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# Dermatological adverse events of immune checkpoint inhibitors

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## ABSTRACT

Treatment with immune checkpoint inhibitors is a landmark in the treatment of melanoma and other cancers. These treatments have been very effective and have increased the survival of cancer patients. The promise of immunotherapy also comes with a variety of adverse events. One of the common sites of immune related adverse events (irAEs) is skin. The cutaneous irAEs present a unique challenge to the success of immunotherapy. It is important to diagnose and understand the mechanism related to these cutaneous irAEs to increase the effectiveness of immune checkpoint inhibitor therapy. In this review, we have characterized the various cutaneous irAEs associated with immune checkpoint inhibitor therapies and their possible mechanisms.

**Keywords:** checkpoint inhibitors, immunotherapy, adverse events

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## Introduction

Immune checkpoint inhibitors are increasingly being used in cancer therapy. These drugs work to enhance the immune response against cancer by targeting the intrinsic inactivation signals of the immune system. Specifically, these signals are cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), and programmed death-ligand 1 (PD-L1). During activation, T-cells are co-stimulated by antigen presenting cells (APCs) by binding of antigen-major histocompatibility complex (MHC) to the T-cell receptor (TCR) and binding of CD80/86 to the CD28 receptor on T-cells. T-cell activation feeds into a negative feedback loop, whereby CTLA-4 expression increases and can bind to the CD28 receptor with greater affinity than CD80/86. As a result, the T-cell response becomes downregulated [1, 2]. In the peripheral tissues, binding of PD-1 on T-cells to PD-L1 on normal or tumor cells reduces the activity and proliferation of T-cells[3, 4]. Therefore, the strategy to block CTLA-4, PD-1, or both has been successfully harnessed in the use of immune checkpoint inhibitors against a variety of cancers.

One of the major downsides of checkpoint blockade is immune-related adverse events (irAEs). These events occur systemically and unpredictably and can lead to serious consequences, including death. Of the many irAEs, the most prevalent reactions occur in the skin with upwards of 30% of patients manifesting with cutaneous events upon checkpoint inhibitor therapy [5-7]. Most cutaneous reactions are relatively mild with rare occurrences of grade 3 or 4 events[8, 9]. The pathogenesis for these events is not well understood, but most explanations center around over-stimulation of the immune system.

In this review, we will describe the reported cutaneous adverse events and examine the underlying mechanisms for these effects.

## Dermatologic Adverse Events

### Maculopapular rash

A maculopapular rash is a type of rash characterized by a flat erythematous area on the skin covered by small confluent bumps. The most common dermatological and overall irAE is a maculopapular rash (MPR). It is the most commonly seen under blockade of CTLA-4 (4-68% patients) in comparison to single treatment with PD-1 or PD-L1 inhibitors (20% patients) [10, 11]. MPR most commonly manifests on the trunk and surface of extremities. It is an early event, which is seen 3-6 weeks after the first treatment and is dependent on the therapeutic dose. Histologically, there is infiltration of CD4+ T-cells and eosinophils in the tissue [12].

### Pruritus

Pruritus is a chronic itchy condition that provokes the desire to scratch. Pruritus is the second most common irAE after MPR and the two are often seen to co-exist. It can occur with or without cutaneous eruption. It is often seen in patients on anti-CTLA4 therapy [13, 14]. A small number of patients (~20%) can also develop pruritis after anti-PD-1/PD-L1 therapy [13-16].

### Lichenoid eruption

Lichenoid eruption is a condition characterized by damage and infiltration between the epidermis and dermis. Lichenoid eruption is seen with PD-1/PD-L1 therapy, although to a much lower extent (0.5-6% patients) compared to MPR [10,17,18]. Unlike MPR, its onset is delayed (mean onset is 6-12 weeks). There eruptions appear as multiple, discrete, erythematous, papules and plaques on chest and back region, but they can be rarely seen on limbs, palmoplantar surfaces, and oral mucosa [12]. Histological evaluation reveals a dense superficial dermal band-like lymphocytic infiltrate with degeneration of vacuoles and apoptotic keratinocytes in the basal epidermal layer [12]. These are different from the conventional lichenoid eruptions in that they consist of increased number of CD163-positive cells of macrophage-monocytic lineage [19-21].

