Cutaneous immune-related adverse events in patients with melanoma treated with checkpoint inhibitors


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Summary

Checkpoint inhibitor (CPI) therapy has vastly improved long-term outcomes in metastatic malignant melanoma (MMM). Therapy takes the form of monoclonal antibody infusions that target immune cell checkpoint proteins, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed death 1/programmed death ligand 1 (PD1/PDL1). Cutaneous immune-related adverse effects (IrAEs) are frequent in patients with MMM treated with CPIs. Our aim was to review the clinical presentations of cutaneous IrAEs associated with CPI therapy in adult patients with MMM. We carried out a literature review of clinical trials, case series and case reports of patients with melanoma and those with other cancers treated with anti-CTLA4, anti-PD1/PDL1, or a combination of these therapies. Diverse clinical presentations of cutaneous IrAEs are recognized. Anti-CTLA4 therapy has a higher associated rate of cutaneous IrAEs than anti-PD1/PDL1 therapies. Low-grade cutaneous IrAEs are common and are usually managed supportively while continuing CPI therapy. Delayed presentations arising after established use of CPIs can make therapy-associated cutaneous IrAEs difficult to distinguish from coincidental dermatological disease. Vitiligo-like depigmentation is a good prognostic indicator of outcome in patients with melanoma. Life-threatening adverse events including toxic epidermal necrolysis are rare. The identification of predictive biomarkers that highlight patients at risk of life-threatening IrAEs remains an unmet need. The involvement of dermatologists in the multidisciplinary assessment of cutaneous IrAEs is increasingly pertinent in the management and care of CPI-treated patients with melanoma.

The treatment of a variety of advanced cancers with checkpoint inhibitor (CPI) therapy has resulted in prolonged survival.1 These agents target immune-cell-surface checkpoint proteins such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed death 1/programmed death ligand 1 (PD1/PDL1), which cancer cells exploit to evade immune detection and destruction. Anti-CTLA4 (e.g. ipilimumab), anti-PD1 (e.g. pembrolizumab or nivolumab) and anti-PDL1 (e.g. atezolizumab) agents are used either alone or in combination to treat advanced melanoma; renal, bladder, lung, breast, head and neck, squamous cell skin and colorectal carcinoma; and haematological malignancies.2 Their use is continually expanding, with 3362 clinical trials of anti-PD1/PDL1 alone or in combination since 2006.3 Of these there were 2975 active clinical trials in 2019 alone – a doubling since 2017 – illustrating the steep rise in use of these agents.1,3

In advanced metastatic melanoma, CPI therapy may be given either adjuvantly following resection or as therapy for unresectable disease. Combination therapy with nivolumab (anti-PD1) and ipilimumab (anti-CTLA4) has vastly improved long-term outcomes in metastatic malignant melanoma (MMM), with half of treated patients alive at 5 years.4 However, the increased response and survival rates are associated with immune-related adverse events (IrAEs). These may involve multiple organs and resemble a wide variety of spontaneous immune-mediated diseases, which are graded using Common Terminology Criteria for Adverse Events (CTCAE)5 according to their severity. The most common IrAEs across CPI-treated patients for all advanced cancer types include skin rashes, colitis, thyroiditis, pneumonitis, arthralgia and hepatitis. Up to 55% of patients developed severe IrAEs in clinical trials of combination therapy (anti-CTLA4 and anti-PD1), with
lower rates seen in patients receiving anti-CTLA4 (10–41.6%) and anti-PD1 (12–20%) as single agents.6 IrAEs typically arise between 3 and 14 weeks from initial dosing but may occur at any point during treatment, and even after discontinuation of the drug.6

