e-ISSN 3050-8460
Journal of Dermatology Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Review Article

Pembrolizumab Induced Grover-like Eruption in a Colorectal Liver Metastasis Patient: A Case and Review

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Citation: Ghalambor T, et al. Pembrolizumab Induced Grover-like Eruption in a Colorectal Liver Metastasis Patient: A Case and Review. J Dermatol Res. 2026;7(2):1-7.

https://doi.org/10.46889/JDR.2026.7205

Received Date: 07-05-2026

Accepted Date: 25-05-2026

Published Date: 02-06-2026

Abstract

Background: Immune Checkpoint Inhibitors (ICIs) are effective in treating advanced malignancies but are associated with immune-related Adverse Events (irAEs), most commonly involving the skin. Transient Acantholytic Dermatosis (TAD, Grover disease) is a rare cutaneous irAE, comprising only 0.2% of reported cases.

Case Presentation: A 64-year-old woman with metastatic colorectal carcinoma developed a pruritic papular eruption after her sixth pembrolizumab infusion. Examination revealed erythematous papules on the trunk and extremities with scattered vesicles. Biopsy demonstrated suprabasilar acantholysis and dyskeratosis, consistent with an ICI-induced Grover-like eruption. She was managed with systemic corticosteroids, topical steroids, antipruritic agents and gabapentin. The eruption partially improved but recurred, requiring ongoing topical therapy.

Methods: We performed a PubMed search using the terms "immune checkpoint inhibitor AND grover," "immune checkpoint inhibitor AND transient acantholytic dermatosis," and "immunotherapy AND transient acantholytic dermatosis." Eleven articles met inclusion criteria, reporting histologically confirmed TAD associated with ICIs. Clinical characteristics, tumor type, ICI regimen, time to onset, treatment and outcomes were extracted.

Results: Including our case, 16 patients with ICI-induced TAD were identified. Patients were predominantly male (75%) with a mean age of 68.3 years. Melanoma was the most common malignancy (56%). Half developed eruptions on PD-1 monotherapy, with mean onset at 3.3 cycles. Topical corticosteroids were used in 93.8% and systemic corticosteroids in 56.3%. Nearly half required interruption or discontinuation of immunotherapy.

Conclusion: ICI-induced TAD is rare but often symptomatic, with management complicated by potential impact on oncologic outcomes. Early dermatology involvement and consideration of steroid-sparing agents may optimize care.

Keywords: Immune Checkpoint Inhibitors (ICIs); Transient Acantholytic Dermatosis; Immunotherapy; Metastatic Colorectal Carcinoma

Introduction

The efficacy of Immune Checkpoint Inhibitors (ICIs) in advanced cancer treatment has been tethered to the emergence of immune related (irAEs), particularly skin toxicity [1]. The skin is the most common and frequent site of irAE, which may result in significant patient discomfort and discontinuation of therapy, leading to worse survival outcomes [1,2]. Compared to other cutaneous irAEs, Transient Acantholytic Dermatosis (TAD), an acquired, pruritic, papular rash involving the trunk and extremities, commonly referred to as Grover disease, remains a rare skin toxicity making up 0.2% of cutaneous irAEs [3,4]. Here,

we present a case of Grover-like eruption in a patient with metastatic colorectal carcinoma on pembrolizumab and a review of the literature of this cutaneous irAE.

Case Presentation

A 64-year-old female with a history of colorectal adenocarcinoma with liver metastasis on pembrolizumab presented to dermatology with a pruritic eruption. On exam, she had scattered erythematous papules of the chest, back, abdomen and arms which began after her 6th dose of pembrolizumab (Fig. 1). Differential diagnosis at the time included a lichenoid eruption versus eczematous eruption related to immune checkpoint inhibitor therapy. She was prescribed 0.1% triamcinolone cream to apply to affected areas of the body, however, two weeks after her initial presentation, her symptoms became progressively worse. Her papules had spread to her shoulders and thighs, with few fluid filled 2 mm tense vesicles and significant increase in pruritus and erythema. Punch biopsy of a papule of the right shoulder was performed which revealed suprabasilar acantholysis and dyskeratosis (Fig. 2,3). Direct immunofluorescence of perilesional skin was negative. The diagnosis of Immune Checkpoint Inhibitor (ICI) Grover-like eruption was made. Due to progression and patient discomfort, she was started on systemic steroids with prednisone 40 mg followed by a taper, while continuing on topical triamcinolone. After one month of therapy, her rash had improved but she still experienced significant pruritus prompting initiation of gabapentin 900 mg, hydroxyzine PRN and over the counter pramoxine hydrochloride lotion. She also started acitretin but discontinued due to side effects. She had spontaneous resolution but shortly after had recurrence which she continues to manage with topicals [5-7].