## 2. Autoimmune Diseases

### Vitiligo

Vitiligo is an autoimmune disease characterized by depigmented macules or patches that originate due to loss of functional melanocytes in the

epidermis [19, 22, 23]. The risk of developing vitiligo after checkpoint inhibitor therapy is 10 times larger than what is seen in the general population [JR]. Development of vitiligo is a positive indicator of the success of therapy with immune checkpoint inhibitors. Vitiligo develops due to an immune reaction by activated CD8+ cytotoxic T-cells against melanocytes after anti-PD-1 or anti-CTLA-4 checkpoint inhibitor therapy [13, 14, 22, 24]. Vitiligo takes several months to develop after initiation of immune checkpoint inhibitor therapy and is not dose-dependent [13 ,14]. The incidence of vitiligo-like depigmentation in also seen in other non-melanoma related cancers but its incidence is unknown [26-28]. Vitiligo that arises after immune checkpoint inhibitor therapy is seen as multiple flecked macules of depigmentation that evolve into large plaques on the skin [72]. Patients who develop vitiligo after immune checkpoint inhibitor therapy have a better progression free and disease free survival and it does not resolve even after completion of therapy [13, 14, 19].

**Bullous pemphigoid-like blisters**

Bulbous pemphigoid (BP) is a rare skin autoimmune disease that causes rash and itchy blisters. BP-like blisters arising after PD-1 inhibitor have been identified in a few cases. These cases are similar with the appearance of tense bullae with serous exudate. In addition, histology revealed subepidermal detachment and eosinophilic infiltration[28-33]. More rarely, other forms of autoimmune blistering diseases may develop. A case report revealed a patient with paraneoplastic pemphigus-like lesions identified by suprabasal acantholytic dermatoses[34]. BP-like blisters are associated with therapy with anti-PD-1/PD-L1 inhibitors for melanoma and other cancers. They have a delayed onset of 14 weeks after therapy [10, 26]. They have a non-bullous phase of pruritis, followed by localized blisters that are filled with hemorrhagic fluid [35]. A humoral component is involved in the development of BP-like blisters that are characterized by autoantibody production, which can be detected by serological methods like ELISA for monitoring the disease [36]. Indirect immunofluorescence can also be performed for circulating IgG autoantibodies [12].

**Scleroderma**

Scleroderma is a group of rare diseases that involve the hardening and tightening of the skin and connective tissues. Scleroderma is an even rarer event that has been reported following PD-1 blockade. These cases involved typical skin tightness of the hands and feet and dermal sclerosis on histology[37, 38]. The underlying mechanism for this is unknown, it is reported that TGF-β cascade is activated within the skin after treatment with anti-PD-1, which results in fibrosis [37].

**Alopecia areata**

Alopecia areata (AA) is an autoimmune disease that results in unpredictable, patchy hair loss. AA is reported in 1-2% cancer patients receiving immune checkpoint inhibitor therapy [38, 39]. AA caused by checkpoint inhibitor therapy shares several features with the classical AA. PD-1/PD-L1 play an important role in immune privileged sites including the hair follicle [11]. In both conditions, there is an infiltration of CD4+ and CD8+ T-cells sparing the stem cell compartment. There is some difference in lymphocyte infiltration. In immune checkpoint inhibitor-induced AA, lymphocytes are seen around the infundibulum of the hair follicle in addition to the peribulbular region as seen in classical AA [40]. Immune checkpoint therapy can also amplify pathology in patients with pre-existing compromise of hair follicle immune privilege [41].

**Systemic Lupus Erythematosus (SLE)**

Systemic Lupus Erythematosus (SLE) is the most common form of lupus, a chronic autoimmune disease that can cause severe fatigue and joint pain. Polymorphisms in CTLA4 and PD1 genes have been shown to cause SLE in humans and animal models [42-44]. Manifestation of SLE is rarely seen after immune checkpoint inhibitor therapy in patients [45].

**3. Inflammatory Reactions**

**Psoriasis**

Psoriasis is an immune-mediated disease that causes inflammation in the body characterized by raised scaly patches to appear on the skin, Psoriasis is caused due to an inflammatory reaction to immune checkpoint inhibitors. Most of these cases were precipitated by PD-1 therapy and involved exacerbations in patients with existing psoriasis, but rarely patients have also developed new psoriasis[46-48]. Notably, the few cases of psoriasis following CTLA-4 therapy occurred in patients with pre-existing psoriasis[49]. The majority of cases are classified as plaque psoriasis, typified by scaly, erythematous plaque lesions on the body [50]. A few cases of guttate and palmoplantar psoriasis have also been reported [51].

### Sarcoidosis

Sarcoidosis is a disease that starts as granuloma and causes inflammation in lungs, skin, or lymph nodes. Sarcoidosis has been reported in several cases after both CTLA-4 and PD-1 blockade with incidence ranging from about 5 - 6.7% of patients[52, 53]. These events are marked by cutaneous nodules of epithelioid histiocytes and giant cells, as well as hilar and/or mediastinal lymphadenopathy[54-57].

### Grover's disease

Grover disease is a common pruritic condition that presents as erythematous papules or papulovesicles, mostly occurs on the trunk. It may be caused by an inflammatory reaction to altered self-antigens [58]. It is conceivable that immune stimulatory effects of checkpoint inhibitor therapy may result in altered homeostasis of immune system and trigger Grover-like irAE in susceptible patients [59].

