Cutaneous Reactions to Oncologic Immunotherapy

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Abbreviations

ADLs	Activities of daily living
AGEP	Acute generalized exanthematous pustulosis
APC	Antigen-presenting cell
ASCO	American Society of Clinical Oncology
BSA	Body surface area
CBC	Complete blood count
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
DIHS	Drug-induced hypersensitivity syndrome
DMARD	Disease-modifying antirheumatic drug
DRESS	Drug rash with eosinophilia and systemic symptoms
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
GVHD	Graft vs. host disease
ICI	Immune checkpoint inhibitor
irAE	Immune-related adverse event
IVIG	Intravenous immunoglobulin G
JAK	Janus kinase
MHCII	Major histocompatibility complex II
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
RA	Rheumatoid arthritis
SCAR	Severe cutaneous adverse reaction
SJS/TEN	Stevens-Johnson syndrome/toxic epidermal necrolysis
TCR	T cell receptor
TEN	Toxic epidermal necrolysis
UVB NB	Ultraviolet B-narrow band

1 Introduction

The introduction of T cell-targeted immunomodulator anticancer therapy in the past decade has revolutionized the treatment of previously incurable cancers. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death ligand 1 (PD-L1). Their efficacy was first demonstrated in metastatic melanoma (Robert et al. 2015), and they are presently used as monotherapy or in combination with chemotherapy as first- or second-line treatments for about 50 solid organ as well as hematologic cancers (Robert 2020).

In brief, ICIs target T cell activation, as this is the rate-limiting step of the adaptive immune

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response. Antigen-presenting cells (APCs) activate T cells through the association of the major histocompatibility complex II (MHCII) receptor with a T cell receptor (TCR) in response to an antigenic stimulus. This interaction occurs concurrently with several other receptor-ligand associations. One of the interactions relevant to modern immunotherapy drugs is that between the CD28 protein on T cells and the B7 protein on B cells, which can be competitively inhibited by the CTLA-4 protein expressed on T cells. Another relevant interaction is that between the PD-1 receptor of T cells and the PD-L1 and PD-L2 ligands found on monocytes and dendritic cells, and leukocytes and peripheral somatic cells, respectively. Upregulation of this interaction may allow cancer cells to evade detection by the immune system. By inhibiting CTLA-4 or PD-L1/PD-1 interactions, ICIs promote immune system upregulation and antitumoral immune response.

However, the immune upregulation caused by ICIs has broad-ranging effects in addition to the intended antitumoral activity, resulting in a variety of immune-related adverse events (irAEs). Among the most frequent irAEs from ICIs is skin toxicity, including rash and pruritus (Bertrand et al. 2015; Sibaud et al. 2016). Cutaneous irAEs affect 30–50% of patients treated with ICIs, and range widely in form and severity (Villadolid and Amin 2015; Donaldson et al. 2018; Hwang et al. 2016; Ishihara et al. 2019). Skin toxicity (along with pneumonitis and arthritis) was also found to be one of the top three reasons for referral to a multidisciplinary irAE toxicity team at a major medical center (Naidoo et al. 2019). In this chapter, we discuss the major classes of immunotherapy and review the epidemiology, clinical features, histopathology, and recommended treatment guidelines for the most frequently encountered cutaneous irAEs. We also provide a synopsis of less commonly encountered cutaneous irAEs, including severe cutaneous adverse reactions (SCARs).

2 Epidemiology

The incidence and severity of irAEs varies by patient population and by agent used (Martins et al. 2019). It is important to categorize the degree of severity in a standardized approach, as higher-grade rashes generally require a more aggressive therapeutic approach and are more likely to impact immunotherapy interruption. The Common Terminology Criteria for Adverse Events (CTCAE), which is maintained by the American Society of Clinical Oncology (ASCO), is popularly used and classifies cutaneous irAEs primarily by body surface area (BSA) involvement and impact on quality of life, as well as evidence of superinfection and potential for life-threatening complications (Brahmer et al. 2018). The ASCO and European Society for Medical Oncology (ESMO) have also put forth recommendations for management of cutaneous irAEs based on disease severity (Brahmer et al. 2018). In this section we characterize the cutaneous irAEs associated with each ICI.

