Cutaneous Immune-Related Adverse Events

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Dermatologic complications arise as the earliest and most frequently observed adverse events among all immune-related adverse events (irAEs), affecting between 30 and 50% of patients on Immune checkpoint inhibitors (ICIs). The symptoms may significantly impair patients' quality of life, and even lead to a pause of immunotherapy treatment. Fortunately, the majority of cirAEs seem to be mild and manageable, but there are still a few serious events (grade III or IV) being observed. Maculopapular rash, pruritus, lichenoid eruptions, and vitiligo are the most widely reported cutaneous adverse events. Severe cutaneous adverse reactions (SCARs), consisting of Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug rash with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP), are rare but potentially life-threatening. Other less-frequent manifestations include ICI-induced dermatomyositis, Sweet syndrome, interstitial granulomatous dermatitis, pityriasis rubra pilaris-like erythroderma, and lupus-like cutaneous reaction.

Keywords: immune checkpoint inhibitor ; immune-related adverse event ; Pruritus

1. Introduction

In recent decades, immune checkpoints inhibitors (ICIs) have been demonstrated to dramatically improve the overall survival for a broad spectrum of advanced malignancies [1][2][3]. These agents are monoclonal antibodies that target the immune checkpoint molecules, including cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death-ligand 1 (PD-L1). To date, seven ICIs have been approved by the U.S. Food and Drug Administration (FDA). Since March 2011, when the first immune checkpoint inhibitor, ipilimumab (an anti-CTLA-4 agent), was approved for the treatment of advanced (either metastatic or unresectable) melanoma [4], additional therapies that target the PD-1/PD-L1 axis have been subsequently approved, showing promising therapeutic outcomes for various solid tumors and hematologic malignancies [5]. Nivolumab, pembrolizumab, and cemiplimab are anti-PD-1 agents, whereas atezolizumab, durvalumab, and avelumab are anti-PD-L1 agents. Other novel therapies targeting the alternative inhibitory pathways are currently under investigation, including lymphocyte-activation gene 3 (LAG-3), T-cell immunoglobulin and ITIM domain (TIGIT), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), V-domain immunoglobulin suppressor of T-cell activation (VISTA), B7 homolog 3 protein (B7-H3), inducible T cell costimulatory (ICOS), and B and T lymphocyte attenuator (BTLA) [6]. While ICIs promote the reinvigoration of the anti-tumor T-cell response, the enhanced immunologic activation may result in a variety of autoimmune-like or inflammatory side effects, termed immune-related adverse events (irAEs), which can involve almost any organ system.

2. Maculopapular Eruption (Eczema-like Dermatitis)

The development of maculopapular rash is observed in approximately 49% to 68% of patients receiving anti-CTLA-4 agents, compared with 20% of patients receiving anti-PD1/PDL-1 therapy, and the eruption usually occurs within the first 3 to 4 weeks after the initiation of ICI therapy [7][8][9]. The clinical presentation is relatively nonspecific and characterized by pruritic erythematous macules and papules coalescing into thin plaques, with the trunk and extremities mainly affected. The lesions usually spare the face, palms, and soles. In some cases, it appears as an exacerbation of a pre-existing skin condition, such as eczema or rosacea [7]. Histologically, superficial, perivascular lymphocytes and eosinophils infiltrate into the upper dermis, and mild epidermal spongiosis can be present [7].

It is important to be aware that on rare occasions, a maculopapular eruption may be the initial presentation of bullous pemphigoid (BP), SJS/TEN, or DRESS, which require a close follow-up [10]. The patient should be carefully assessed for the appearance of blister formation, mucosal involvement, skin pain, fever, lymphadenopathy, or erythroderma [10]. Laboratory investigation and skin biopsy should be considered if there is an evolution of lesions or the development of any concerning symptom or sign.