Cutaneous IrAEs in CPI-treated patients with MMM are heterogeneous, and presentations can include inflammatory eruptions, cutaneous sarcoid and vitiligo-like depigmentation.7 In the skin, IrAEs of any grade are recognized to affect 47–68% of anti-CTLA4-treated patients, and 30–40% of anti-PD1/PD1-L1-treated patients (across all cancer types) in clinical trials.8 The frequency of severe (CTCAE grade 3 or 4) skin rash is low, reported as < 5% of those receiving combination immunotherapy and < 3% occurrence in monotherapy.6 A permanent discontinuation of therapy due to toxicity has been reported in 5% of patients treated with anti-PD1 therapy.9 Life-threatening IrAEs such as toxic epidermal necrolysis are uncommon but have been reported.10 The impact of cutaneous IrAEs may be underestimated, as the quality-of-life tools used within trials to assess toxicities capture the impact of pruritis or rash only if global health or physical functioning is affected.11 Recognition and management of cutaneous IrAEs are important, as they can facilitate continuation on CPIs. In this review we survey the presentations of dermatological IrAEs in patients with MMM treated with CPIs. A summary of the literature search methods and inclusion criteria is provided in Appendix S1 (see Supporting Information).

**Checkpoint inhibitors in metastatic malignant melanoma**

Dacarbazine was previously the mainstay of therapy for stage IV melanoma, with an overall response rate (ORR) of 20% and a 5-year overall survival (OS) of 8-8%.12 The advent of BRAF/mitogen-activated protein kinase kinase (MEK) inhibitor combination therapy in the form of dabrafenib and trametinib improved the ORR to 64% and increased 5-year OS to 34%.13 The use of combination CPI therapy further increased the ORR to 72-1% and the 5-year OS rate to 52%, and is associated with a reduced frequency of adverse events.4 Single-agent anti-PD1 therapy has also shown good efficacy in MMM, with prolonged clinical responses.14 Anti-PD1/L1 therapy has not yet been approved for use as a single agent in metastatic melanoma, although early-phase studies have confirmed safety and tolerability,15 and it has recently been approved in combination with BRAF/MEK inhibitor therapy for stage IV melanoma in the USA.16 Trials of anti-PDL1 in combination with anti-CTLA4 are ongoing.17 Another emerging therapeutic combination is of anti-PD1 or anti-CTLA4 with localized oncolytic virus therapy such as talimogene laherparepvec, which may further enhance the immune response by facilitating release of melanoma-specific antigens.18

Awareness of typical treatment regimens and clinical decision-making processes in oncology is increasingly relevant to dermatologists as there is expansion of use of CPIs in multiple tumour types, and patients with advanced melanoma, for example, live longer due to increased efficacy.4 In the UK, a typical example of a CPI treatment regimen for a patient with stage IV melanoma in whom performance status is 0–1 would be four cycles of 3-weekly combination nivolumab (anti-PD1) and ipilimumab (anti-CTLA4) followed by 4-weekly maintenance nivolumab. This regimen is preferred in fit patients due to the enhanced OS and rate of complete response. In the USA, the recent American Society for Clinical Oncology guidelines on systemic therapy for melanoma identified combination CPI therapy as the most cost-effective initial CPI regimen.19,20 Use of ipilimumab as a single agent is no longer recommended as a first-line option given the superior outcomes with anti-PD1 agents.19

CPI therapy is continued until disease progression or toxicity, or a decision is made to stop at 2 years in responders in some countries, such as the UK.4 Response is assessed clinically and radiologically using computed tomography imaging of the chest, abdomen and pelvis (with magnetic resonance imaging of the brain in those with known brain metastases) after four cycles of combination therapy and thereafter on a 12-weekly basis. In patients who are less fit (or have relative contraindications such as coexistent autoimmune disease, other comorbidities or advanced age) or whose personal preference is to avoid the higher toxicity rate of combination CPIs, there are options for 48 months of single-agent therapy with nivolumab given every 2–4 weeks, 48 months of pembrolizumab given every 3–6 weeks, or 3 months of ipilimumab given every 3 weeks, or sequential treatment with these agents. In the adjuvant setting, patients with surgically resected stage IIIA/B/C/D disease are offered treatment with nivolumab or pembrolizumab for 12 months.