2.1 Anti-CTLA-4 Therapy: Ipilimumab

Ipilimumab, a recombinant human monoclonal antibody, is an anti-CTLA-4 ICI that first demonstrated a survival benefit in metastatic melanoma patients (Hodi et al. 2010). irAEs generally occur in a dose-dependent pattern for patients treated with ipilimumab. Pooled analysis of patients treated with 10 mg/kg ipilimumab for 3 weeks showed Grade 3 or 4 irAEs (across all categories) in 25.2% of patients, vs 7% of patients treated with 3 mg/kg dose of ipilimumab (Weber et al. 2012). Specifically in the skin, a study of ipilimumab given at a 10 mg/kg dose showed an incidence of 34.2% for rash of any grade vs. another study of ipilimumab given at a 3 mg/kg dose that showed an incidence of 19.1% for rash of any grade (Hodi et al. 2010; Eggermont et al. 2016). In patients treated with ipilimumab, cutaneous irAEs have the earliest latency of onset (usually within 3–6 weeks after initiation of cancer therapy) (Eggermont et al. 2016). Thus, cutaneous irAEs have the potential to interrupt cancer therapy most prematurely.

The most common cutaneous irAE associated with ipilimumab, affecting 14–26% of patients, is a morbilliform eruption similar to that seen from antibiotic use, which typically manifests on

the trunk and extremities (sparing the head, palms, and soles) (Sibaud et al. 2016; Minkis et al. 2013; Jaber et al. 2006; Zimmer et al. 2012). The morbilliform rash is commonly associated with pruritus, and occasionally with peripheral eosinophilia (Minkis et al. 2013; Jaber et al. 2006; Zimmer et al. 2012). Of note, vitiligo-like depigmentation, which has been linked to improved prognosis during treatment of melanoma patients with interferon, has also been observed in patients treated with ipilimumab (Babai et al. 2020; Gogas et al. 2006; Collins et al. 2017). Other less common cutaneous irAEs linked to ipilimumab include pruritus, toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), and prurigo nodularis (Collins et al. 2017; Voskens et al. 2013).

2.2 Anti-PD-1 Therapy: Nivolumab, Pembrolizumab, and Cemiplimab

Nivolumab, pembrolizumab, and cemiplimab are currently the three United States Food and Drug Administration (FDA)-approved anti-PD-1 ICIs. They are generally thought to induce less severe toxicities compared to ipilimumab (Hwang et al. 2016; Collins et al. 2017). The most common cutaneous irAEs associated with single-agent anti-PD-1 therapy are pruritus (11–18% of patients on anti-PD-1 therapy), morbilliform exanthem (15% of patients treated with single-agent anti-PD-1 therapy), vitiligo-like depigmentation, and lichenoid reaction (20% of patients on anti-PD-1 therapy) (Tattersall and Leventhal 2020). Interestingly, a recent study of 82 patients receiving single-agent anti-PD-1 therapy found that of the 40 patients who developed cutaneous irAE, 11 developed a combination of lichenoid reaction, eczema, and vitiligo (Hwang et al. 2016). They concluded that there was a statistically significant association among the presence of these three conditions (Hwang et al. 2016). Unlike with anti-CTLA-4 therapy, studies of the safety profile of anti-PD-1 therapy have not suggested a dose-dependent effect on cutaneous AE thus far (Shulgin et al. 2020; Sanlorenzo et al. 2015). Also in contrast with anti-CTLA-4 therapy, the cutaneous irAEs linked to anti-PD-1 therapy have a more variable time of onset, but generally occur within 10 months of starting therapy (Hwang et al. 2016).

2.3 Anti-PD-L1 Therapy: Atezolizumab, Avelumab, Durvalumab

Anti-PD-L1 agents approved by the FDA include atezolizumab, avelumab, and durvalumab. Their overall safety profile (including cutaneous reactions) is generally thought to be similar to that of anti-PD-1 agents, but it has been suggested that anti-PD-L1 agents may theoretically be more safe considering that PD-L2 signaling is preserved (Collins et al. 2017; Shi et al. 2016; Khoja et al. 2017). In fact, atezolizumab had the best overall safety profile in a systematic review and meta-analysis of phase II and III trials of ICIs (Xu et al. 2018). Overall safety profile was characterized by incidence of grade 1–5 adverse events and grade 3 or 4 adverse events, for which atezolizumab showed a pooled incidence of 66.4% and 15.1% respectively, in an analysis of 1210 patients who received the drug (Xu et al. 2018).

In terms of skin toxicity, atezolizumab showed an odds ratio of 1.21 for pruritus and 1.13 for rash when compared to nivolumab as a control (Xu et al. 2018). Only 1.3% of the 310 patients enrolled in a phase II trial of atezolizumab for locally advanced or metastatic urothelial carcinoma were observed to have grade III rash (Ning et al. 2017; Balar et al. 2017). Another study of 70 patients receiving atezolizumab for renal cell cancer showed the most common irAE to be a grade I rash affecting 20% of patients (McDermott et al. 2016). Durvalumab and avelumab, which were more recently approved by the FDA in 2018 and 2020 respectively, have also shown promising cutaneous AE profiles similar to that of atezolizumab (Kelly et al. 2018; Powles et al. 2017; Patel et al. 2018).

