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Pembrolizumab-induced follicular eruption and response to isotretinoin

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Abstract

Background: Pembrolizumab is a monoclonal antibody targeting programmed cell death receptor-1 (PD-1). Folliculitis secondary to pembrolizumab has rarely been reported in the treatment of malignant melanoma (MM).

Case: A 49 year old with a history of mild lower limb folliculitis developed metastatic MM, and immunotherapy with pembrolizumab was initiated. Following 19 doses of pembrolizumab, a folliculocentric pustular eruption developed on the lower legs. Biopsy was consistent with folliculitis. Treatment with topical corticosteroids, high dose prednisolone, lymecycline, clarithromycin, trimethoprim, and clindamycin was unsuccessful. Pembrolizumab was stopped after 22 cycles, but the folliculitis persisted. Oral isotretinoin was required for disease control.

Discussion: Drug-induced follicular eruptions have rarely been described with anti PD-1 therapy. Isotreinoin may be required to achieve remission.

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Lay Abstract

Pembrolizumab (trade name Keytruda) is a type of immune therapy that stimulates the body's immune system to fight cancer cells. This immune therapy can cause a variety of rashes. In this article, we describe a patient who developed a rash around hair follicles that is not commonly described with pembrolizumab. A man with a history of mildly infected hair follicles on his legs was diagnosed with advanced melanoma and was treated with pembrolizumab. After 19 treatments, he developed a rash on his legs, centered around hair follicles. Treatment with steroid ointments, steroid tablets, and antibiotic tablets was not helpful. Pembrolizumab was stopped, but the rash persisted. A medicine called isotretinoin was required to control the rash. This type of

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rash has rarely been described with this kind of immune therapy, and isotretinoin might be required to treat it.

Key words

Folliculitis; acneiform eruption; adverse drug reactions; pembrolizumab; melanoma

Case Presentation

Pembrolizumab is a monoclonal antibody that targets programmed cell death receptor-1 (PD-1) [1]. It is used in the treatment of several malignancies including malignant melanoma (MM), non-small cell lung cancer, head and neck squamous cell carcinoma, and urothelial carcinoma [2]. Adverse cutaneous effects are common (approximately 40%) with pembrolizumab and may reflect an enhanced therapeutic response in the treatment of MM [3]. Folliculitis or acneiform eruptions secondary to pembrolizumab have rarely been reported.

A 49-year-old man had a 1.4mm Breslow thickness, non-ulcerated MM excised from his right arm in 2012. Wide local excision and sentinel lymph node biopsy were negative for MM. Mild lower limb folliculitis was noted on melanoma follow up in 2015, which resolved with topical therapy. Right axillary lymphadenopathy developed in 2016 and fine needle aspiration of a lymph node was consistent with metastatic MM, which was BRAF V600 wild type. Radiological staging in 2016 demonstrated pulmonary metastases and further imaging in 2017 showed suprarenal metastases. In 2017, immunotherapy with pembrolizumab was initiated.

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Following his 19th dose of pembrolizumab, a folliculocentric eruption with some follicular pustules developed on the lower legs (Figure 1A and 1B). The folliculitis did not extend distally to involve skin covered with socks. Skin biopsy showed a striking acute and chronic folliculitis and perifolliculitis as illustrated (Figures 2A-2C). In addition, there was a prominent superficial perivascular lymphocytic infiltrate as well as some lichenoid changes suggestive of lichen simplex chronicus.

The extensive follicular eruption, coupled with some elements of a lymphocytic folliculitis on histology, was consistent with a follicular lichenoid drug reaction. An infective aetiology was also considered considering his previous history of bacterial folliculitis. However, treatment with topical corticosteroids and oral prednisolone 60mg (0.75mg/kg) once daily for four weeks provided minimal benefit. Given the lack of response to immunosuppression, a bacterial aetiology was reconsidered. A trial of oral lymecycline (408mg once daily for three months) was unsuccessful. The folliculitis deteriorated with further doses of pembrolizumab (Figure 3). Immunotherapy was stopped after 22 cycles, and the eruption improved but persisted. Repeat biopsy was similar to prior biopsies with an acute and chronic folliculitis and perifolliculitis. Oral clarithromycin (500mg twice daily) and trimethoprim (300mg twice daily) were unhelpful. Oral clindamycin (300mg twice daily) provided some improvement. Despite the sparing of folliculitis in areas under compression by regular socks, prescribed compression stockings were not helpful.