Treatments mainly include symptomatic management, and pruritus can be managed with emollients, topical steroids, and oral antihistamines. Since the symptoms are usually mild and self-limiting with resolution within 2 to 3 months, interruption or discontinuation of ICIs is not always necessary [7]. However, severe cases (grade III or above) may require systemic steroids and withholding ICI therapy.

3. Pruritus

Pruritus is among the most prevalent cutaneous adverse reactions to ICI therapy, with its all-grade incidence ranging from 13 to 20% with nivolumab and pembrolizumab, respectively [11][12][13]. A higher incidence was reported in patients treated with anti-CTLA-4 agents (25–36%), and the highest incidence was reported in patients treated with combination therapy (33–47%) [12]. Although it is typically concomitant with maculopapular rash, it can precede it or develop independently on normal-appearing skin. Symptoms are usually mild-to-moderate in severity (grade I or II), but high-grade pruritus occurs in less than 1% of patients and can severely impair the quality of life [2][13][14].

The treatment depends on the severity of the pruritus. Mild cases may respond to topical emollients or first-generation antihistamines, while topical or systemic glucocorticoids or topical calcineurin inhibitors should be considered in more severe cases [3][15]. The efficacy of aprepitant has been described in a Japanese patient with severe refractory pruritus during nivolumab treatment [16]. Additional medications, including doxepin, gabapentin, pregabalin, and naloxone, have been documented [3][15][17].

4. Lichenoid Dermatitis

Lichenoid drug eruptions are reported to be relatively common among cirAEs and occur more frequently in patients receiving anti-PD-1/PD-L1 blockades than in patients receiving anti-CTLA-4 blockades [10][14][18][19][20]. Lichenoid dermatitis affects nearly one-fifth of patients treated with anti-PD-1 agents, and the time to onset of lichenoid dermatologic toxicity ranges from 3 days to 13 months from the initiation of anti-PD-1 therapy [21][22]. The clinical presentation is characterized by erythematous-to-violaceous scaly plaques in a variety of distributions, with either discrete papules or plaques in a localized area or a more generalized distribution with a predilection for the trunk and extremities[21][23]. While cutaneous lichenoid reactions have emerged as common side effects, involvement of the oral mucous membrane is rarely described [18][24][25][26]. In a case series, oral lichenoid eruptions were documented in 10 cases treated with pembrolizumab, nivolumab, or atezolizumab, whereas another report presented two cases developing ulcerative oral lichenoid reactions after nivolumab treatment [25][26]. Other clinical variants, including inverse presentation, bullous lichen planus pemphigoid, and erosive and hypertrophic variants, have been documented [22][27][28][29]. The pathologic features are similar to lichen planus, with the presence of hyperkeratosis, hypergranulosis, a saw-tooth rete ridge pattern, lichenoid and interface lymphocytic infiltrates, and basal vacuolar changes [18][19]. However, unlike typical lichen planus, parakeratosis, epidermal spongiosis and necrosis, and eosinophils may be present [3][18][19][22].

The treatment initially consists of high-potency topical steroids, and in most of the cases, interruption of ICI therapy is not necessary, while systemic corticosteroids and cessation of ICI therapy may be required in cases of high-grade toxicity. Alternative therapies for severe cases include oral acitretin and phototherapy, which were both reported to be effective [10][30][31]. It is also important to note that erosive oral or genital lichenoid reactions should be treated aggressively with systemic retinoids or oral prednisolone due to their scarring potential [10].

5. Psoriasiform Dermatitis

Psoriasiform dermatitis can be either de novo or a flare-up of pre-existing psoriasis in patients treated with anti-PD-1/PD-L1, and approximately 3% of patients in Japan treated with nivolumab developed psoriasis-like reactions [32][33][34][35][36]. In a study of 21 patients, the average duration between anti-PD1 initiation and psoriasis flare-up was about 50 days, which is a shorter duration than that of de novo psoriasiform eruptions (91 days) [33]. The typical presentation is plaque psoriasis, although guttate, pustular, inverse, and palmoplantar variants have been less frequently described [33][34][35]. The skin lesions are characterized by sharply bordered, erythematous scaly plaques, mostly at localized extensor sites. The histopathological features are similar to typical psoriasis vulgaris, with the presence of hyperkeratosis, hypogranulosis, acanthosis with elongated rete ridges, and a perivascular lymphocytic infiltration [32][37].