Inevitably, alongside increased patient exposure to CPIs, the incidence and prevalence of toxicity will rise. The treatment strategy has shifted, with a greater focus on adjuvant systemic therapies for earlier stage III disease, which is now standard-of-care treatment, with adjuvant anti-PD1 halving the risk of recurrence in resected disease.21,22 This underscores the importance of tools utilized to assess impact on patients’ quality of life, which may under-represent the toxicity burden in patients receiving CPIs.

**Mechanism of action of checkpoint inhibitors**

An overview of the immune response in health is pertinent to give insight into the mode of action of CPIs against melanoma and the pathogenesis of IrAEs. In the skin and other tissues, regulation of effector immune responses is controlled by a complex network of costimulatory and inhibitory signals, collectively known as immune checkpoints. A fine balance between these signals is critical for maintaining immune homeostasis and self-tolerance, protecting tissues from collateral damage by controlling immune responses to pathogens and autoantigens. There are several inhibitory receptors, ligands and molecules that act to dampen immune responses, and many of these are upregulated in exhausted T cells, which arise due to chronic stimulation, as seen in cancer.
Two of the most studied inhibitory immune checkpoints, which are also the targets of successful CPI therapies (Figure 1), are CTLA4 and PD1. Both CTLA4 and PD1 are receptors predominantly expressed by T cells, which regulate T-cell responses by a variety of mechanisms.\textsuperscript{23–25} CTLA4-mediated immune regulation is induced at the early stages of T-cell priming and activation, when naive T cells in lymphoid tissues initially respond to their cognate antigen. CTLA4 can reduce the amplification signal needed for T-cell activation.\textsuperscript{23} In addition, CTLA4 can dampen T-cell activation by actively removing receptors from the surface of antigen-presenting cells (APCs) through a process known as trans-endocytosis, and directly through the delivery of inhibitory signals that limit the signalling potential of the T-cell receptor. Of relevance, regulatory T cells (Tregs), specialized T cells that regulate immune responses in the periphery, constitutively express CTLA4.

PD1 regulates T-cell responses at a different stage of activation than CTLA4, namely effector T-cell responses within tissues.\textsuperscript{23} PD1 is expressed by activated T cells, and ongoing inflammation in the tissues induces expression of PD1 ligands, PDL1 and PDL2, on several different cell types including APCs and nonlymphoid cells. Binding of PD1 to its ligand causes an intracellular signalling cascade within the T cell that ultimately inhibits T-cell-receptor signalling leading to a reduction in cell survival and proliferation, and effector cytokine production. PD1 and PDL1 are also highly expressed by Tregs, and engagement of PD1 with its ligand increases the proliferation and suppressive ability of Tregs.

Cancers can exploit inhibitory immune checkpoints, as well as other immune regulation mechanisms, to evade the immune system, allowing for their continued survival. Tumours themselves, as well as tumour-infiltrating T cells, express many inhibitory checkpoints and associated molecules, including CTLA4 and PD1 and its ligands. Expression of these within the tumour microenvironment causes a general suppression of antitumour immune responses either directly through inhibition of T-cell responses or indirectly via the enhancement of Treg responses.

Generally, it is thought that anti-CTLA4 therapy affects the early stage of T-cell activation in lymphoid tissue by restoring T-cell priming in response to tumour antigens presented by APCs, which can enhance CD4\textsuperscript{+} T helper cell-dependent immune responses. In addition, blockade of CTLA4 may result in the reduction of Tregs’ suppressive ability, due to Treg depletion in tumour tissue via antibody-dependent cell-mediated cytotoxicity.\textsuperscript{26} Blockade of PD1 enhances exhausted T-cell-effector function and may reduce the number and/or suppressive ability of Tregs, as well as enhancing B-cell and natural killer cell activity.