2.4 Combination CTLA-4-PD-1 Inhibition Therapy

The first FDA-approved combination immunotherapy regimen was ipilimumab and nivolumab for treatment of advanced melanoma in 2015; since then, this combination has been approved for several other cancers such as metastatic colorectal cancer, unresectable mesothelioma, and metastatic NSCLC (The ASCO post n.d.). Combination CTLA-4/PD-l inhibition has been shown to improve overall survival in patients with advanced melanoma, with a phase III trial reporting a 58% 3-year survival rate for patients in the combined immunotherapy group compared to 52% in the nivolumab and 34% in the ipilimumab group (Wolchok et al. 2017). However, the rate of grade III-IV adverse events was increased overall in the combination therapy group, with 59% of patients experiencing such effects (Wolchok et al. 2017). Similar to single-agent ICI therapy, the most common toxicities associated with combination therapy were cutaneous (affecting 62% of patients), including pruritus (35%), vitiligo (9%), and maculopapular rash (12%) (Wolchok et al. 2017).

3 Clinical Features and Histopathology of Cutaneous irAE

ICIs are associated with a diverse range of cutaneous irAE, but most commonly with pruritus, morbilliform rash, vitiligo-like depigmentation, and lichenoid reactions. With the increasing use of ICIs in the past decade, less common cutaneous adverse events such as immunobullous eruptions and SCARs have also been observed. Finally, rare instances of Sweet's syndrome, granulomatous reactions, and other autoimmune disorders (e.g., lupus, dermatomyositis) have been demonstrated in association with ICIs. In this section, we provide a discussion of the clinical presentation, histopathology, grading criteria, and recommended management of the predominant cutaneous irAE.

3.1 Common Cutaneous AE

Pruritus

Pruritus with or without associated rash is one of the most common findings in patients treated with ICIs. Generally, pruritus independent of rash may appear at varying times after initiation of therapy. For example, one study of cutaneous irAE in patients on pembrolizumab found a median time of three treatment cycles prior to onset, with a range of 1–17 cycles prior to onset (Sanlorenzo et al. 2015). The most common clinical presentations of independent pruritus in patients treated with ICIs are prurigo nodularis and prurigo simplex with discrete excoriations.

Recommendations for management of pruritus depend on the grade. For mild independent pruritus, gentle skin care and moisturizer are recommended, with topical camphor/menthol for symptomatic relief (Malviya et al. 2020). Antihistamines taken when pruritus is most severe (often at night) may also provide symptomatic relief (Wu and Lacouture 2018). Potent/Ultrapotent topical corticosteroids such as clobetasol or betamethasone are advised for grade I or II pruritus (Puzanov et al. 2017). Alternative agents for rash of this severity include gabapentin or pregabalin and ultraviolet B-narrow band (UVB NB) therapy (Wu and Lacouture 2018). Grade III pruritus is rare and may necessitate interrupting or discontinuing ICI therapy. Patients should be referred to dermatology if possible when making this decision, as many patients may be able to continue with ICI therapy on a combination of antipruritic medications (Malviya et al. 2020). Patients with severe pruritus are usually treated with systemic corticosteroids; naloxone or naltrexone and the neurokinin-1 receptor antagonist aprepitant may also provide benefit (Tattersall and Leventhal 2020; Malviya et al. 2020; Puzanov et al. 2017). Finally, cases of recalcitrant pruritus should be worked up for potentially more severe causes (e.g., bullous pemphigoid), with basic laboratory evaluation (complete blood count (CBC), electrolytes, liver and kidney function) as well as consideration for

skin biopsy and direct immunofluorescence (to rule out prebullous stages of bullous pemphigoid) (Malviya et al. 2020).

3.2 Morbilliform Rash

Morbilliform eruption is a common cutaneous adverse event that may occur from numerous types of ICIs, but is most common with anti-CTLA-4 therapy or combination anti-CTLA-4/PD-1 therapy (Sibaud et al. 2016; Minkis et al. 2013; Jaber et al. 2006; Zimmer et al. 2012). Interestingly, the development of morbilliform rash has been demonstrated to have a statistically significant association with improved overall survival in patients treated with nivolumab and combination ipilimumab-nivolumab (Freeman-Keller et al. 2016; Quach et al. 2019). Patients classically present within weeks of starting immunotherapy with blanching, coalescent erythematous macules and papules on the trunk and extremities, often accompanied by pruritus (Fig. 1). The face and palmoplantar surfaces are usually spared. Of note, morbilliform rash associated with ipilimumab may involve peripheral eosinophilia (Malviya et al. 2020).

