Adverse Cutaneous Outbreaks by programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) immune checkpoint inhibitors: A Review.

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Abstract

The therapeutic use of humanized monoclonal anti-programmed cell death 1 (PD-1) (pembrolizumab, and nivolumab) and anti-programmed cell death ligand1 (PD-L1) (atezolizumab, avelumab, durvalumab) as potent anticancer therapies is rapidly increasing. The mechanism of signaling of anti-PD-1/PD-L1 involves triggering cytotoxic CD4+/CD8+T cell activation, which induces specific immunologic adverse events. The anti-PD-1/PD-L1 drugs can cause numerous cases of cutaneous reactions, hence these toxicities are characterized as the most frequent immune-related adverse events (irAEs). The majority of cutaneous irAEs triggered by immune checkpoint inhibitors range from nonspecific eruptions to detectible skin manifestations, which may be self-limiting and present an acceptable skin toxicity profile, while some may produce mild to life-threatening complications. This review aims to illuminate the associated cutaneous adverse events related to the drugs used in oncology along with the relevant mechanism(s). With this review article, an overview of the various adverse cutaneous manifestations of anti-PD-1 (pembrolizumab, and nivolumab) and anti-PD-L1 (atezolizumab, avelumab, durvalumab) therapy, as well as suggestions, have been provided, so that their recognition at early stages could help in better management and would prevent treatment discontinuation.

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Running head: Cutaneous Adverse Effects caused by PD-1/PD-L1 immune checkpoint inhibitors.

Key Words- Cutaneous eruptions; immunotherapy; immune-related adverse events (irAEs); anti PD-1; pembrolizumab; nivolumab; anti-PD-L1; atezolizumab; avelumab; durvalumab.

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Figure 1: Various adverse cutaneous reactions by programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) immune checkpoint inhibitors. MHC- major histocompatibility complex; TCR- T-cell receptor.

Figure 1: Classification of cutaneous irAEs into six main categories.

Figure 3: PD-1/PD-L1 induced cutaneous adverse effects with each percentage indicated.

Figure 4: Pathogenesis of PD-1/PD-L1 induces vitiligo.

Abstract

The therapeutic use of humanized monoclonal anti-programmed cell death 1 (PD-1) (pembrolizumab, and nivolumab) and anti-programmed cell death ligand1 (PD-L1) (atezolizumab, avelumab, durvalumab) as potent anticancer therapies is rapidly increasing. The mechanism of signaling of anti-PD-1/PD-L1 involves triggering cytotoxic CD4+/CD8+T cell activation, which induces specific immunologic adverse events. The anti-PD-1/PD-L1 drugs can cause numerous cases of cutaneous reactions, hence these toxicities are characterized as the most frequent immune-related adverse events (irAEs). The majority of cutaneous irAEs triggered by immune checkpoint inhibitors range from nonspecific eruptions to detectible skin manifestations, which may be self-limiting and present an acceptable skin toxicity profile, while some may produce mild to life-threatening complications. This review aims to illuminate the associated cutaneous adverse events related to the drugs used in oncology along with the relevant mechanism(s). With this review article, an overview of the various adverse cutaneous manifestations of anti-PD-1 (pembrolizumab, and nivolumab) and anti-PD-L1 (atezolizumab, avelumab, durvalumab) therapy, as well as suggestions, have been provided, so that their recognition at early stages could help in better management and would prevent treatment discontinuation.

Article highlights

- Cutaneous adverse effects are the most prevalent immune-related adverse events induced by anti-PD-1/PD-L1 immune-checkpoint antibodies.
- Cutaneous toxicities mainly manifest in the form of maculopapular rash and pruritus.
- More specific cutaneous complications can also occur, including vitiligo, worsened psoriasis, lichenoid dermatitis, mucosal involvement (e.g.oral lichenoid reaction), dermatomyositis, lupus erythematosus.
- Cutaneous manifestations can be life-threatening including stevens-johnson syndrome/toxic epidermal necrolysis (TEN).
- Dermatologic toxicities are usually mild, readily manageable, and rarely result in significant morbidity.
- Adequate management of the cutaneous adverse event and recognition in early stages could lead to the prevention of worsening of the lesions and limit treatment disruption.