Ultimately oral isotretinoin was required for disease control. Initially isotretinoin (20mg once daily) was combined with clindamycin, with significant improvement. Clindamycin was then withdrawn, with sustained improvement on isotretinoin monotherapy (30mg

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once daily). Following twelve months of therapy with isotretinoin, the follicular eruption has remained quiescent. Recent repeat imaging showed no new lesions.

Discussion

Pembrolizumab is a humanized monoclonal IgG4 antibody approved for the therapy of several malignancies, including MM [1]. Disruption of the PD-1 receptor and PD-1 ligands (PDL-1) permits engagement of T-cells in cytotoxic anti-cancer effects [4]. Therefore, it acts as an immune checkpoint inhibitor and has shown significant survival benefits in patients with advanced MM [5].

Approximately 40% of patients develop cutaneous adverse effects with pembrolizumab, with maculopapular eruptions, pruritus, and hypopigmentation being most commonly seen [3]. However, potentially life-threatening reactions such as Stevens-Johnson syndrome have been reported [6]. Hypopigmentation is more frequently seen in patients treated for MM [7]. The development of cutaneous adverse effects, especially hypopigmentation in patients with MM, is associated with significantly longer progression-free intervals [3].

Drug-induced follicular eruptions have been described with oral corticosteroids, androgenic hormones, EGFR inhibitors, calcineurin inhibitors, lithium, and anticonvulsants [8]. However, the clinical presentations vary significantly according to the causative drug. Corticosteroid- and androgen-induced follicular eruptions mainly manifest as monomorphic pustules, whereas the follicular eruption associated with EGFR inhibitors is not monomorphic and is associated with significant pruritus and

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crust formation. The variations in clinical manifestations may be due to effects on toll-like receptors, [9] keratinocyte differentiation, [10] or neutrophil chemotaxis [11]. Drug-induced follicular eruptions have rarely been reported with anti PD-1 therapy, although they have been described with cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) immunotherapy with ipilimumab [12].

While drug-induced follicular or acneiform eruptions usually occur relatively quickly following initiation of treatment, delayed presentations may occur, particularly with complex biologic medicines such as pembrolizumab. The temporal improvement in folliculitis with cessation of pembrolizumab is also supportive of drug-induced aetiology. The follicular eruption in this case was strikingly monomorphic and inflammatory, with a lack of comedones and cysts, typical of drug-induced folliculitis. It was also unusually severe and resistant to therapy, given that previous folliculitis had been very mild and responsive to basic topical antimicrobial therapy. This eruption may have represented an exacerbation of previous folliculitis or a *de novo* follicular eruption with superimposed bacterial folliculitis. In either case, pembrolizumab had a temporal relationship with its development and exacerbation.

Lichenoid eruptions have been well-described in relation to anti-PD1 therapy, [13] but not in a folliculocentric pattern. There are also reports of neutrophilic dermatoses in patients on anti-PD1 immunotherapy [14-16]. This unusual presentation could fit with a follicular lichenoid reaction with some neutrophilic folliculitis. This might explain the poor response to antibiotics and the success seen with isotretinoin. Retinoids can be beneficial in treating lichenoid drug reactions, especially if the drug reaction is persistent of if continued therapy with the causative drug is necessary [17]. Retinoids

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modify keratinocyte differentiation and are therefore useful in disorders of keratinization such as acneiform eruptions [18]. Additionally, the previous history of folliculitis could explain why some of the follicles showed pustules and neutrophils on biopsy during the anti-PD1 treatment.