The immune mechanisms of ICI-mediated psoriasiform eruptions remain uncertain. In murine models, PD-1 blockade, either by a genetic deficiency or monoclonal antibody treatment, was found to enhance the production of interleukin (IL)-17A and IL-22 by activated γδ-low (GDL)-expressing T cells, promote neutrophil infiltration into the epidermis, and thereby induce psoriasiform skin inflammation [36][38][39][40].

Management should be carried out by applying a multidisciplinary approach. The initial treatment includes topical corticosteroids, topical vitamin D analogs, or topical retinoids. Phototherapy with narrowband ultraviolet B (NB-UVB) light may be helpful when used in conjunction [38]. Systemic options may be considered when topical treatment is ineffective. In a multicentric study of 115 European patients, acitretin, apremilast, and methotrexate were found to be efficacious and safe options for ICI-mediated psoriasis [41]. Biologic agents, particularly tumor necrosis factor (TNF)-α inhibitors, are contraindicated since they may promote the occurrence and progression of cancers [3][10][42][43]. IL-12/23 inhibitors, such as ustekinumab, act upstream of the immune signaling and may carry a higher risk of infection due to immunosuppression [10][44]. However, biologic agents targeting IL-23 or IL-17 may be considered in severe or recalcitrant cases given their selective inhibition of the T helper 17 (Th17) axis in psoriasis, minimal immunosuppressive effect, and rapid onset of action [10][45]. It is also important to note that, similar to spontaneous psoriasis, systemic steroids should be carefully prescribed, since they may carry the risk of a severe rebound of psoriasis upon steroid withdrawal [3][10][42].

6. Vitiligo-like Depigmentation (VLD)

Vitiligo-like depigmentation (VLD) appears most frequently in patients treated for melanoma, although other cancers have rarely been reported [46][47][48][49]. In a retrospective study in Italy, VLD was induced by anti-CTLA-4 inhibitors, anti-PD-1 inhibitors, and the combination therapy in 32%, 56%, and 12% of patients, respectively, with a median onset time of around 26 weeks [50]. Larsabal M. et al. [51] reported that ICI-induced vitiligo is distinct from idiopathic vitiligo in that it consists of multiple flecked lesions coalescing into patches on the photoexposed areas, and it is not associated with the Koebner phenomenon. The histologic features of VLD include an inflammatory infiltrate in the dermis with a predominance of T cells and a lack of melanocytes [3][46]. Immunotherapy-induced vitiligo potentially corresponds to a cross-reaction against melanocyte differentiation antigens (MART-1, gp100, and tyrosinase-related proteins 1 and 2) shared by healthy and malignant melanocytes, and cytotoxic T lymphocytes are thought to be the main effector cells that recognize these shared antigens, which were found to infiltrate both tumor and vitiligo tissues [46][52].

There is no definite treatment for ICI-induced vitiligo, and most of the cases with VLD do not resolve after discontinuation of ICIs [3]. Photoprotection with sunscreen and clothing should be encouraged to avoid sunburns, and camouflaging can be performed to limit the psychosocial impact [3][46]. Moreover, the occurrence of VLD in patients treated for melanoma may represent a positive prognostic factor, with a favorable response and prolonged overall survival [46][53][54].

7. Bullous Pemphigoid (BP)

Compared with other dermatoses, immunobullous disorders are relatively rarely reported in the literature, with most associated with anti-PD-1/PD-L1 blockades [29][55][56][57][58]. In a retrospective analysis including 853 patients receiving anti-PD-1/PD-L1, the incidence of bullous skin toxicity was approximately 1%, with bullous pemphigoid (BP) appearing to be the most common presentation, followed by bullous lichenoid dermatitis and linear IgA bullous dermatosis [55]. The clinical manifestation of BP is usually characterized by pruritic, tense bullae overlying the urticarial plaques mainly on the trunk and extremities; however, urticarial-like or eczematous rash may be the prodromal presentation or the “non-bullous” variants [59][60]. Involvement of the mucosal membrane is less frequent [24][61].