Introduction

The evolution of immune checkpoint inhibitors as an effective anticancer treatment constitutes one of the greatest and successful approaches in the world of anticancer therapy [1]. They are widely used in the treatment of various cancers such as metastatic melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCCs), and urothelial cancer (UC)They are also employed in other types of malignancy such as head and neck squamous cell carcinomas (HNSCC), breast cancer, colorectal cancer, follicular lymphoma, ovarian cancer, pancreatic cancer, gastric cancer, sarcoma, colorectal cancer, metastatic merkel cell carcinoma (MCC), prostate cancer, and hematological malignancies[1]. Immune checkpoint inhibitors are of two

types: drugs that target PD-1/PD-L1 proteins and drugs which target cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) protein. Drugs that act against PD-1 protein are known as PD-1 inhibitors; these are pembrolizumab, nivolumab, cemiplimab while drugs that act against PD-L1 protein are atezolizumab, avelumab, and durvalumab[2]. PD-1/PD-L1 inhibitors exhibit various immune-related adverse events, particularly due to the misguided stimulation of the immune system. Various organ-specific adverse effects related to anti-PD-1/PD-L1 therapy include gastrointestinal, endocrine, cardio, ocular, renal, and skin as well as adverse events attributed to systemic inflammation [3]. Since their approval by the US Food and Drug and Administration (2014) and European Medicines Agency (2015), several cases of cutaneous adverse reactions were reported. The most frequent immune-related adverse events (irAEs) are related to cutaneous (dermatological) toxicities (Figure1). The characteristic of these irAEs ranges from non-specific eruptions to recognizable skin appearances, which may present acceptable to mild to life-threatening skin toxicities [4]. Most of the cutaneous adverse reactions occurring with PD-1/PD-L1 inhibitors are usually mild to moderate in nature and readily manageable with proper supportive care, and usually resolved following their withdrawal from the drug regime. Thus, it is essential to establish a strong surveillance system to monitor the proper safety and toxicity profile of the potential PD-1/PD-L1 inhibitors. Early recognition is the key in the management and prevention of cutaneous irAEs, which may limit treatment interruption and can improve quality of life. The objective of this article is to evaluate the rate of cutaneous adverse reactions consistent with anti-PD-1 and anti-PD-L1 drugs and their associated control management.

Methodology

Literature search –Literature was searched from 2018 up to June 2021 from several databases like PubMed, Google Scholar for studies on adverse events (AEs) induced by the anti-PD-1 and anti-PD-L1 drugs. The drugs were searched only for cutaneous adverse effects. The following keywords were used (alone or in combination). "adverse drug reaction", "adverse effects", "cutaneous adverse effects" "PD-1 inhibitors", "pembrolizumab", "nivolumab"."PD-L1 inhibitors", "avelumab", "atezolizumab", "durvalumab", "lichenoid dermatitis", "granulomatous skin reactions", "vitiligo", "pruritus", "psoriasiform rashes", "bullous pemphigoid", "dermatomyositis", "lupus erythematosus", "stevens-johnson syndrome/ toxic epidermal necrolysis (TEN)", "oral lichenoid dermatitis". The search mainly included research articles, retrospective studies, case reports, and clinicopathological findings. The authors reviewed the abstracts and titles of studies that include the cases of cutaneous adverse events and treatment with either PD-1 inhibitors (pembrolizumab and nivolumab) or with PD-L1 inhibitors (atezolizumab, avelumab, durvalumab).