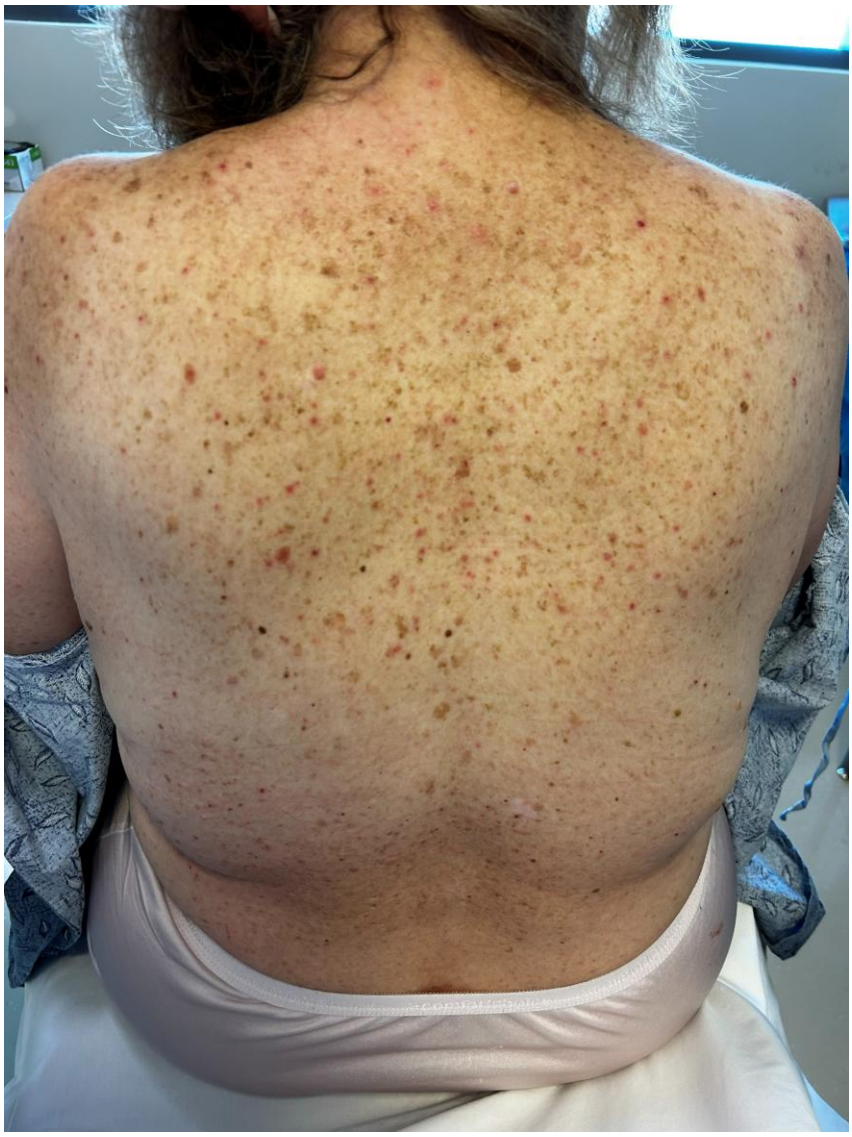

Figure 1: Scattered erythematous papules.

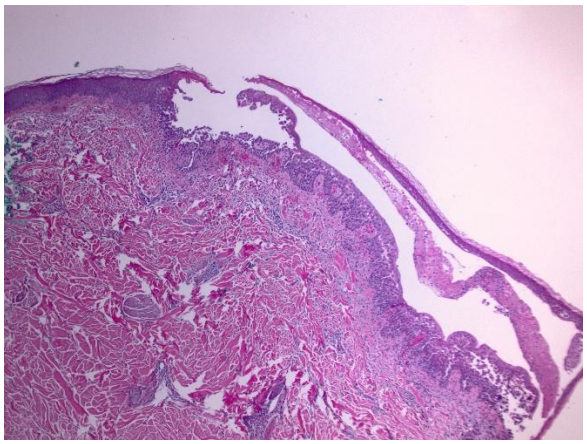

Figure 2: Punch biopsy of a papule of the right shoulder was performed which revealed suprabasilar acantholysis.

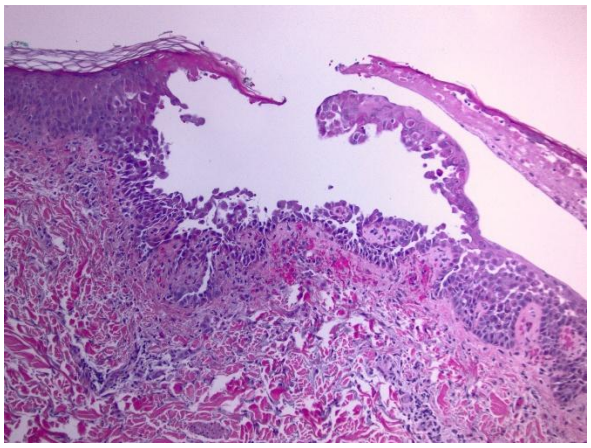

Figure 3: Punch biopsy of a papule of the right shoulder was performed which revealed dyskeratosis.

