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Case report

Aprepitant for refractory nivolumab-induced pruritus

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ARTICLE INFO

Abbreviations:
ICIs
immune checkpoint inhibitors
irAEs
immune-related adverse events
NK-1R
neurokinin-1 receptor
NSCLC
non-small-cell lung cancer
SJS
Stevens-Johnson syndrome

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ABSTRACT

Although substantial progress has been made in the treatment of non-small-cell lung cancer (NSCLC) patients with immune checkpoint inhibitors (ICIs), severe immune-related adverse events (irAEs) sometimes occur. Here, we report a case of severe refractory pruritus after Stevens-Johnson syndrome (SJS) in a patient with NSCLC treated with nivolumab. The patient was a 76-year-old Japanese woman with advanced NSCLC treated with nivolumab. After the second dose, she experienced severe rash with mucous involvement. We diagnosed SJS and started 50 mg of oral prednisolone (1 mg/kg). The rash completely resolved after prednisolone was started, but we could not manage the severe pruritus with emollients, antihistamines, and steroids. Finally, we administered aprepitant, an oral neurokinin-1 receptor antagonist, for her refractory pruritus. Her symptoms improved within 5 days. Severe refractory pruritus can arise from ICIs, and aprepitant may be a useful treatment.

1. Introduction

Immune checkpoint inhibitors (ICIs) have shown antitumor activity in multiple malignancies, and they can cause inflammatory side effects called immune-related adverse events (irAEs).

Skin-related irAEs are the major toxicities caused by ICIs, with rash and pruritus being the most commonly observed. They are generally mild, but severe cases have been also reported [1]. Therefore, with the increasing use of ICIs, recognition and management of irAEs will become more important for restricting dose-limiting toxicities and preventing a deleterious impacts on a patient's health-related quality of life. Aprepitant, an oral neurokinin-1 receptor (NK-1R) antagonist, has been reported to improve refractory pruritus attributable to various causes [2]. However, its efficacy for treating refractory pruritus caused by ICIs is unknown. Here, we report a case of severe refractory nivolumab-induced pruritus with a good response to aprepitant.

2. Case presentation

A 76-year-old Japanese woman with lung adenocarcinoma (cT4M3N1b, stage 4, exon 19 deletion) was admitted to our hospital with grade 3 skin rash after 2 cycles of nivolumab as a fourth-line therapy (gefitinib, erlotinib and pemetrexed were used prior to nivolumab). She had no history of smoking, drug allergies, or autoimmune disease. Although she had been using other drugs for several years, nivolumab was her only new medication. She presented with facial erythema, and maculopapular rash on her trunk and extremities (Fig. 1). Mucous membrane involvement with conjunctival injection and odynophagia was also observed. In addition, she had a fever but her other vital signs were stable on presentation. The results of her blood tests were mostly within normal limits. Histological examination of a biopsy specimen from a lesion on her thigh revealed interface dermatitis with intercellular edema, accompanied by lymphocytic infiltrates and scattered necrotic keratinocytes in the epidermis. Immunohisto-

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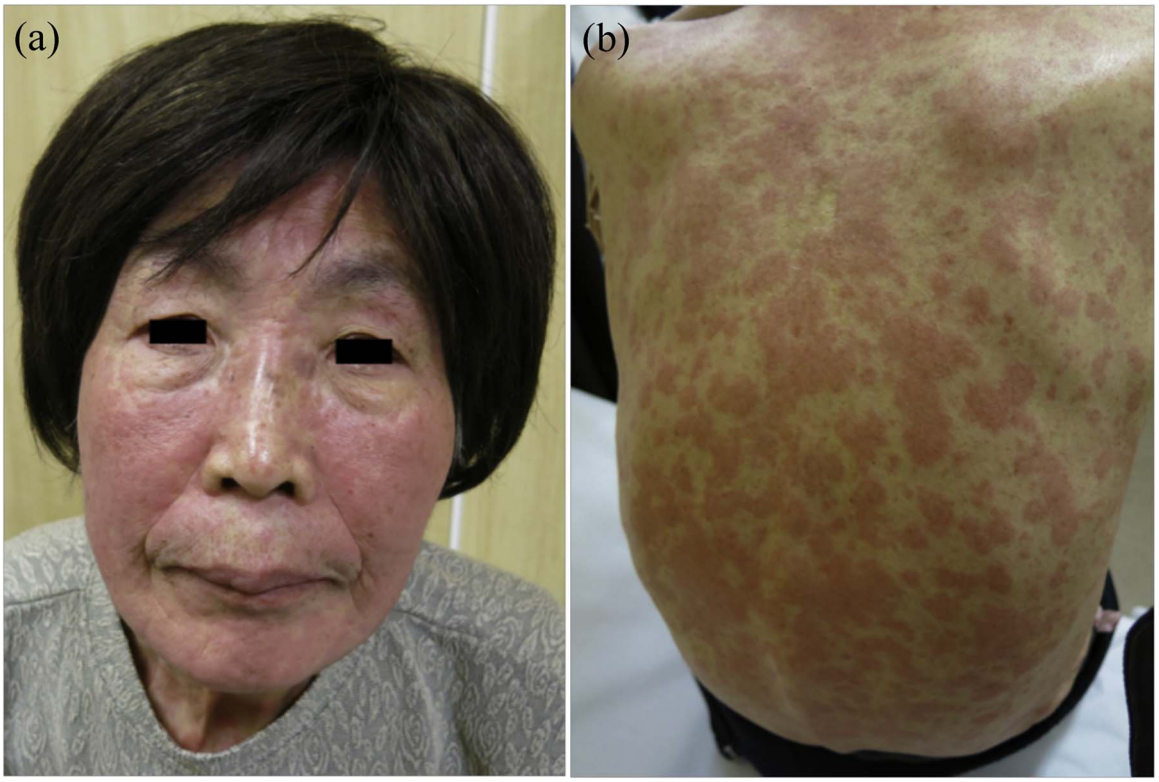

