

## A case of Stevens–Johnson syndrome in a patient on ipilimumab

**Mohini Pathria, Jyoti Mundi, Joshua Trufant**

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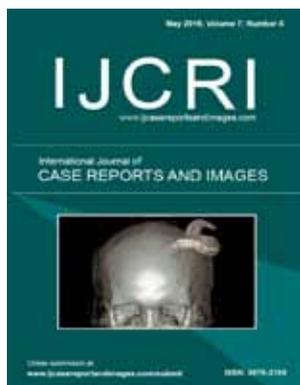
**Introduction:** Stevens–Johnson syndrome is a rare complication of ipilimumab therapy. A brief review of literature on the dermatologic adverse effects of ipilimumab is presented. This paper aims to heighten awareness of the significant risk and potential severity of cutaneous adverse effects associated with the use of ipilimumab.

**Case Report:** A case of 71-year-old woman being treated with ipilimumab for stage IV choroidal melanoma who presented with Stevens–Johnson syndrome 2.5 weeks after her last ipilimumab infusion.

**Conclusion:** Delayed diagnosis of Stevens–Johnsons syndrome in patients receiving ipilimumab therapy can lead to devastating outcomes.



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# A case of Stevens–Johnson syndrome in a patient on ipilimumab

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**Introduction:** Stevens–Johnson syndrome is a rare complication of ipilimumab therapy. A brief review of literature on the dermatologic adverse effects of ipilimumab is presented. This paper aims to heighten awareness of the significant risk and potential severity of cutaneous adverse effects associated with the use of ipilimumab. **Case Report:** A case of 71-year-old woman being treated with ipilimumab for stage IV choroidal melanoma who presented with Stevens–Johnson syndrome 2.5 weeks after her last ipilimumab infusion. **Conclusion:** Delayed diagnosis of Stevens–Johnsons syndrome in patients receiving ipilimumab therapy can lead to devastating outcomes.

**Keywords:** Ipilimumab, Melanoma, Stevens–Johnson syndrome

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## INTRODUCTION

Ipilimumab is a monoclonal human antibody directed against cytotoxic T lymphocyte antigen-4 (anti-CTLA-4). The medication helps increase T cell activation [1]. The therapy has been recently approved for management of metastatic melanoma. Common adverse effects involve the gastrointestinal tract and skin [2]. Skin reactions can range from mild to severe, including Stevens–Johnson syndrome (SJS) [2]. Stevens–Johnson syndrome is characterized by epidermal death and separation involving less than 10% of the skin surface. If more than 30% of the skin is involved, the syndrome is considered toxic epidermal necrolysis (TEN), with SJS/TEN overlap for involvement of 10–30% of the skin surface [3]. Stevens–Johnson syndrome (SJS) and/or toxic epidermal necrolysis (TEN) with ipilimumab therapy is a rare complication and the exact frequency is unknown. Delayed diagnosis can lead to devastating complications.

## CASE REPORT

A 71-year-old female was being treated for stage IV choroidal melanoma with ipilimumab. Two and a half weeks after her third infusion, she presented with a progressively painful rash on her face, trunk, and extremities, ocular discharge, and dysuria. Physical examination revealed conjunctival injection, painful crusted erosions on her vermilion, mucosal lip and labia majora, and dusky targetoid patches on her forehead and extremities. The patient's trunk was diffusely

erythematous and tender. Nikolsky's sign was present and spontaneous sloughing was noted over approximately 25% of the patient's body surface area (Figure 1). The affected epidermis was submitted for frozen sections and a 4-mm punch biopsy was performed (Figure 2A–B). The biopsy demonstrated full-thickness epidermal necrosis with a sparse perivascular lymphocytic infiltrate. The clinical and histologic findings were consistent with Stevens–Johnson syndrome. The patient was transferred to a burn unit. The patient was treated with supportive measures including artificial tears and Lacrilube to the eyes. Daily vitamin A and vitamin D ointment and xeroform was applied to denuded skin. She received intravenous fluid resuscitation and tube feedings to enhance protein intake. She has fully recovered from this episode and has resumed her baseline quality of life.

