider contact dermatitis to be one of the differential diagnoses because it is important to avoid causative antigens in this disorder. As well, it is crucial to cooperate with dermatologists in the practice of lung cancer to obtain an appropriate diagnosis.

Declaration of competing interest

The authors declare no Conflicts of Interest (COI) in association with this article.

References

[1] P. Jain, C. Jain, V. Velcheti, Role of immune-checkpoint inhibitors in lung cancer, Ther. Adv. Respir. Dis. 12 (2018), 1753465817750075, https://doi.org/10.1177/1753465817750075.
[2] C. Connolly, K. Bambhania, J. Naidoo, Immune-related adverse events: a case-based approach, Front. Oncol. 9 (2019) 530, https://doi.org/10.3389/fonc.2019.00530.
[3] V. Sibaud, Dermatologic reactions to immune checkpoint inhibitors: skin toxicities and immunotherapy, Am. J. Clin. Dermatol. 19 (3) (2018) 345–361.
[4] A.B. Patel, O. Pacha, Skin reactions to immune checkpoint inhibitors, Adv. Exp. Med. Biol. 995 (2018) 117–129.
[5] J.R. Brahmer, C. Lacchetti, B.J. Schneider, et al., Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline, J. Clin. Oncol. 36 (17) (2018) 1714–1768.
[6] D.B. Johnson, W.J. McDonnell, P.I. Ericsson-Gonzalez, et al., A case report of clonal EBV-like memory CD4+ T cell activation in fatal checkpoint inhibitor-induced encephalitis, Nat. Med. 25 (8) (2020) 1243–1250.
[7] J.S. Smith, S. Rajagopal, A.R. Atwater, Chemokine signaling in allergic contact dermatitis: toward targeted therapies, Dermatitis 29 (4) (2018) 179–186.
[8] M. Vocanson, A. Hennino, A. Rozières, et al., Effector and regulatory mechanisms in allergic contact dermatitis, Allergy 64 (12) (2009) 1699–1714.
[9] F.C. Santini, H. Rizvi, A.J. Plodkowski, et al., Safety and efficacy of re-treating with immunotherapy after immune-related adverse events in patients with NSCLC, Cancer Immunol. Res. 6 (9) (2018) 1093–1099.