Cessation of the causative drug or switching to an alternative agent should be considered when there is significant impairment related to follicular drug eruptions. However, persistence of the cutaneous eruption can be seen, especially with drugs with a long half-life such as pembrolizumab [19]. Treatment of persistent follicular eruptions can be difficult. Tetracyclines may be useful when used prophylactically [20] but isotretinoin may be required to achieve remission [21].

This case highlights the difficulties in ascertaining the underlying aetiology of follicular eruptions with immunotherapy and supports the early use of retinoids for persistent follicular eruptions with anti-PD1 therapy.

Summary Points

- Pembrolizumab is a monoclonal antibody that targets programmed cell death receptor-1 (PD-1).
- Adverse cutaneous effects are common (approximately 40%) with pembrolizumab and may reflect an enhanced therapeutic response.
- Folliculitis or acneiform eruptions secondary to pembrolizumab have rarely been reported.

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- We report a 49-year-old man with metastatic melanoma who developed a folliculocentric pustular eruption following 19 doses of pembrolizumab.
- The clinical and histological features shared overlap between a lichenoid and neutrophilic folliculitis, complicating categorization.
- Treatment with oral corticosteroids and oral antibiotics was unhelpful.
- Treatment with oral isotretinoin was rapidly beneficial, which may be due to its modification of keratinocyte differentiation.
- Management of pembrolizumab-induced folliculitis can be difficult, and oral retinoids should be considered as an early option to induce remission.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants, or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

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Figure Legends

Figure 1A-B

Perifollicular papulopustular eruption of lower legs with sparing of skin where socks were providing pressure.

Figure 2A-C

A – Low power view of skin biopsy with hair follicle plugged with neutrophils and surrounding dermis with an acute and chronic inflammatory infiltrate.

B – High power view of hair follicle with acute folliculitis highlighting the neutrophilic infiltration of the follicular epithelium and neutrophilic infiltrate and hair shaft within the follicle

C – High power view of hair follicle with acute folliculitis and perifolliculiitis with the overlying epidermis showing some epidermal hyperplasia, hyperkeratosis and changes of lichen simplex chronicus

Figure 3

Progression of folliculitis with further cycles of pembrolizumab, showing almost confluent erythema of the anterior shins.

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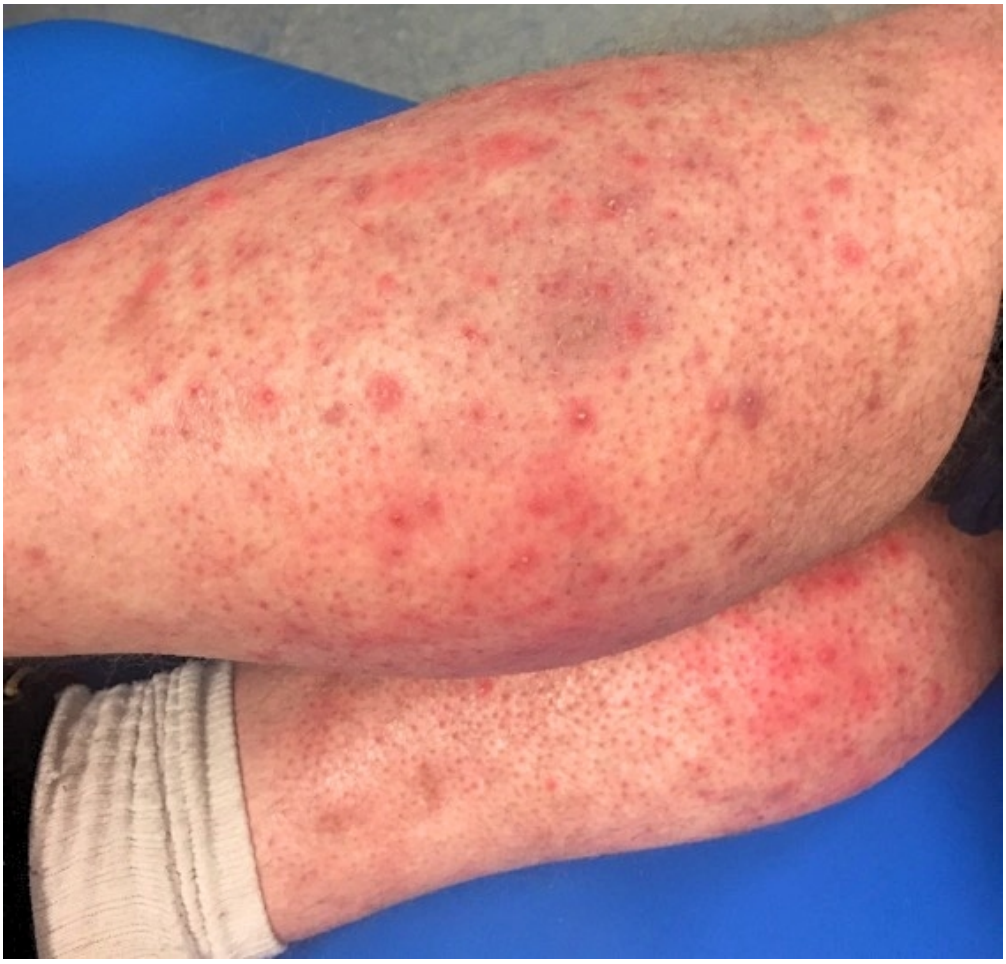