Literature review - About 200 articles were searched and a total of 150 publications were included in this article. These publications reported a total of 179 cases in which cutaneous irAEs were discussed. The cutaneous adverse effects encountered are lichenoid dermatitis (30/179), granulomatous skin reactions (24/179), vitiligo (10/179), pruritus (3/179), psoriasiform rashes (21/179), bullous pemphigoid (29/179), dermatomyositis (15/179), lupus erythematosus (11/179), stevens-johnson syndrome/toxic epidermal necrolysis (TEN) (18/179), oral lichenoid dermatitis (18/179). The data gathered from the cases have been compiled in Table 1.

Cutaneous adverse eruptions.

Cutaneous irAEs are one of the most prevalent irAEs caused by anti-PD-1/PD-L1 agents. In the case reports studied, both anti-PD-1 agents (nivolumab and pembrolizumab) and anti-PD-L1 agents (atezolizumab, durvalumab, avelumab), presented cutaneous irAEs in 30-40% of the patients. However, the vast majority of these cutaneous irAEs caused by immune checkpoint inhibitors are self-limiting and present an acceptable skin toxicity profile [4]. These cutaneous irAEs can be classified into six main categories: bullous eruptions, pruritus, pigmentary disorders, inflammatory dermatoses, severe cutaneous adverse reactions (SCARs), or life-threatening drug reactions [5](Figure 2).

Based on the histological and clinical severity and percentage of skin/body surface area involvement, the cutaneous adverse events are mainly classified into the following grades:

Grade 1: asymptomatic with macules/papules covering majorly <10% of the body/skin surface area

Grade 2: macules/papules covering 10% to 30% of the body/skin surface area can be symptomatic as well as asymptomatic.

Grade 3: about >30% of the body/skin surface area is covered. The appearance of macules/papules with or without symptoms.

Grade 4: it is the most severe cutaneous response and can be life-threatening such as Stevens-Johnson syndrome, TEN, and bullous dermatitis involving about >30% of skin/body surface area. Intensive care should be taken for the proper management.

Other notable dermatologic irAEs include pruritus and vitiligo, with high-grade pruritus occurring in less than 2% of patients. 8% of patients developed vitiligo, primarily those with melanoma[6]. The incidence of all-grade rash due to anti-PD-1 therapy is 14-17% and the severe rash is less than 2% as shown in the figure (Figure3). The most common cutaneous irAEs associated with immune checkpoint mAb therapy is skin rash, including lichenoid (lichenoid dermatitis and bullous disorders including bullous pemphigoid), which poses a greater risk due to their severity and potentially life-threatening consequences. The pathophysiological mechanisms involving cutaneous toxicities of immune checkpoint inhibitors are mainly unknown, but the majority are T-cell mediated. The development of these cutaneous irAEs involves blockade of a common antigen, which is co-expressed on both tumor cells and dermo-epidermal junction, and/or other parts of the skin. They likely target the antigens in the dermis/epidermis of the skin by reactivating CD4+/CD8+ T cells and producing the inflammatory response after cross-reaction with normal skin[7].

Inflammatory Skin Reactions

Lichenoid dermatitis

Lichenoid reactions are severe inflammatory reactions mediated by T cells which comprise several maculopapular rashes, with lichenoid interface dermatitis and basal vacuolar changes, and are observed with anti-PD-1/anti PDL-1 therapy. Histological and clinical features show a dense, band-like lymphocytic infiltrate beside the dermal-epidermal junction of the skin, a vacuolar interface, and co-existing spongiosis. Patients experience asymptomatic scaly, sharp bordered erythematous psoriasiform plaques and lesions on the trunk, arms, and limbs, which may be present as discrete, multiple, or confluent lesions in a generalized, inverse, localized, palmoplantar, or mucosal (i.e. oral or genital) distribution. The number of these eruptions may range from tens to hundreds[8]. Lichen sclerosis (LS) is an autoimmune severe inflammatory disease affecting mainly the anogenital area which is characterized by autoreactivity of T-cells, increased levels of T-helper 1-specific cytokines[9].