Novel therapies under investigation for combination with anti-PD1/PDL1 or anti-CTLA4 include targets for other immune inhibitory pathways, including LAG-3 (lymphocyte-activation gene-3), TIM-3 (T-cell immunoglobulin and mucin domain-3), VISTA (V-domain Ig suppressor of T-cell activation) and BTLA (B and T lymphocyte attenuator).\textsuperscript{27} Stimulatory pathways in combination with CPIs are also under investigation, including OX40, ICOS (inducible T-cell costimulator), 41BB, vaccines, cytokines and oncolytic viral agents.\textsuperscript{27} Given the augmentation of the immune response induced by CPIs, it is perhaps unsurprising that cutaneous inflammation arises frequently as an adverse event.

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**Figure 1** Immune checkpoint molecules are cancer drug targets. The interactions between some of the multiple immune checkpoints on cancer cells, T cells and antigen-presenting cells are shown. Checkpoint inhibitor (CPI) targets for drugs in the clinic and in development are indicated in colour, and established therapies (anti-PD1, anti-PDL1 and anti-CTLA) are indicated in black. The oncolytic virus talimogene laherparepvec (TVEC), which facilitates neoantigen release, can potentiate the immune effector response. CPIs in use in the clinic and in clinical trials are listed in the inset. CTLA, cytotoxic T-lymphocyte-associated protein; Gal-9, Galectin-9; LAG, lymphocyte-activation gene; MHC, major histocompatibility complex; PD, programmed death; PDL, programmed death ligand; TIM, T-cell immunoglobulin and mucin domain.
Cutaneous immune-related adverse events in patients with metastatic malignant melanoma treated with checkpoint inhibitors

The reporting of cutaneous IrAEs in patients treated with CPIs does not routinely involve dermatologists. As such, the characterization of the heterogeneous presentations is variable, with limited descriptive clinical information and skin biopsy data to support specific dermatological diagnoses. These caveats have to be borne in mind in the interpretation of the data reported from landmark studies, where terminology as limited as ‘rash’ is used to capture diverse cutaneous IrAEs. Additionally, due to the importance of continuing CPI therapy, classical tests for drug reactions such as challenge–rechallenge testing are not routinely performed. It may also be difficult to distinguish coincidental dermatological disease from cutaneous IrAEs, particularly when there is a long period of latency between the start of treatment and the onset of the IrAE.

There is evidence to suggest that there are melanoma-specific skin adverse reactions in CPI-treated patients, in addition to IrAEs seen across all CPI-treated cancers. Retrospective studies reporting patient assessment that have included dermatologists and oncologists give an indication of the presentations seen in the context of MMM, although these are mainly for anti-PD1 therapies. Voskens et al. reported 752 patients with melanoma treated with anti-CTLA4 therapy, reporting cutaneous reactions as common, but severe reactions (grade 3 or 4) as rare. Hofmann et al. reported on 496 patients with melanoma treated with anti-CTLA4 therapy, reporting cutaneous reactions as common, but severe reactions (grade 3 or 4) as rare. Hofmann et al. reported on 496 patients with melanoma treated with anti-PD1 agents and identified 43 patients with a skin reaction out of 496 (8.7%). These included ‘rash’ and eczema in 19 patients (3.8%), vitiligo in 13 (2-6%), alopecia in seven (1.4%) and lichenoid skin reactions in four (0.8%). Only three cutaneous AEIs were regarded as CTCAE grade 3 severity, namely lichenoid skin reaction, lichen ruber mucosae, and Sweet syndrome. All led to a pause of treatment.

Bottlaender et al. recently reported on 189 patients with melanoma treated with anti-PD1 therapy alone and identified a frequency of cutaneous IrAE of 49%, with 92 patients in their observational cohort study experiencing skin toxicity of any grade. Of these 18 had a ‘skin eruption’, 16 vitiligo, five isolated pruritis, four xerosis, three sarcoidosis, two psoriasis, two Grover disease, two vasculitis and one dermatomyositis. Only five toxicities were graded as severe, and all led to treatment interruption; one of these toxicities (flare of pre-existing psoriasis) was fatal.