Figure 1A-B
Perifollicular papulopustular eruption of lower legs with sparing of skin where socks were providing pressure.

199x190mm (72 x 72 DPI)

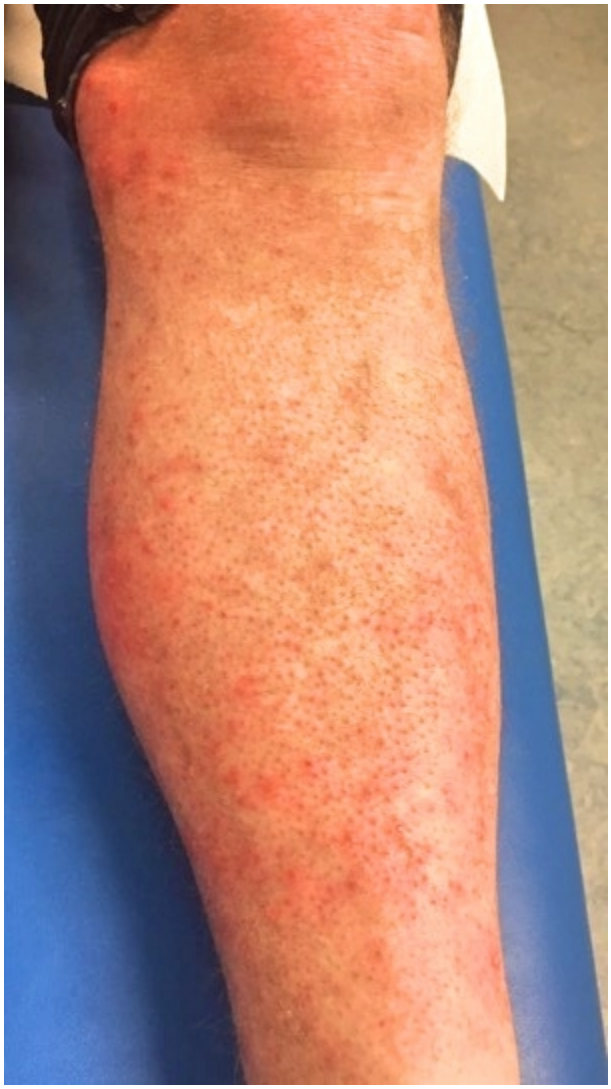


Figure 1A-B
Perifollicular papulopustular eruption of lower legs with sparing of skin where socks were providing pressure.