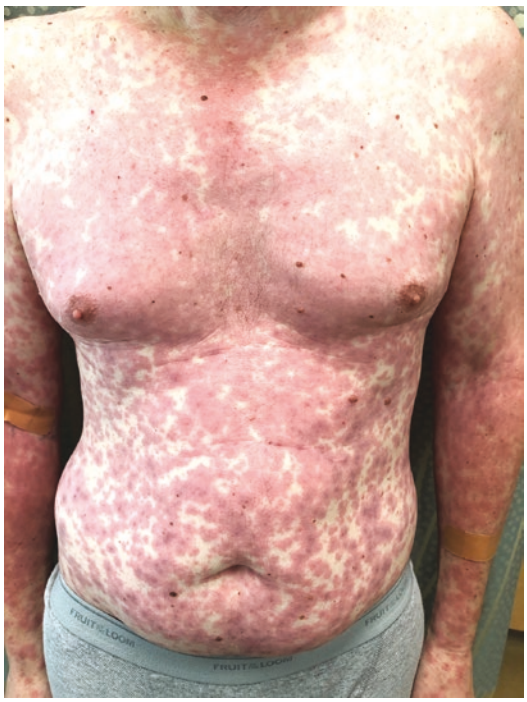

Fig. 1 Morbilliform exanthem to combination ipilimumab and nivolumab in a patient with metastatic melanoma

The differential diagnosis should include morbilliform eruption to other medications, viral exanthem (though typically less pruritic and often associated with other symptoms like cough or conjunctivitis), or acute graft vs. host disease (GVHD) in the correct clinical setting (Malviya et al. 2020). Additionally, patients should be monitored for signs of progression to more severe reactions like DRESS.

Grading of the ICI-associated morbilliform rash depends on % BSA affected and the impact on quality of life. Grade 1 rashes (<10% BSA) and grade 2 rashes (10–30% BSA, with or without impact on instrumental activities of daily living) can be managed with topical corticosteroids, liberal moisturizer use, and oral antihistamines (Common Terminology Criteria for Adverse Events (CTCAE) 2017). Grade 3 reactions involve >30% BSA involvement and limitations of self-care activities of daily living (ADLs), and are generally treated with systemic corticosteroids and treatment interruption (Common Terminology Criteria for Adverse Events (CTCAE) 2017). Most patients will be able to resume ICI therapy once the rash returns to grade 1 (Puzanov et al. 2017).

3.3 Lichenoid Reaction and Other Papulosquamous Disorders

Lichenoid eruptions are well-characterized and common mucocutaneous reactions in patients on PD-1 or PD-L1 agents, occurring in up to 15–25% of patients on these therapies (Hwang et al. 2016; Shi et al. 2016; Coleman et al. 2019; Geisler et al. 2020; Curry et al. 2017; Phillips et al. 2019; Kaunitz et al. 2017). The clinical presentation includes multiple erythematous, violaceous papules and plaques favoring the torso and extremities (Fig. 2), but hypertrophic variants, palmoplantar involvement, and mucosal lesions may also occur. In addition, uncommon presentations like inverse lichen planus or lichen planus

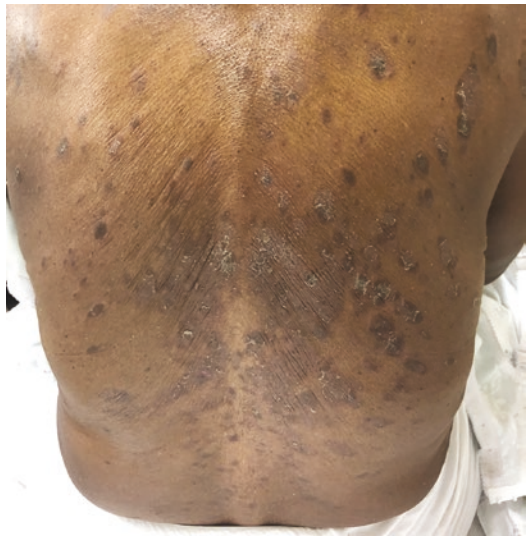

Fig. 2 Lichenoid dermatitis in a woman with lung cancer on pembrolizumab

pemphigoides may be seen (Malviya et al. 2020; Geisler et al. 2020). The mean time of onset for a lichenoid reaction is 6–12 weeks after initiation of therapy, but time of onset can vary widely from days after initiation to a year into therapy (Malviya et al. 2020; Geisler et al. 2020; Tetzlaff et al. 2017). Some cases of lichenoid reactions may even persist after discontinuation of immunotherapy (Tetzlaff et al. 2017).