Pathogenesis: The immunologic mechanism of lichenoid dermatitis is supposed to be a T-cell mediated response. The blocking of PD-L1 binding with PD-1 results in the increased immune response by activation of tumor-specific T-cells. Also, increased self-immunity and antigenic immune reaction occur, which leads to non-specific activation of T-cells. This results in various adverse reactions involving multiple organ systems, such as the skin[10]. They specifically affect PD-L1 expressing keratinocytes in the sub-epithelium, resulting in keratinocytes necrosis. Furthermore, lymphocytic infiltration of the basal membrane causes spongiotic dermatitis, acanthosis, and hypergranulosis[11].

Clinical incidence: There were thirty cases involving lichenoid dermatitis reported with PD-1/PD-L1 immunotherapy. Thirteen of them were associated with nivolumab therapy [9, 12-17] and thirteen with pembrolizumab (PD-1)[10,18-25]. Four cases were reported with PD-L1 inhibitors like one with avelumab[26] and three with duvalumab[27-29] inhibitors. Lesions appear as flat-topped, erythematous, or violaceous, and pruritic papules and plaques that may coalesce over the trunk, limbs, and extremities although a spreading of the lesions is possible. Lichenoid dermatitis occurs in the age ranges from 25-87 years (mean=66). A case was reported with nivolumab therapy where the patient developed variations on fingernails leading to the rapid development of proximal or lateral onycholysis and causing detachment of *nail* plate, consequent loss of nails [15]

Treatment: First line: The first-line treatment for lichenoid dermatitis in the reported cases

were systemic treatment and systemic prednisolone was the first choice of systemic treatment(0.5-80mg/kg)[14, 16, 18, 19, 21-24, 27], and methylprednisone (60 mg/kg) [12, 14] and were effective in the majority of cases.

2nd line treatment*:* Topical therapies including corticosteroid creams and ointments, clobetasol propionate 0.05% [9, 12-14, 18, 20, 27, 28], topical fluocinonide ointment (0.05%)[25]. Intralesional triamcinolone acetonide[15, 25, 26]were used for hypertrophic lichen planus besides acitretin (0.2mg) [25]. In one case report patient was treated with promethazine [17]. Lesions were also treated with topical calcineurin inhibitors e.g., tacrolimus 0.1% ointment twice daily[20]. One patient was treated with a short course of cyclosporine [22]. Consequently, tapering systemic steroids led to the recurrence of dermatitis which was then treated with narrowband ultraviolet B (NBUVB) phototherapy thrice weekly [13, 24].

Granulomatous skin reactions:

Sarcoidosis or sarcoid-like granulomatous reaction is characterized by the development of epithelioid and multinucleated giant cell granulomas involving multi-organ systems, affecting the skin, lungs, and eyes. The development of these reactions is characterized by compartmentalization of CD4+ T- cells and co-activation of monocyte/ macrophages in the organs involved [30].

Pathogenesis: The immune-pathogenesis of granulomatous skin reactions is characterized by Th-1/Th-17 type inflammation which is mediated primarily by the release of the pro-inflammatory cytokines such as interferon-gamma (IFN-γ), interleukin (IL)-17 producing cells including CD4+ T helper 17(Th17) cells, and tumor necrosis factor (TNF-α). [31, 32]. The alteration in the ratio between cytotoxic T cells, Th1/Th17 and regulatory T-cells due to immune checkpoint inactivation leads to hyperactivation of the Th-17 with the secretion of tumor necrosis factor-alpha (TNF-α) and increased expression of interleukin- 17 which act as an inflammatory mediator generating the granulomas with epithelioid and multinucleated giant cells. Additionally, granulomatous skin reactions can also be induced by the activity of CD8+ cells on dendritic cells (DC) and macrophages through the production of cytokines favoring Th1 and Th17 cells[33].