106x190mm (72 x 72 DPI)

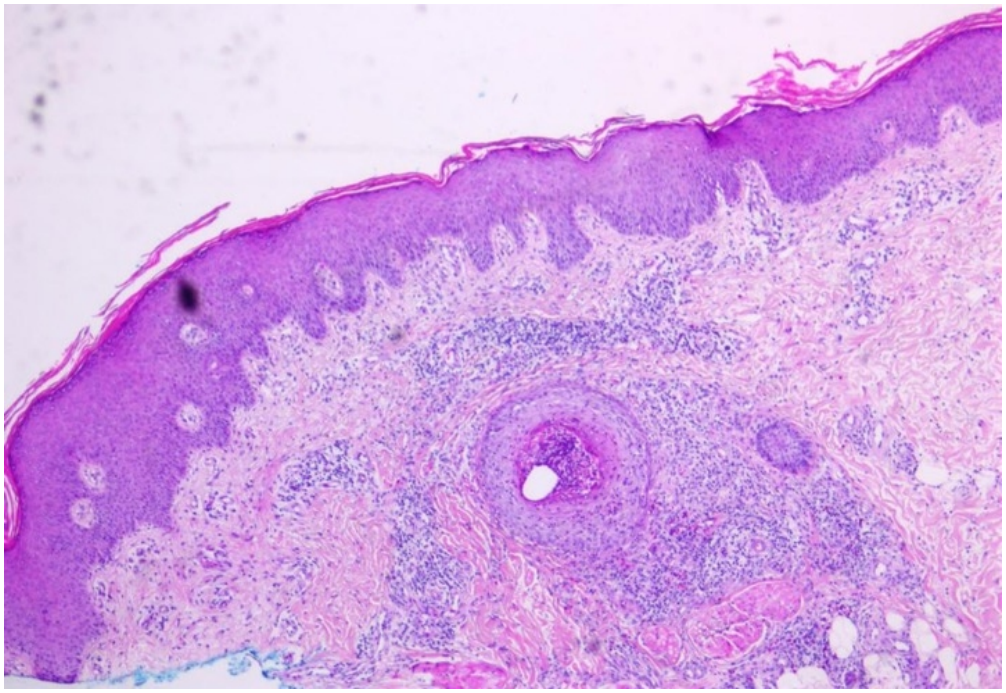


Figure 2A – Low power view of skin biopsy with hair follicle plugged with neutrophils and surrounding dermis with an acute and chronic inflammatory infiltrate.

60x41mm (300 x 300 DPI)