Fig. 1. Cutaneous manifestations 11 days after the second dose of nivolumab (on the day of admission). (a) Facial erythema, sparing areas around the eyes. (b) Maculopapular rash on the trunk.

chemical staining (CD4, CD8) revealed a $CD8^+$-predominant T-cell infiltrates (Fig. 2). She received 50 mg (1 mg/kg) of oral prednisolone and a topical steroid based on the diagnosis of Stevens-Johnson syndrome (SJS). Her skin rash improved to grade 1, and she was discharged with 25 mg/day of oral prednisolone on day 8 of her hospital stay. Two weeks after discharge, the rash completely disappeared; however, she came to our emergency department twice per week for severe pruritus with sleep disturbance (grade 3), despite intensive therapies such as emollients, antihistamines, topical steroids, and 25 mg/day of oral prednisolone. Therefore, we administered aprepitant 80 mg/day for 5 days. Her symptoms improved from the score of 8 to 2 on the Visual Analogue Scale within 5 days. Although pruritus did not recur, she was not re-challenged with nivolumab because of tumor growth.

3. Discussion

Our patient developed severe rash during nivolumab treatment. We could manage the rash with oral steroids; however, the patient developed refractory pruritus thereafter.

Pruritus is a common skin-related irAEs. It has an incidence of 9%–16%, and can severely affect the health-related quality of life and psychological well-being of patients [1,4]. Although the pathogenesis of pruritus has been reported to differ depending on the underlying diseases, Substance P (SP) is a key mediator of pruritus. It causes mast cell degranulation and release of pruritogens through the activation of NK-1R in keratinocytes, mast cells, and the neurons of the sensory dorsal root ganglion[2,5]. Therefore, NK-1R seems to be a promising target for antipruritic treatment. Aprepitant is the first commercially available NK-1R antagonist for treating chemotherapy-induced nausea and vomiting. It acts by inhibiting NK-1R binding with SP [2,5]. Recently, aprepitant was reported to be a successful treatment for pruritus attributable to several causes (Table 1) [2,5–14]. Especially, in a phase 2 trial, 45 metastatic solid tumor patients with severe refractory pruritus caused by biological drugs (i.e. epidermal growth factor receptor tyrosine-kinase inhibitors) were treated with aprepitant and showed a significant improvement within 1 week [5]. During this study, no patients discontinued biological treatment because of pruritus, and none showed adverse events related to aprepitant over an average follow-up period of 12 weeks. Different dosing regimens of aprepitant for pruritus have been used in previous reports. In our case, we did not use an additional dose, because pruritus was significantly reduced after using of 80 mg daily for 5 days. The optimal dosing regimen of aprepitant for pruritus remains unclear, and further studies as are needed for clarification.

Our patient also experienced severe rashes. ICIs-induced rashes are usually mild, but severe cases have been also reported [1]. We diagnosed SJS by dermatologic examination and skin biopsy. The biopsy results showed interface perivascular, and periadnexal lymphocytic dermatitis, with few plasma cells and eosinophils as shown in the previous reports [1]. Additionally, our patient also had necrotic keratinocytes in the epidermis, which is consistent with histological features of SJS [3]. Interestingly, refractory pruritus occurred after the patient experienced improvement of the rash.

We presented a case of refractory pruritus after SJS in a NSCLC patient treated with nivolumab. This case highlights the importance of recognition and management of skin-related irAEs in successful use of ICIs, and suggests the efficacy of aprepitant for refractory pruritus caused by ICIs.

Conflict of interests

All authors declared no conflicts of interest.

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