Histopathological examination has special implications for a supposed lichenoid drug reaction in response to immunotherapy. Similar to idiopathic lichen planus, lichenoid drug reaction shows superficial band-like lymphocytic infiltrate with vacuolar degeneration and keratinocyte necrosis at the basal layer of the epidermis. Variable degrees of epidermal spongiosis with eosinophils may be seen. Immunotherapy-induced lichenoid reaction has also been associated with increased CD163+ histiocytic infiltrates and increased epidermal necrosis, with no changes in expression of CD3, CD4, CD8, CD20, PD-1, CD25, and PD-L1 (Shi et al. 2016; Schaberg et al. 2016). This difference is particularly interesting in the context of evidence suggesting that lichenoid reaction during or after immunotherapy may have positive prognostic implications (Min Lee et al. 2018). A study of 114 patients who had received pembrolizumab, nivolumab, or atezolizumab showed that the 20 patients who developed lichenoid dermatitis had better progression-free survival and overall survival time compared with the 94 patients who did not develop lichenoid dermatitis (Min Lee et al. 2018). More research is necessary to determine the molecular mechanism for this phenomenon.

Treatment of lichenoid reaction most commonly involves high-potency topical corticosteroids twice a day, without interruption of immunotherapy, for grade 1 or 2 reaction (Brahmer et al. 2018; Coleman et al. 2019). Patients with recalcitrant lichenoid reaction after a trial of topical corticosteroids may be treated with systemic corticosteroids, narrowband ultraviolet phototherapy, or acitretin (Malviya et al. 2020; Geisler et al. 2020). Interruption of immunotherapy is only advised if the reaction is grade 3 or higher (Malviya et al. 2020; Geisler et al. 2020).

Other papulosquamous disorders may present similarly to lichenoid dermatitis, including psoriasiform and eczematous reactions. Regarding psoriasiform rashes, existing disease which flares is more common than new-onset psoriasis. For example, a case series of five patients who developed psoriasis during treatment with PD-1 or PD-L1 agents showed that four of the patients had either personal or family history of psoriasis (Voudouri et al. 2017). The clinical presentation of psoriasis in these patients was variable, ranging from guttate and/or plaque psoriasis to psoriatic arthritis (Voudouri et al. 2017). Furthermore, a multicenter study of adverse effects from ICIs showed that of 31 patients with pre-existing history of psoriasis, 21 experienced a flare while being treated with an ICI (Tison et al. 2019). ICI-induced psoriasis may be treated similarly to idiopathic psoriasis, starting with topical corticosteroids and considering UVB NB therapy, acitretin, apremilast, and other systemic biologic agents in recalcitrant cases after discussion with oncology.

Eczematous reactions, which may have overlapping features with lichenoid reactions, may also occur from immunotherapy. Clinically, these patients present with pruritus and pink, scaly

papules, patches, or plaques, resembling atopic or nummular dermatitis (Kaunitz et al. 2017). Histopathologically, spongiotic dermatitis with eosinophils is seen (Sibaud 2018).

In addition to these dermatoses, atypical squamous proliferations may develop uncommonly and can be associated with concurrent lichenoid inflammation (Antonov et al. 2019). Eruptive keratoacanthomas and squamous cell carcinomas may occur and can be challenging to distinguish from hypertrophic lichen planus. Conservative management of these atypical squamous proliferations and treatment of concurrent lichenoid dermatitis is recommended.

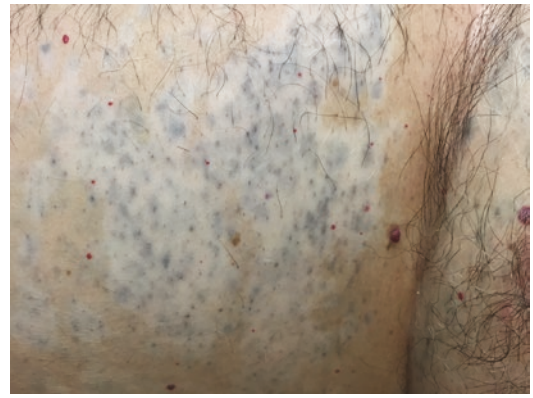

Fig. 3 Vitiligo-like depigmentation surrounding in-transit melanoma metastases during ipilimumab/nivolumab therapy

3.4 Vitiligo-like Depigmentation

Vitiligo-like depigmentation is a common cutaneous irAE that has been associated with improved overall survival in patients with melanoma, but may also occur less often in patients with other malignancies (e.g., acute myeloid leukemia, lung cancer, and renal cell cancer) (Teulings et al. 2015; Lolli et al. 2018; Yin et al. 2017; Yun et al. 2020; Nishino et al. 2018). Unlike the timeline of pruritus or morbilliform rash associated with ICIs, vitiligo-like depigmentation onset is more gradual with lesions forming progressively over months of treatment (Teulings et al. 2015; Hua et al. 2016). Several clinical features help differentiate ICI-associated vitiligo-like depigmentation from primary vitiligo (Larsabal et al. 2017). The lesions for ICI-associated vitiligo are often distributed in a sun-exposed pattern (Fig. 3), unlike primary vitiligo which often appears on acral and periorificial areas (Larsabal et al. 2017). ICI-associated depigmentation has been reported to occur together with poliosis (Wolner et al. 2018).