### Other

### Sweet syndrome

Sweet syndrome is a very rare skin inflammatory skin condition characterized by a sudden onset of fever and painful rash on the arms, legs, trunk, face or neck. Sweet syndrome has been reported after treatment with anti-CTLA-4 therapy. It occurred early in the course of treatment and was found to be dose dependent [60].

### Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)

Stevens-Johnson syndrome (SJS) is a rare serious disorder of the skin and mucous membranes. A more severe form of the condition is called toxic epidermal necrolysis (TEN). Acute SJS/TEN presentations can occur with immune checkpoint inhibitor therapy. They resemble the features of classical SJS/TEN. Most cases are seen in patients with melanoma but they can occur in cases of other cancers as well. Fever and clinical manifestations can occur before appearance of skin lesions, which rapidly manifest on trunk and extremities and are associated with mucosal involvement (ocular, oral or urogenital) [61]. Majority of cases are seen after first or second infusion of anti-PD-1 therapy [62, 63]. The diagnosis of SJS/TEN can be done clinically and histopathologically. Histological evaluation of early lesions show scattered apoptotic keratinocytes in the basal epidermis but more full-thickness epidermal necrosis in more advanced lesions [62, 63].

### Mechanisms of AEs

The mechanism of cutaneous irAEs is widely thought to relate to excessive activation of the immune system, which may eventually result in auto-immune conditions. Furthermore, the pathogenesis for CTLA-4 inhibitors and PD-1/PD-L1 inhibitors are different, as illustrated by their contrasting downstream pathways[64]. Generally, the adverse events of CTLA-4 blockade are more severe than those of PD-1 blockade[65]. A phase 3 clinical trial showed that nivolumab and ipilimumab combined therapy produced a greater incidence of adverse events than with either treatment alone[66]. This further supports the notion that CTLA-4 and PD-1 act along different pathways and thus carry more potential to cause adverse effects.

### Enhanced T-cell response

When specific tumor T-cell infiltrating populations in reponse to immune checkpoint inhibitors were compared, it was found that anti-PD-1 and anti-CTLA-4 operate through distinct cellular

mechanisms. PD-1 blockade induces proliferation of CD8 T cells, while CTLA-4 blockade induces proliferation of inducible T-cell co-stimulator (ICOS)+ Th1-like CD4 T cells as well as exhausted-like CD8 T-cells. Furthermore, a correlation was observed between the frequency of CD4+ and CD8+ T-cell populations and tumor growth [64]. In an infection model, it was found that PD-1 blockade can restore the function of exhausted T cells [67]. PD-1 activation has been used to control inflammatory cytokine production in diseases like psoriasis. These cytokines of T helper cells can contribute to ongoing inflammation. T-cell activation by inhibition of PD-1 could possibly exacerbate psoriasis in patients with previous history [51]. Th1 activation also implicated in sarcoidosis. Complete regression of stage IV melanoma after anti-PD-1 therapy was seen in a patient who developed pulmonary and cutaneous sarcoidoisis as a side effect [57]. Activation of autoreactive T cells was seen in immune checkpoint inhibitor mediated autoimmune blistering diseases. A possible mechanism could be the epitope spreading from checkpoint inhibitor induced injury causing immune activation and formation of autoreactive T-cells. Another possible mechanism could be the recruitment of immune cells to the skin and dysregulation of cytokines [34].

### Enhanced Humoral Immunity

PD-1 blockade may play role in modulating humoral immunity. Transient hyperthyroidism accompanied by anti-thyroid antibodies was observed after PD-1 therapy for non-small cell lung cancer (NSCLC) and this was associated with improved outcomes. This highlighted the role of antibody-mediated toxicity in T-cell-directed therapy [68]. PD-1 is more broadly expressed than CTLA-4 on B cells. Therefore, it may also enhance humoral immunity indirectly via T cells or directly on B cells [69, 70]. This may be significant in the case of antibody-mediated autoimmune diseases such as bullous pemphigoid, especially considering that bullous pemphigoid manifested after PD-1 blockade (Naidoo). PD-1 is also expressed on NK cells and inhibits their lytic activity. PD-1 blockade can enhance activity of NK cells is tumors and other tissues [71, 72].

## Conclusion

Immunotherapy with immune checkpoint inhibitors have revolutionized the therapeutic approaches for melanoma and other cancers. Most commonly used immune checkpoint inhibitors include PD-1/PD-L1, CTLA-4, and several other emerging candidates. These therapies have been very effective in treating these cancers but are associated with adverse events including the ones associated with skin. These include inflammatory and autoimmune skin conditions caused by hyperactivation of the immune system. More research is needed to investigate the mechanism of action of these cutaneous events so they can be effectively managed for better outcomes.

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