Methodology

A review of literature was performed to identify all case reports discussing Grover-like eruption in patients receiving ICIs. PubMed was searched 3 times using the terms "immune checkpoint inhibitor AND grover" and "immune checkpoint inhibitor AND transient acantholytic dermatosis" and "immunotherapy AND transient acantholytic dermatosis", yielding 30 results. After assessment of relevance, removal of duplicates and articles not in English, 8 articles remained. Only articles with clinical and histologic findings of TAD were included. Of those 8 articles, each of their references were examined for any possible missing articles, of which 3 additional articles were found, totaling 11 articles. Each article was examined for patient age, sex, primary tumor, ICI, location of eruption, time of onset from ICI initiation, treatments, need for discontinuation of ICI and response of TAD to the treatments provided. For studies that included quantification of the time the ICI was initiated, cycle completion could be inferred and was included in the chart, otherwise time of onset was listed as unclear [8-12].

Results

Including our patient, a total 16 patients have been reported with clinical and histological findings of TAD due to ICI therapy (Table 1). The majority of the patients were male, making up 75% of the cohort. The ages ranged from 51 to 80 years old, with an average age of 68.3 years. The primary tumors included melanoma (56%), renal cell carcinoma (12.5%), non small cell lung cancer (12.5%), prostate cancer (6.25%), colorectal cancer (6.25%) and squamous cell carcinoma (6.25). The majority of the patients (50%) were on single agent PD-1 inhibitors, 25% of patients were on CTLA-4 inhibitors and 25% on combination therapy. For the 14 patients that had the specific time of onset of their rash documented, the average time of onset was after 3.3 cycles of ICI. Half of patients (50%) did not need to discontinue or pause their ICI and were able to manage their eruption with prescribed therapy. However, 43.75% of patients required to either pause their ICI or completely discontinue treatment. The majority of patients (56.25%) received systemic steroid therapy and 93.75% of patients used topical steroids. There were 3 patients where TAD preceded a diagnosis of Bullous Pemphigoid (BP) and their rash resolved with either dupilumab or rituximab [13-15]. The use of dupilumab for recalcitrant TAD without bullous pemphigoid was found to be successful in one report [14].

Author	Date	ICI	Age	Sex	Primary Tumor	Location	Time of Onset	Treatment	Need for ICI Discontinuation	Response to Treatment
Munoz, et al., [5]	2014	ipilimumab	53	M	Melanoma	Trunk and proximal limbs	2nd cycle	Moisturizer and antihistamines	No	Yes, immediately after treatment completion
Koelzer, et al., [6]	2016	ipilimumab	73	M	Melanoma	Chest, abdomen, back, shoulders and proximal limbs	2nd cycle	Hydrocortisone butyrate 0.1% lotion with menthol 1%	No	Yes, but 2 months post treatment completion
Belum, et al., [7]	2016	nivolumab	64	F	Melanoma	Upper trunk	5th cycle	Triamcinolone spray BID	No	Yes
	2016	pembrolizumab	80	M	Non Small Cell Lung Cancer	Trunk and upper limbs	3rd cycle	Clobetasol foam/spray BID, Hydroxyzine 25mg BID	Lost to follow up	Lost to follow up
Uemura, et al., [8]	2016	ipilimumab	73	M	Melanoma	Chest, upper limbs and back	2nd cycle	IV methylprednisolone, topical steroids, antihistamines	Yes	No and flared after restarting due to progressive melanoma
Perret, et al., [9]	2017	ipilimumab	65	F	Melanoma	Lower abdomen and central chest	2nd cycle	Topical corticosteroids	No	Yes
Kuanitz, et al., [10]	2017	anti-PD-1 and anti-CTLA-4	60	M	Melanoma	Trunk, distal limbs	1st cycle	Prednisone, triamcinolone	Delayed dose, then resumed	Yes
		anti-PD-1 and anti-CTLA-4	51	F	Melanoma	Trunk	1st cycle	Prednisone	Delayed dose, then resumed	No
		anti-PD-1 and anti-CTLA-4	74	M	Non Small Cell Lung Cancer	Trunk, arms, legs	2nd cycle	Prednisone, triamcinolone	No	Yes
Chen, et al., [11]	2018	pembrolizumab	64	M	Melanoma	Chest, trunk, back, limbs progressing to hands and feet	5th cycle	Triamcinolone 0.1% cream and hydroxyzine 25 mg, then doxycycline 100 mg and oral prednisone 100 mg after withholding ICI	Yes, after 11th cycle	Yes
Khan, et al., [12]	2020	pembrolizumab	78	M	Prostate	Upper back, chest and upper limbs	2nd cycle	Topical corticosteroids	No	Yes
Jendoubi, et al., [13]	2022	Nivolumab	78	M	Melanoma	Trunk, upper and lower limbs[a]	Unclear	High potency topical corticosteroids, acitretin, UVB phototherapy, omalizumab, then dupilumab and	No	Yes, after dupilumab and prednisone