ICI-associated vitiligo-like depigmentation is thought to be a separate biological disease process from primary vitiligo. Murine experiments have shown that blockade of the PD-1 pathway induces expression of the chemokine CXCL10 by IFN-y, thereby causing CXCR3+ CD8 T cell migration to tumor sites (Peng et al. 2012). Interestingly, a study of blood samples and biopsies from eight patients with vitiligo-like depigmentation from nivolumab or pembrolizumab found prominent CXCR3+ CD8 T cell skin infiltration (Larsabal et al. 2017).

As is the case with primary vitiligo, treatment of vitiligo-like depigmentation can be difficult. Depigmentation may progress after completion of immunotherapy, as demonstrated in a study of patients treated with nivolumab (Freeman-Keller et al. 2016). Vitiligo-like depigmentation in patients treated with ICIs, which is largely asymptomatic without medical complications, can be Grade 1 (<10% BSA affected) or Grade 2 (>10% BSA affected and/or has a psychosocial impact on patient) (Brahmer et al. 2018). Most cases require no treatment; however, patients with grade 1 disease may be managed with topical steroids or topical calcineurin inhibitors. For grade 2, patients may try narrowband UVB phototherapy as well as topical corticosteroids (Miyagawa et al. 2017). Janus kinase (JAK) inhibitors, which have demonstrated efficacy in primary vitiligo, should be avoided until further studies evaluate its impact on immune response in this population (Malviya et al. 2020).

Bullous Eruptions

Bullous eruptions, typically in the form of bullous pemphigoid, may uncommonly occur with ICIs. Between 2015 and 2020, a total of 58 cases of bullous pemphigoid eruptions linked to anti-PD-1 or anti-PD-L1 agents was reported, and one

study noted an incidence rate of ~1% in patients on these therapies (Siegel et al. 2018; Tsiogka et al. 2021). A unique feature of bullous pemphigoid associated with immunotherapy, compared to other cutaneous irAE, is that the time of onset is delayed, with a mean time of 6 months after treatment initiation (Coleman et al. 2019; Siegel et al. 2018). Furthermore, clinical suspicion for bullous pemphigoid must be sustained after initiation of immunotherapy, as the condition typically presents with a nonspecific, nonbullous pruritic prodromal phase prior to the development of classical urticarial papules, plaques, and tense vesicles and bullae (Fig. 4). Mucosal involvement may occur in some cases. Recent research suggests that lesions of idiopathic BP as well as of pemphigus vulgaris show increased expression of PD-1, and thus further investigation may help elucidate the molecular mechanism of immunotherapy-associated BP (Ernst et al. 2021). Hemidesmosomal antigens may also be present in various malignancies.