Clinical incidence: Twenty-four case reports of granulomatous reactions were reported as adverse reactions. The period of inhibition of PD-1/PD-L1 and onset of granulomatous skin reactions is two weeks to two years. Ten cases of pembrolizumab immunotherapy presented with cutaneous sarcoidosis and sarcoid-like granulomatous reaction[34-39]; eight cases with nivolumab[33, 35, 40-42]; one case associated with atezolizumab[43]; one with avelumab[44] and four cases were with durvalumab immunotherapy [45-48]. The clinical and histological findings suggest the development of subcutaneous nodules[35, 39] and indurated papules and plaques on the skin surface [34, 39]. A case of nivolumab therapy was reported which involve pulmonary, mediastinal lymph node, and skin involvement that did not require immunosuppressive therapy and, pulmonary and parotid gland involvement that rapidly improved with steroid treatment.

Treatment: All responded well with systemic prednisolone (30 mg). In one case betamethasone dipropionate 0.05% ointment was used as a treatment [34] while the other cases were treated with prednisolone and hydroxychloroquine combination[34], clobetasol propionate 0.05% cream [47].

B. Pigmentary Disorders

Vitiligo:

Vitiligo is a skin disorder categorized by hypopigmented lesions (white spots) on the skin and occurs due to the destruction of functional melanocytes from the epidermis layer. Vitiligo can disturb any area, but it most commonly affects the neck, face, hands, and legs. Vitiligo is classified as generalized or localized vitiligo based upon the spread of the lesions and the appearance of hypopigmented cutaneous areas[49].

Pathogenesis: The analysis of blood and skin samples showed increased levels of CXC motif ligand 10 in the blood serum. The pathogenesis of vitiligo involves raised levels of tumor necrosis factor-alpha (TNFα) and interferon-gamma (IFN-γ) and CD8+ T cells mediated skin infiltration expressing CXC motif receptor 3.

Alternatively, vitiligo-like lesions can be caused by microphthalmia-associated transcription factor (MITF) that allows the transcription of many genes, essential for promoting the survival of melanocytes. MITF-associated genes are tumor-specific neoantigens, and genes that may signify melanocyte lineage-specific antigens. Therefore, immune system activation against MITF-associated epitopes with PD-1/PD-L1 blockers could destroy normal melanocytes causing the development of vitiligo-like lesions [50](Figure 4).

Clinical incidence: Ten cases of vitiligo, hypopigmentation, or loss of pigment after the anti-PD-1/PD-L1 therapy have been reported. Six of them were associated with nivolumab therapy [13, 51-53], three of them with pembrolizumab therapy[54-56], and one of them with anti-PD-L1 atezolizumab[57]. The time from initiation of anti-PD-1/PD-L1 therapy to the progression of disease ranges from six days to nine months. Vitiligo was observed in patients with age from 30-75 years. Vitiligo-like hypopigmentation (or melanoma-associated leukoderma) was reported in melanoma patients (3.4 to 28%) and other metastatic cancers. The overall incidence of vitiligo is assessed to be 5.5% respectively with anti-PD-1/ PD-L1 checkpoint inhibitors. The distribution of PD-1/PD-L1 induced vitiligo typically involves the upper body, such as the face, neck, upper torso, and upper limbs. Focal patches may also be seen around scars or sites of skin metastases. Mainly asymptomatic lesions can occur, categorized by hypopigmented macules in the photo exposed areas, which can be headed by pruritis or nonspecific maculopapular rash [58]. Hypopigmentation has been reported in a patient with metastatic melanoma resulting in whitening of eyelashes, eyebrows, body hair, and scalp in accumulation to vitiligo, with pembrolizumab immunotherapy [55].

Treatment: Despite the presence of hypopigmentation or vitiligo most of the patients continued to PD-1/PD-L1 immunotherapy. Vitiligo can spontaneously be treated with high potency topical corticosteroids and excimer laser therapy[56]. Other therapies include intravenous immunoglobulin therapy (IVIg) clobetasol propionate 0.05%[59], topical tacrolimus (0.1% ointment) (n=2)[53, 60], calcipotriol and calcineurin inhibitors[60], 0.05% fluticasone propionate[13], triamcinolone 0.1% cream[53]. Sun protection for the prevention of hypopigmented areas from burning.