In addition to serologic investigations, the standard diagnostic work-up for bullous diseases comprises a dermatologic referral and biopsy specimens for initially establishing whether the site of splitting is intraepidermal or subepidermal [57]. Further assessments including direct immunofluorescence (DIF) and indirect immunofluorescence (IIF) are also necessary [57]. The histopathologic features are similar to those of classic BP, which include a subepidermal cleft with numerous eosinophils and linear deposition of complement component 3 (C3) and immunoglobulin G (IgG) along the basement membrane zone on DIF [57].

A number of theories have been developed to explain the immunologic mechanism of ICI-related BP. It is evident that BP is mediated by autoantibodies against BP180, the hemidesmosomal proteins that are expressed both on certain tumor cells (such as melanoma and non-small cell lung carcinoma) and the basement membrane of the skin [57][62]. In anti-PD-1/PD-L1-induced BP, it is possible that the reinvigoration of the T-cell response targets BP180 on cancer cells, as well as the basement membrane of the skin, thereby inducing BP [57].

As for the treatment strategy for ICI-induced BP, a mild presentation (grade I, < 10% body surface area (BSA)) may respond to high-potency topical steroids, whereas patients with more extensive (grade II and above, >10% BSA) eruptions or with mucosal involvement may require systemic corticosteroids as well as the interruption of ICI therapy, either temporary or permanent [55]. Other steroid-sparing agents include methotrexate, doxycycline with or without nicotinamide, and omalizumab, which are reported to be effective therapies [55][61][63][64]. Interestingly, in contrast to classic

BP, which typically resolves upon discontinuation of the offending agent, ICI-induced BP may persist for several months after the cessation of the causative agent owing to prolonged immune activation [13][23][57]. The administration of rituximab, an anti-CD20 monoclonal antibody, may be considered in severe or recalcitrant cases, and successful use has been demonstrated in the literature [65][66][67][68].

8. Stevens–Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)

Severe cutaneous adverse reactions (SCARs), consisting of Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), are rare dermatologic toxicities that can be potentially life-threatening and, hence, should be managed aggressively [69][70][71][72]. The occurrence of SCARs is related to both anti-CTLA-4 and anti-PD1/PD-L1 blockades, with the latency periods varying from 5 to 91 days [72][73]. In SJS/TEN, the constitutive symptoms, including fever, anorexia, and malaise, are followed by skin eruptions of flaccid blister formation with a positive Nikolsky's sign and rapidly progressive and extensive epidermal necrosis and desquamation. Mucosal involvement of the oral tract, gastrointestinal tract, respiratory tract, and genitalia may occur [74][75]. It is important to note that nonspecific morbilliform eruptions may precede the severe drug reactions; therefore, the careful monitoring of patients with morbilliform rash is necessary to assess a possible evolution [10][70]. Biopsy specimens typically reveal full-thickness epidermal necrolysis with extensive keratinocyte necrosis, subepidermal bullae, and varying degrees of inflammation containing lymphocytes, eosinophils, and neutrophils in the superficial dermis.

In these severe cases, permanent ICI cessation is necessary. The mainstay of management requires intense supportive care ensuring the homeostasis of fluid and electrolytes, as well as minimizing the infectious risks with wound care and topical or systemic antibiotics treatment. High-dose systemic corticosteroids (methylprednisolone at 1 to 2 mg/kg/day) and intravenous immunoglobulin (IVIG) should be administered [69][76]. Additional medications, such as TNF-α inhibitors (infliximab or etanercept), mycophenolate mofetil, or cyclosporin, may be considered [69][76][77]. Plasmapheresis can be used in some cases [10][78].

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