These available data guide our focus in the following section on cutaneous IrAE presentations in patients with melanoma treated with CPIs from the wider literature. The variation in rates of reported cutaneous IrAE across these studies may reflect factors such as reporting bias associated with retrospective studies, different CTCAE thresholds for reporting cutaneous IrAEs, and variable availability of dermatology services for patient assessment across treatment centres.

Inflammatory eruptions

The term ‘inflammatory eruption’ is used by Coleman et al. to capture lichenoid, eczematous psoriasiform reactions and maculopapular drug exanthems, which appear to be recurrent reactions in patients with melanoma treated with CPIs.

Drug-associated maculopapular exanthem

The drug-associated maculopapular exanthem (MPE) reaction described in an early study of nine patients treated with anti-CTLA4 is thought be similar to typical antibiotic drug eruptions. Presentations of MPE may have been categorized as a ‘rash’ or ‘skin eruption’ in the studies by Bottlaender and Hofmann, respectively. A consistent finding of drug-associated MPE is the trunk being the main site that is affected, with sparing of the face, palms and soles. It is possible that a proportion of the clinically diagnosed maculopapular and morbilliform rashes reported may represent some of the biopsyped proven rashes discussed below at earlier stages of evolution.

Lichenoid reactions

Lichenoid reactions in CPI-treated melanoma can present as violaceous or erythematous papules or plaques associated with itch. Palmoplantar, mucosal and nail involvement has been reported. Occasionally patients present with mucosal lesions alone. Hwang et al. highlighted the usefulness of biopsy data to support a clinical diagnosis of a lichenoid reaction, as these may be otherwise misclassified as other dermatoses when presenting with atypical features. Microscopically, a bandlike crowded lymphocytic infiltrate that is either mixed CD4/CD8 positive or predominantly CD4 positive is seen along the dermoepidermal junction with hyperkeratosis and hypergranulosis. Atypical histological features such as the presence of parakeratosis can be seen.

Eczematous reactions

Eczematous reactions can present as classic pruritic, ill-defined patches or plaques of discoid eczema. Some of these patients have a prior history of atopy, and Bottlaender et al. identified atopy as a risk factor for cutaneous IrAEs. The distribution is typically over the torso and extremities, although the face, scalp, axillae and genital areas can become involved. Hwang et al. showed that up to one-quarter of anti-PD1-treated patients with MMM develop eczema after 10 months of therapy, with an increased risk associated with longer treatment. In addition, there is an increased risk of co-presentation of eczema and lichenoid reactions in a subset of patients.

Psoriasiform reactions

Psoriasiform reactions may be either de novo or a flare of pre-existing psoriasis. In anti-PD1-treated patients, the average time to presentation with psoriasis is 50 days, although those
with pre-existing psoriasis tend to flare prior to this. The presence of pink-red papules with silvery scale at localized extensor sites is the most frequent presentation, although uncommonly inverse-pattern psoriasis or palmoplantar pustulosis is seen.

**Pruritus**

Pruritus is reported as one of the most common skin IrAEs. This is usually associated with one of the inflammatory eruptions described above, but it can happen uncommonly in isolation. Itch can have a huge impact on quality of life in CPI-treated patients with MMM and is thought to affect 14–21% of those receiving anti-PD1 treatment and 25–36% of those receiving anti-CTLA4 treatment. Itch is most frequently reported in those receiving combination treatment (33–47%).

**Cutaneous sarcoidosis**

Cutaneous sarcoidosis, or sarcoid-like granulomatous reactions, can present as subcutaneously embedded erythematous, papular or nodular lesions, distributed on the arms and intertriginous areas. It is thought to be seen more frequently in anti-CTLA4-treated patients with melanoma than in those treated for other cancers, and may be an indicator of response in some patients with MMM. The lesions can be annular or coalesce into plaques. Histologically noncaseating epithelioid granulomas are seen. There are reports of isolated development of cutaneous sarcoid at immunotherapy infusion sites. Erythema nodosum can also be the presenting feature of immunotherapy-induced sarcoidosis. Other organs may be affected, and cutaneous sarcoid presenting in combination with bilateral anterior uveitis alongside a raised serum angiotensin-converting enzyme level has been reported. Patients may also present with pulmonary involvement (such as mediastinal lymphadenopathy or inflammatory lung disease), which can be clinically difficult to differentiate from disease progression of MMM.