## DISCUSSION

Ipilimumab is a monoclonal immunoglobulin G1 antibody directed against cytotoxic T lymphocyte antigen-4 (anti-CTLA-4). The medication received FDA approval in 2011 as monotherapy for metastatic melanoma for four cycles at a dose of 3 mg/kg administered intravenously



Figure 1: Neck and upper back – Note diffuse erythema and spontaneous sloughing of skin on the upper back.

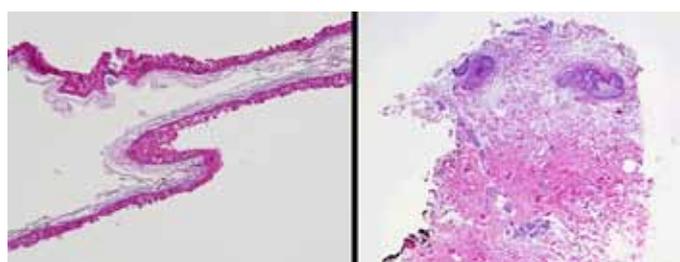


Figure 2: Punch biopsy specimen of skin. (A) Epidermis demonstrating full-thickness epidermal necrosis (H&E stain, x200), (B) Dermis demonstrating sparse perivascular lymphocytic infiltrate (H&E stain, x100).

every three weeks for 90 minutes [1]. CTLA-4 diminishes T cell activation by competing with CD28 on T cells for co-stimulatory molecules on antigen presenting cells [1]. In metastatic melanoma, T cells are functionally impaired, while inhibitory receptors, such as CTLA-4, are upregulated [4]. In vivo studies have demonstrated that CTLA-4 blockade can promote antitumor immunity [5].

Antibody inhibition of CTLA-4 is associated with immune-related adverse events (IRAEs), mainly affecting the skin, gastrointestinal, and endocrine systems. Cutaneous IRAEs occur after 2 to 3 weeks, gastrointestinal IRAEs occur after 6 to 7 weeks, and endocrinologic IRAEs have been described after an average of 9 weeks. A dose-dependent increase in the frequency of IRAEs of any grade has been noted [2].

Dermatologic adverse effects include rash, pruritus, and vitiligo. The incidence of all-grade rash in patients receiving ipilimumab was 24.3%. The overall incidence of high-grade rash was 2.4% [1]. Cutaneous lesions associated with ipilimumab have been described as itchy, erythematous, discrete, mildly scaly papules coalescing into thin plaques on the trunk and proximal aspects of extensor extremities. The head and neck can be involved, while palms and soles are usually spared. Koebnerization may occur. Patients can develop a peripheral eosinophilia. On histology, a perivascular CD4+ T cell infiltrate with eosinophils is seen in the superficial dermis. Epidermal spongiosis and, rarely, dyskeratosis are also observed. Other skin findings include alopecia of the scalp, eyebrows, face, pubic region, and trunk as well as a photosensitive eruption [6]. Additionally, anti-CTLA-4 antibodies may stimulate an immune response against melanocytes. The development of vitiligo in a subset of patients and the identification of Melan-A-specific CD8+ T lymphocytes near apoptotic melanocytes in biopsy specimens supports this theory [2, 6].

Stevens–Johnson syndrome and toxic epidermal necrolysis is a rare yet severe cutaneous adverse effect of ipilimumab. Recommended management of SJS and TEN involves early removal of the causative drug. Supportive therapy is initiated with protective measures for the exposed skin and mucosa, early detection and management of infection, fluid and nutritional support, and pain control [3]. Although initiation of prednisone at 1–2 mg/kg is recommended in patients with high grade IRAEs due to ipilimumab [2], caution is urged as the benefit of systemic corticosteroids in the treatment of SJS-TEN is debated and their use may be detrimental [3].

## CONCLUSION

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, but potentially fatal occurrences while undergoing ipilimumab therapy. The TEN has a high risk of mortality due to infections and retrospective data supports early referral to a burn unit. Given the increasing use of ipilimumab in patients with

metastatic melanoma, it is important for oncologists and dermatologists to be aware of the significant risk and potential severity of cutaneous adverse effects associated with the medication.

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### Author Contributions

Mohini Pathria – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Jyoti Mundi – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Joshua Trufant – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

### Guarantor

The corresponding author is the guarantor of submission.

### Conflict of Interest

Authors declare no conflict of interest.

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