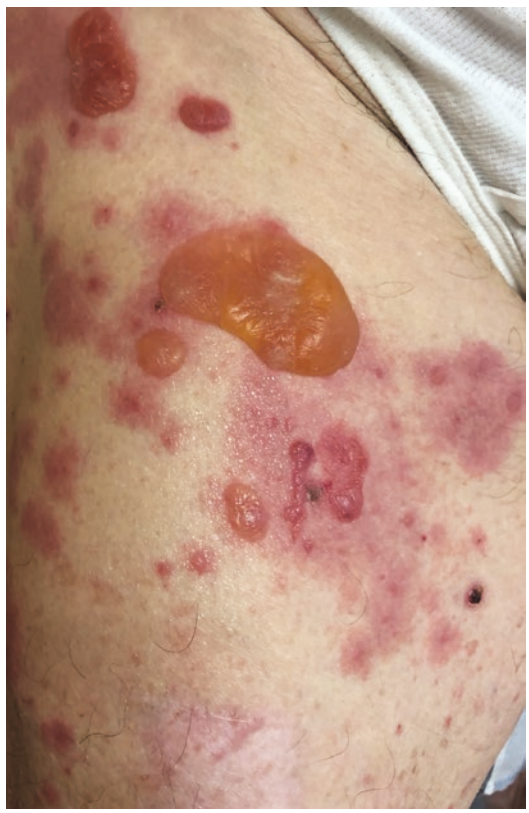

Fig. 4 Bullous pemphigoid in a patient on pembrolizumab for metastatic melanoma

Treatment of immunotherapy-associated BP is similar to that of idiopathic BP. Grade 1 eruptions can be treated with topical corticosteroids without interruption of immunotherapy. Doxycycline with or without niacinamide may be helpful for lower grade cases. Grade 2 reactions may require systemic corticosteroids, as well as holding immunotherapy until rash returns to Grade 1 (Brahmer et al. 2018). Grade 3 or 4 immunotherapy-associated BP should be treated with discontinuation of immunotherapy, intravenous corticosteroids, and close following by dermatology (Brahmer et al. 2018). Rituximab may be used in recalcitrant cases (Geisler et al. 2020). It is important to note that immunotherapy-associated BP may persist even after immunotherapy discontinuation (Heymann 2018; Naidoo et al. 2016). Other potential treatment agents include methotrexate, dapsone, omalizumab, dupilumab, and intravenous immunoglobulin G (IVIG) (Damsky et al. 2016; Czernik 2014).

SCARs

SCARs that have been reported with immunotherapy include DRESS syndrome, acute generalized exanthematous pustulosis (AGEP), and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) (Malviya et al. 2020). Because of the severity of these potentially life-threatening conditions, a diagnosis of a SCAR of any grade mandates interruption, or more likely, discontinuation of immunotherapy (Brahmer et al. 2018). Of note, the use of targeted therapy with BRAF inhibitors after the use of immunotherapy is associated with a particularly high risk for the development of SCARs (Harding et al. 2012). Furthermore, atypical presentations of SCARs including delayed reactions of SJS/TEN-like eruptions may occur, necessitating a high index of suspicion when any "red-flag" signs or symptoms occur (e.g., skin pain, blisters, mucosal involvement, fevers). The time of onset of SCAR after initiation of immunotherapy may vary between 1 and 20 weeks (Chen et al. 2018). The Society for Immunotherapy of Cancer Toxicity Management Working Group recom-

mends: hospitalization and immediate dermatology consult for suspected SJS/TEN or severe mucocutaneous reaction; same-day dermatology consult for blisters covering >1% BSA, mucosal rash, painful rash, any rash >30% BSA, and any grade III cutaneous toxicity; and nonacute dermatology referral for rashes of unclear diagnosis, grade 2 rash, and erythema multiforme (Puzanov et al. 2017).

SJS/TEN has been reported with most ICIs, including ipilimumab, nivolumab, pembrolizumab, atezolizumab, and combination immunotherapy (Coleman et al. 2019; Haratake et al. 2018; Chirasuthat and Chayavichitsilp 2018; Dika et al. 2017; Logan et al. 2020). Patients usually present with painful pink dusky-centered papules and plaques that quickly develop into vesicles and bullae, often with mucosal involvement. Histopathology demonstrates epidermal necrolysis. The grade of SJS/TEN depends on BSA involved, although any SJS/TEN is at least a grade 3 reaction, and grade 4 reactions involve >10% of BSA (Brahmer et al. 2018). Treatment is with discontinuation of immunotherapy, hospitalization, and intravenous systemic corticosteroids. Cyclosporine, IVIG, and TNF-alpha inhibitors have also been used to treat SJS/TEN-like reactions associated with immunotherapy (Woolridge et al. 2018; Zhang et al. 2020).

AGEP has also been reported in patients undergoing immunotherapy, including combination ipilimumab and nivolumab, and pembrolizumab with chemotherapy (Matsubara et al. 2020; Page et al. 2018). Like classic AGEP, these cases presented with an initial erythematous eruption with small nonfollicular pustules concentrated in the axillary and inguinal folds (Matsubara et al. 2020; Page et al. 2018). Histopathology demonstrated subepidermal mixed cellular infiltrate with eosinophils, diffuse spongiosis, and subcorneal pustules (Matsubara et al. 2020; Page et al. 2018). Management of AGEP generally involves discontinuation of the offending agent and systemic corticosteroids (ranging from 0.5 to 2.0 mg/kg/daily of prednisone based on % BSA involvement) (Brahmer et al. 2018).