**Vitiligo-like depigmenting rash**

Vitiligo-like depigmenting rash (VLDR) presents several months after commencement of CPI therapy and occasionally following completion of treatment. VLDR is relatively common in patients with melanoma, affecting approximately 1 in 10 patients treated with anti-PD1 agents. However, it is rarer in other tumour types such as lung cancer. Depigmented, well-demarcated macules form initially, and then merge into patches (Figure 2a). Distribution typically includes the face, neck, upper torso and upper limbs. Focal patches may be seen affecting scars or sites of skin metastases. While lesions are mainly asymptomatic, their emergence can be preceded by pruritis or nonspecific maculopapular rash. Typically there is no family history of autoimmune disorder. VLDR is strongly associated with improved tumour response to CPIs. Depigmentation persists after withdrawal of the CPI, although there has been a case report of repigmentation associated with cancer relapse. The typical histological features include absence of epidermal melanocytes at the dermoeidermal junction and a CD8 T-cell infiltrate that overexpresses CXCR3 in addition to raised interferon-γ and tumour necrosis factor levels. VLDR is hypothesized to be caused by a cross-reactivity against shared antigens between healthy melanocytes and melanoma tumour, such as MART-1, GP100, tyrosinase-related proteins 1 and 2 or tyrosinase. Regression of melanocytic naevi is also a well-recognized phenomenon. Patients can also develop eyelash poliosis (Figure 2b). Hypopigmentation of solar lentigines, seborrhoeic keratoses, melanocytic naevi and widespread poliosis of body hair have been reported in a patient with metastatic melanoma treated with pembrolizumab.

In an important retrospective study, Nakamura et al. described improved progression-free survival (PFS) and OS from metastatic melanoma in those who developed VLDR. This supported previous work by Hua et al. in a prospective

![Figure 2](https://example.com/figure2.jpg)
cohort of patients with melanoma, which confirmed a higher incidence of vitiligo in patients who developed complete or partial tumour responses. More recently, Bottlaender et al. demonstrated an association between improved PFS and OS and any type of cutaneous IrAE in MMM, and Teraoka et al. similarly showed improved PFS in patients with non-small cell

Table 1 Summary of key characteristics of presentations of less frequent cutaneous immune-related adverse events (IrAEs) in patients with melanoma treated with checkpoint inhibitors (CPIs)