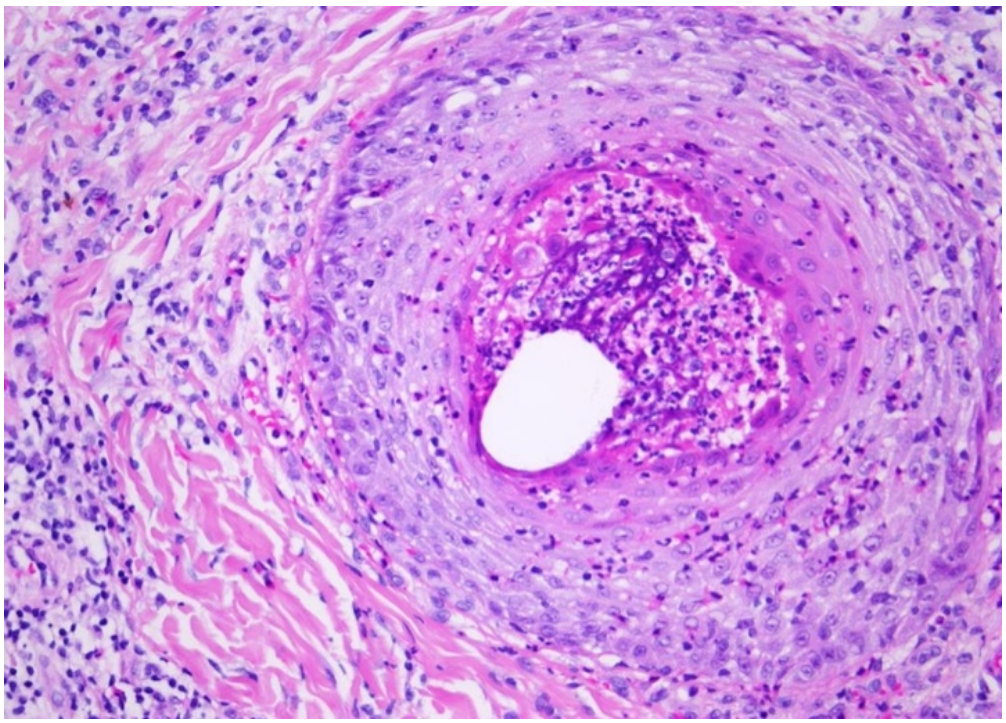


Figure 2B – High power view of hair follicle with acute folliculitis highlighting the neutrophilic infiltration of the follicular epithelium and neutrophilic infiltrate and hair shaft within the follicle.

60x43mm (300 x 300 DPI)

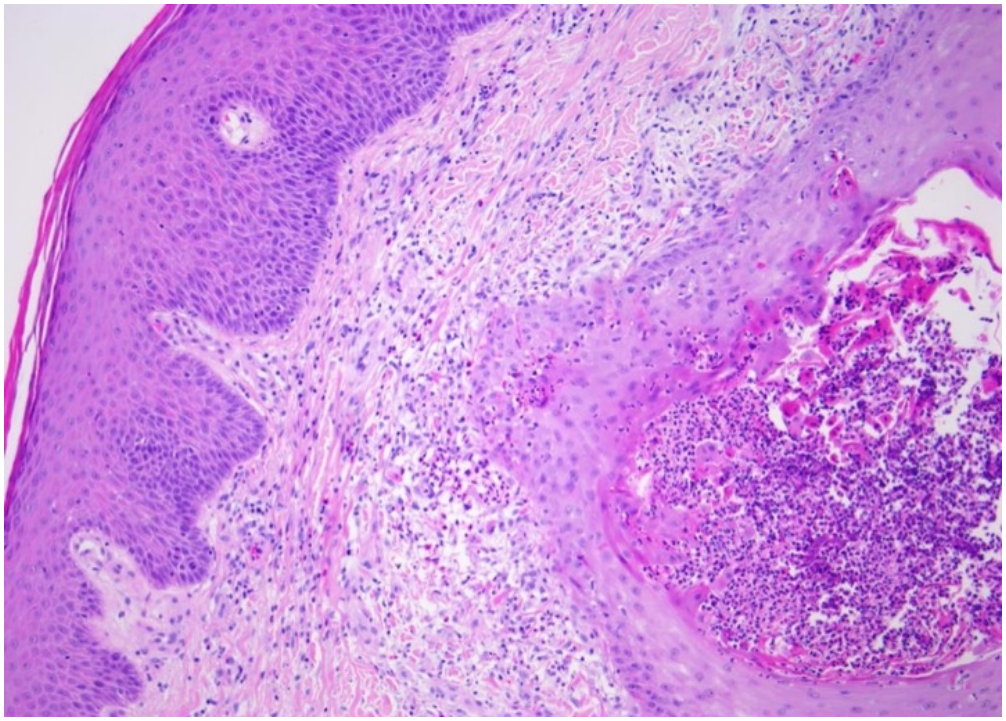


Figure 2C – High power view of hair follicle with acute folliculitis and perifolliculiitis with the overlying epidermis showing some epidermal hyperplasia, hyperkeratosis and changes of lichen simplex chronicus.

60x43mm (300 x 300 DPI)



Figure 3 - Progression of folliculitis with further cycles of pembrolizumab, showing almost confluent erythema of the anterior shins.

172x190mm (72 x 72 DPI)