C. Pruritus

Pruritus is one of the most common adverse skin responses with immune checkpoint inhibitors. Pruritus can present with or without a rash and patients may have skin changes i.e. erosions, ulcerations, nodules secondary to pruritus [58].

Pathogenesis: The pathophysiological mechanism for these cutaneous manifestations is not fully known, but it includes CD4+ and CD8+T-cells which are likely activated by the anti-PD-1/PD-L1 immunotherapy target an antigen present in the epidermis or dermis[61].

Clinical incidence: A total of three cases were reported with pruritus reactions. Two cases were reported with pembrolizumab[22, 62], and one with nivolumab[61] therapy. Grade I pruritus includes mild symptoms with the localized distribution, whereas Grade II pruritus causes irregular, intense symptoms with persistent skin changes or intermittent widespread distribution. Grade III and grade IV pruritus are most adverse with widespread constant distribution, intense indications with persistent skin changes that interfere with sleep patterns [58].

Treatment: For grade III and grade IV pruritus, treatment was initiated with systemic steroids methylprednisone or oral prednisolone (0.5-1 mg/kg/day) with persistent immunotherapy while other managements include cyclosporine [22]. Treatment of pruritus also includes narrowband UVB therapy [61].

Autoimmune skin disorders

PD-1/PD-L1 signaling pathway involves the pathophysiology of numerous autoimmune skin diseases. Moreover, these monoclonal antibodies can also induce the progression of de novo autoimmune cutaneous diseases like bullous pemphigoid, psoriasis, vasculitis, and dermatomyositis.

Psoriasis

Psoriasis/psoriasiform rashes are skin reactions that cause red, itchy scaly patches, present most commonly on the knees, elbows, trunk, and scalp. Most commonly these itchy scaly patches occur in a patient with a former history of psoriasis before starting the immunotherapy, but few cases show the new onset of psoriasis [63, 64]. Plaque psoriasis is one of the most common forms of psoriasiform rashes, but the occurrence of other forms has also been reported, including pustular psoriasis, palmoplantar psoriasis, guttate psoriasis, nail psoriasis, inverse psoriasis, erythrodermic psoriasis. Clinical description of the disease includes well-demarcated, erythematous, scaly papules and plaques. Importantly, cases of exacerbation or de-novo incidence of psoriatic arthritis with cutaneous psoriasis, have also been reported[65, 66].

Pathogenesis: PD-1/PD-L1 blockade activates the T-cell which stimulates an inflammatory state and leads to the development of psoriasiform lesions. Psoriasis is T-cell and dendritic cell (DCs)-mediated disease generally mediated by Type 1 and 17 helper T cells (Th1/Th17). In psoriatic patients, dendritic-cell (DCs) of skin secretes IL-23 that induces the production of pro-inflammatory cytokines released by Th-17 mainly IL-17A, IL-17F, and IL-22. Dermal Th-1 lymphocytes are also activated by dermal DCs to produce interferon-gamma (IFN- γ), tumor necrosis factor (TNF)-alpha. PD-1/PD-L1 signaling pathway causes down-regulation of Th1/Th17 cells, whereas inhibition of this pathway causes an up-regulation of Th-1/Th17 cells stimulating overexpression of pro-inflammatory cytokines IL-17 and IL-22. These inflammatory mediators cause the stimulation and hyperproliferation of keratinocytes on the skin surface. Activated keratinocytes produce key pro-inflammatory cytokines, chemokines, and antimicrobial peptides, which can recruit and activate immune cells in the inflamed skin, leading to epidermal hyperplasia, acanthosis, and hyperparakeratosis. Since Th17 is an important factor for the development of psoriasis, checkpoint inhibitors initiate new psoriasis or cause exacerbation of existing diseases [64, 67].