<table>
<thead>
<tr>
<th>Clinical subtype of IrAE toxicity</th>
<th>Clinical features</th>
<th>Associated drugs</th>
<th>Data type and study</th>
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<tbody>
<tr>
<td>Dermatomyositis (DM)</td>
<td>DM and scleroderma have been reported in CPI-treated MMM; some of these cases may represent a paraneoplastic phenomenon. DM presents with heliotrope erythema and V-neck distribution of chest erythema with or without muscle weakness. Polymyositis can be present with only muscle weakness and without any skin features. Onset can be rapid, even after a single dose of CPI. Elevated CK, CRP and ESR may be present, or findings can be normal. Inflammatory myopathy autoantibodies including anti-synthetase (e.g. anti-Jo-1), anti-Mi-2, anti-transcription intermediary factor-1-γ, and anti-nuclear matrix protein 2 antibodies were negative in the cases reported to date.</td>
<td>Anti-PD1</td>
<td>Case reports, Bottlaender 2020, Marano 2019, Yu 2018</td>
</tr>
<tr>
<td>Bullous pemphigoid (BP)</td>
<td>Two cases of BP in patients with melanoma are described out of a series of nine CPI-treated patients with blistering disease. In both cases treatment with CPI was interrupted. Two further cases are reported from a separate series, where one of these cases developed blisters while on anti-PDL1 therapy. Worsening BP symptoms were also reported after infusions. Classical histological linear IgG and C3 deposition is reported at the dermoepidermal junction with a blister roof on direct immunofluorescence, alongside subepidermal vesicular dermatitis with eosinophil deposition.</td>
<td>Anti-PD1, anti-PDL1 and anti-CTLA4</td>
<td>Case series, Siegel 2018 and Naidoo 2016</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
<td>In this isolated case clusters of pink papules were reported on the anterior and posterior torso and upper limbs. Histology confirmed a neutrophil-rich superficial dermal mixed inflammatory infiltrate, suggestive of dermatitis herpetiformis. Granular IgA deposition within the dermal papillae was seen.</td>
<td>Anti-CTLA4</td>
<td>Case report, Mochel 2016</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Rare cases have been reported of severe vasculitis associated with livedo and digital necrosis. In one case, renal and neurological involvement was reported, leading to cessation of anti-PD1 therapy with resolution of symptoms</td>
<td>Anti-PD1</td>
<td>Case series, Bottlaender 2020</td>
</tr>
<tr>
<td>Sweet syndrome</td>
<td>Sweet syndrome presenting with a fever and crusted nodules affecting the face and upper limbs and also without fever and affecting the dorsum of the hands has been reported in two patients with melanoma. Both had a good response to oral prednisolone, and in one case ipilimumab therapy was not reinstated.</td>
<td>Anti-CTLA4</td>
<td>Case reports, Kyllo 2014 and Gormley 2014</td>
</tr>
<tr>
<td>DRESS</td>
<td>DRESS has been reported in a patient who presented with a diffuse maculopapular rash, fever and general deterioration, which progressed to erythroderma, associated with a peripheral hypereosinophilia. Nephritis was also evident. A good response to oral prednisolone was seen.</td>
<td>Anti-CTLA4</td>
<td>Case series, Voskens 2013</td>
</tr>
<tr>
<td>Grover disease</td>
<td>Grover disease typically presents as a papulokeratotic or vesicular eruption, which can be diffuse and persist for many months after CPI withdrawal. Acantholysis is seen on skin biopsy.</td>
<td>Anti-PD1 and anti-CTLA4</td>
<td>Case series, Bottlaender 2020 and Koelzer 2016</td>
</tr>
<tr>
<td>Acneiform rash and rosacea</td>
<td>Pre-existing facial papulopustular rosacea can flare following CPI exposure. Acneiform rashes can also affect the torso.</td>
<td>Anti-CTLA4 and anti-PD1</td>
<td>Case series, Voskens 2013 and Sibaud 2018</td>
</tr>
<tr>
<td>Alopecia</td>
<td>1–2% of patients can develop alopecia as an IrAE with either the alopecia areata or universalis phenotype. Regrowing hair is often affected with poliosis and is sometimes of a different texture from baseline.</td>
<td>Anti-CTLA4 and anti-PD1</td>
<td>Case series, Zarbo 2017</td>
</tr>
</tbody>
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CK, creatine kinase; CRP, C-reactive protein; DRESS, drug reaction with eosinophilia and systemic symptoms; ESR, erythrocyte sedimentation rate; MMM, metastatic malignant melanoma; PD, programmed death; PDL, programmed death ligand.
lung cancer who developed rash,\textsuperscript{45} suggesting future work may reveal additional cutaneous IrAEs with prognostic utility.

**Severe or life-threatening skin reactions**

The CTCAE criteria describe grade 3 cutaneous eruptions as those affecting > 30\% body surface area, with moderate or severe symptoms that limit self-care activities of daily living.\textsuperscript{5} These reactions may lead to a cessation of CPI therapy. Cutaneous reactions that have been reported in this grade include dermatomyositis, bullous pemphigoid and cutaneous vasculitis, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (Table 1). A limitation of current CTCAE skin criteria is that generalized eczema may be consistent with grade 4, but may not be reasonable cause for therapy dis- continued, yet < 10\% skin detachment in TEN may require CPI withdrawal.