		nivolumab	78	M	Squamous cell carcinoma	Trunk, upper and lower limbs[a]	unclear	prednisone High potency topical corticosteroids, acitretin, UVB phototherapy, omalizumab, then dupilumab and prednisone	Yes	Yes, after rituximab and intravenous immunoglobulin
Shelton, et al., [14]	2022	ipilimumab and nivolumab	71	M	Renal cell carcinoma	Chest, arms, back	4th cycle	Prednisone, 0.1% triamcinolone ointment with sauna suit, gabapentin, aprepitant, hydroxyzine, diphenhydramine, cetirizine, UVB phototherapy, then dupilumab	DC nivolumab but restarted after dupilumab	Yes, after dupilumab
Khazaeli, et al., [15]	2023	nivolumab	73	M	Renal cell carcinoma	Chest and back[a]	9th cycle	Topical steroid, doxycycline, dapsone, multiple courses of prednisone	Yes	Yes, after dupilumab
Patient 1	2024	pembrolizumab	64	F	Colorectal cancer	Chest, back, abdomen, limbs	6th cycle	Prednisone, topical steroids, gabapentin, hydroxyzine, pramoxine hydrochloride	No	No

Table 1: Patient characteristics from analysis of 11 articles of ICI induced TAD. A: Indicates patients who initially presented with Grover-like eruptions which progressed to bullous pemphigoid.

Discussion

While TAD is usually a self-limited disease that lasts for weeks to months, for some patients it can last for years [16]. For patients with TAD on ICIs, their presentation is often more symptomatic, resolving only after completion of ICI therapy or requiring systemic steroids, which may reduce the efficacy of ICI therapy. While some studies show no difference in survival outcomes in patients receiving oral steroids for irAEs [17,18]. others have found shorter progression free survival and shorter overall survival in patients who receive higher doses or receive them earlier in the course of their ICI treatment [19-22]. This uncertainty highlights the need for further research to elucidate the optimal approach to managing TAD and other irAEs without compromising the effectiveness of cancer immunotherapy. In cases where immunotherapy induced TAD proves refractory to conventional therapies, the use of dupilumab, an IL-4 and IL-13 inhibitor, has shown promise in providing relief and improving patient outcomes [14]. Its use has been shown to be successful for TAD patients not on ICI therapy, underscoring the importance of exploring this therapy's FDA approval for use in this disease [23-25]. Interestingly, studies have shown that patients receiving ICIs often exhibit elevated levels of IL-4, a cytokine implicated in the pathogenesis of various inflammatory skin conditions, including TAD [26-27]. The relationship between IL-4 and TAD suggests a potential mechanism underlying the development and persistence of this dermatological complication in patients undergoing immunotherapy. Additionally, dupilumab has shown efficacy in bullous pemphigoid and is pending FDA approval for this indication. In the setting of ICI therapy, there have been multiple cases where patients developed TAD before BP. Although the relationship between these two conditions is not well understood, their temporal relation and responsiveness to IL-4 and IL-13 inhibition warrants further investigation. It is also important for clinicians to be aware that ICI induced TAD may precede bullous pemphigoid. Since BP in the setting of ICI therapy often presents in the pre-bullous phase, a high degree of suspicion is necessary to make the appropriate diagnosis [28]. For cases of TAD that are unresponsive to conventional therapy and cases with uncontrolled pruritus, clinicians should have a low threshold for repeating a skin biopsy with direct immunofluorescence as well as serum antibody testing [2,28,29].

Conclusion

In this review, we found that the majority of patients with TAD in the setting of ICI therapy received systemic steroids. This highlights the importance of reporting other efficacious treatments for this condition as well as the importance of collaborative care of cancer patients by medical oncologists and dermatologists. Due to the concern that ICI efficacy may be reduced in the setting of systemic steroids, dermatologic consultation for these patients is recommended since patients who are seen by dermatologists for their cutaneous irAEs are less likely to be treated with systemic steroids. Furthermore, dermatologists are less likely to recommend ICI discontinuation and their patients are found to have better overall survival. By optimizing the management of TAD and other cutaneous irAEs through collaborative care, providers can enhance the quality of life and treatment outcomes for individuals affected by TAD and other dermatologic complications of cancer therapy.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial or non-profit sectors.

Acknowledgement

The authors have no acknowledgments to declare.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Not Applicable.

Authors' Contributions

All authors contributed equally to this paper.

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