Finally, DRESS, also known as drug-induced hypersensitivity syndrome (DIHS), has been reported in patients on nivolumab, ipilimumab, and pembrolizumab (Lu et al. 2019; Di Palma-Grisi et al. 2019; Naqash et al. 2019). Patients with DRESS present with systemic symptoms including fever and lymphadenopathy, laboratory abnormalities including eosinophilia, atypical leukocytosis, and abnormal liver function testing, and skin findings of diffuse maculopapular eruption and marked facial edema. Histopathology of DRESS can vary and may show overlap with several different conditions, but typically demonstrates an interface dermatitis with eosinophilia. Management of DRESS requires close monitoring of abnormal laboratory findings (particularly CBC with differential and peripheral smear, basic metabolic panel, liver function tests, thyroid function tests, and baseline echocardiogram), withdrawal of the offending agent, and systemic corticosteroids (again ranging from 0.5 to 2.0 mg/kg/daily of oral prednisone based on severity) with taper over 6–8 weeks (Brahmer et al. 2018). All cases of immunotherapy-associated DRESS were managed successfully with systemic corticosteroids (Lu et al. 2019; Naqash et al. 2019).

3.5 Miscellaneous Reactions

In addition to the above categories of cutaneous irAEs, a variety of other cutaneous reactions have been reported in association with immunotherapy agents. For example, connective tissue disorders including subacute cutaneous lupus erythematosus, eosinophilic fasciitis, and dermatomyositis have all been reported (Kosche et al. 2019, 2020; Blakeway et al. 2019; Chan et al. 2020). In severe presentations impacting quality of life or those resulting in joint immobility (e.g., eosinophilic fasciitis), immunotherapy interruption and treatment with oral prednisone (with or without other steroid-sparing immunosuppressive agents) may be required.

Another group of dermatological adverse effects to ICIs includes granulomatous reactions (Cornejo et al. 2019). A 2019 review of granulo-

matous reactions to ICIs identified 59 reported cases of sarcoidosis-like reactions (Cornejo et al. 2019). Interestingly, most of these patients did not have a history of sarcoidosis or other granulomatous pulmonary disease (93.2%) (Cornejo et al. 2019). Clinical presentation usually involves pulmonary lesions (84.7% of patients), with cutaneous lesions presenting as papules, plaques, and nodules on any area of the body but sometimes within past tattoos or scars (Cornejo et al. 2019). In addition to sarcoidosis-like reactions, granuloma annulare may occur, and presents as pink papules or annular plaques on the extremities or torso. Contrary to sarcoidosis-like reactions, granuloma annulare does not have systemic involvement (Cornejo et al. 2019). Other less common granulomatous reactions such as erythema nodosum-like panniculitis or interstitial granulomatous dermatitis may occur. In general, sarcoidosis responds well to treatment with systemic corticosteroids (Cornejo et al. 2019). Hydroxychloroquine may be used as steroid-sparing therapy (Korsten et al. 2013).

Finally, patients with a pre-existing autoimmune disease may experience flares while on ICIs, as was discussed previously in the psoriasis section. One multicenter study found that of patients with pre-existing rheumatoid arthritis (RA) treated with ICIs, 60% had a flare of RA (Tison et al. 2019). Rates of flare were lower for the other autoimmune diseases examined in this study, including inflammatory bowel disease, lupus, and polymyalgia rheumatica (Tison et al. 2019). One important note is that some flares of pre-existing autoimmune disease may be severe enough to require additional immunomodulating therapy; 54% of patients with pre-existing autoimmune disease who developed an ICI-induced flare in this study required treatment with a form of immunosuppressive agent (including systemic corticosteroids, disease-modifying antirheumatic drug (DMARD), or acitretin) (Tison et al. 2019).

4 Conclusion

The development of ICIs has changed the landscape of cancer therapy for years to come. As these agents modulate the function of the immune system, they induce irAEs in most organ systems, ranging from mild pruritus to severe multisystem organ dysfunction. Although some of these adverse events require new therapeutic solutions, they also allow for a detailed examination of the molecular mechanisms of skin diseases in ways that were not possible before. The association of positive antitumor response with various cutaneous irAEs underscores the importance of promptly diagnosing and managing these untoward reactions, to allow patients to remain on these potentially life-sustaining therapies.

In conclusion, this chapter presented an overview of the clinical presentations, diagnosis, grading, and therapeutic strategies for cutaneous adverse events associated with currently available immunotherapy agents. In particular, we presented the treatment regimens with a focus on whether immunotherapy must be discontinued or withdrawn in each of these scenarios, as this is the question that is often most important for the primary oncologic team. The diversity of effects and severities as outlined here demonstrates the critical role of the oncodermatologist and of integrated oncodermatology clinics (Kwong 2020). There is evidence to suggest that an embedded oncodermatology clinic in cancer hospitals is associated with reduction of unnecessary discontinuation of cancer therapy, as well as of rehospitalizations (Naidoo et al. 2016; Chen et al. 2020). As some studies have suggested, one potential model for the future may be a multidisciplinary team dedicated to irAE at cancer hospitals (Naidoo et al. 2019).

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