Cases of TEN have been reported with anti-PD1 alone or in combination with anti-CTLA4, but appear to be rare.\textsuperscript{46} TEN can evolve over time before erosions are apparent and can become fatal if refractory to immunosuppression.\textsuperscript{10} One case report described a slow evolution from a morbilliform eruption to overt TEN, over 3 months, that ultimately led to the patient’s demise.\textsuperscript{47} In both this case and the case reported by Nayar et al.,\textsuperscript{10} an initial biopsy demonstrated an interface dermatitis, which later developed to show tissue necrosis and epidermal detachment. The risk of clinical dehydration associated with loss of barrier function related to these cutaneous toxicities can be compounded by IrAEs affecting other organ systems, such as colitis or hypophysitis, and therefore careful assessment of patients with these eruptions caused by exposure to CPIs is required.\textsuperscript{34} SJS has been reported in one case of anti-PD1-treated MMM,\textsuperscript{48} and is recognized as a feature of CPI therapy in patients with other cancers.\textsuperscript{49,50}

**Other reported cutaneous reactions**

There have been several case series reporting cutaneous IrAEs in CPI-treated patients with MMM that occur less frequently, and these are summarized in Table 1.

**Multidisciplinary management of cutaneous immune-related adverse effects in advanced metastatic melanoma**

The rate of hospitalization due to all IrAEs in CPI-treated patients is recognized to be high, with a recent multicentre report of 2125 patients demonstrating an admission rate of 42\%.\textsuperscript{51} However, the rate of hospitalization due to cutaneous toxicity is not known, and these data are important to improve equity of provision of dermatology services to patients receiving CPIs. Some centres provide an oncodermatology service.\textsuperscript{32} Ideally, a multidisciplinary assessment involving dermatologist review is desirable for clinical diagnosis in each new case, which may include a skin biopsy and management tailored to the pertinent cutaneous IrAE. Several pragmatic guides have been proposed for treating oncologists,\textsuperscript{30,51–53} which include indications for stopping CPI therapy and suggested therapeutic strategies. These include the use of topical corticosteroids and antihistamine therapy. Such strategies may be helpful in mild cases; however, they may still benefit from harmonization in a future consensus guideline given the lack of standardization of therapeutic approaches. In particular, extensive cutaneous involvement (CTCAE grade > 3), blistering lesions, unusual clinical features, persistent or recurrent eruptions, and rash significantly affecting quality of life should prompt dermatology review. For severe reactions, systemic steroid treatment may be needed in addition to withholding CPI treatment until the toxicity improves. In the case of severe toxicity the decision to restart CPIs should be taken within a multidisciplinary team, evaluating the risks and benefits, as there is a risk of recurrence of severe cutaneous IrAEs.\textsuperscript{32,54}

**Conclusions**

CPI-treated patients with melanoma may present with a diverse range of presentations of cutaneous IrAEs. Multidisciplinary teams involving dermatologists in the assessment of IrAEs may enhance care of patients receiving CPIs, and could be evaluated in future studies. Dermatologists can refine characterization of cutaneous IrAEs, allowing for the development of much-needed predictive biomarkers. Already, machine learning approaches to identify at-risk individuals receiving anti-PD1 therapy\textsuperscript{55} have shown promise, and these strategies could be improved with deep-phenotyped cases. Importantly, selected cutaneous IrAEs may also have prognostic relevance. It is of interest that comprehensive immune cell profiling using single-cell approaches has begun to improve characterization of the impact of CPIs on the immune system,\textsuperscript{56} and may offer insights into the pathogenesis of cutaneous IrAEs in both MMM and common dermatological disease.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Appendix S1. Supplementary methods.