Clinical incidence : A total of twenty-one cases of psoriasiform rashes were found including psoriasis and psoriasis induced psoriatic arthritis with PD-1/PD-L1 inhibitors. Whereas, twenty cases were reported with anti-PD-1 which includes nine cases with pembrolizumab[68-72], eleven cases with nivolumab therapies [64-66, 72-80] while one case was reported with the PD-L1 inhibitor atezolizumab[81] therapy. In reported cases, the median age was 68 years. The occurrence of psoriasis ranges from 12%% in patients with anti-PD-1/PD-L1 immune therapy. The time from initiation of anti-PD-1/PD-L1 treatment to the development of psoriasis ranges from 2 to 14 months and psoriasis cases were found more in males as compared to females. Clinical psoriasis is reported as an adverse event that extends from guttate psoriasis to plaque psoriasis, inverse psoriasis, palmoplantar psoriasis, and nail psoriasis to erythrodermic psoriasis. The patients that developed concurrent psoriasis involved psoriatic arthritis of several joints.

Treatment: The first-line treatment of psoriasis was topical corticosteroids [64] and systematic steroids like oral prednisone [70] or methylprednisolone therapy at doses of 16 mg (n=1) [69], 1000 mg (n=1) [65]. One patient was prescribed triamcinolone ointment 0.1%, hydrocortisone cream 2.5%, and methylprednisolone, further the eruption was controlled with the combination of topical and oral steroids.[80]Other treatments include clobetasol propionate 0.05% ointment [68, 78] applied on both nails and skin, 50% urea gel on nails [74]. A case has been reported with nivolumab immunotherapy in which skin lesions were treated with the combination of psoralen and long-wave ultraviolet radiation (PUVA) [75]. Two patients with immune-mediated psoriasiform reactions from anti-PD-1 inhibitor had been treated with UVB-NB light therapy also known as UV7001K phototherapy.[72]. Treatment with intravenous fluconazole, apremilast[76], acitretin[71], subcutaneous injections of secukinumab (300 mg once every two weeks) had also been introduced. In one case, a patient with widespread psoriasiform lesions responded well to anti-interleukin 17A treatment[71]. In the case of nivolumab immunotherapy, a patient with drug-induced psoriasis was treated well with risankizumab-rzaa[79]. A patient with psoriasis-induced psoriatic arthritis was treated well with apremilast at a dose of 30 mg BID[66].

Bullous Pemphigoid

BP is an autoimmune disease mediated by IgG and IgE autoantibodies against hemidesmosome proteins which are responsible for the adhesion between the epidermis and dermis. In bullous pemphigoid appearance of tense bullae and blisters over urticarial plaques can arise on the cutaneous layer which is accompanied by intense pruritus[82].

Pathogenesis: The hypothesized mechanism of immunotherapy-induced BP is dysregulation of T cell immune response and synthesis of IgG and IgE autoantibodies against hemidesmosome proteins bullous pemphigoid antigen 2 [BPAG2] or BP180, and a plakin family protein BP230 or bullous pemphigoid antigen1(BPAG1). Both the antigens are specific for the hemidesmosomes which are responsible for the degradation of the basement membrane zone and increased inflammatory cell infiltration at hemidesmosomes found in keratinocytes [82]. It is a humorally mediated autoimmune disease, but auto-reactive T cells and T regulatory (Tregs) cells have also been found to play a role. The termination of immune response involves both Tregs and PD-1 and PD-L1 pathway, and elimination of any one of these results in tolerance breakdown and autoimmunity development[83].

Clinical incidence : Twenty-nine cases of bullous pemphigoid were reported with the anti-PD-1/PD-L1 immunotherapy where thirteen cases were associated with pembrolizumab[84-93], twelve with nivolumab[92-97], three with atezolizumab[93, 98, 99], and one with durvalumab therapy [93]. The occurrence of BP was found in 16-30% of patients receiving anti-PD-1/PD-L1 immunotherapy and is generally longer than that of other cutaneous toxicities. It generally has an onset of 3 weeks-6 years. Most patients were clinical, histologic, and immunologic features of classic bullous pemphigoid which manifest with tense blisters over urticarial plaques seen on the trunk and extremities escorted by intense pruritus[93, 100]. Before the expansion of bullae, patients developed pruritus with nonspecific cutaneous lesions. A total of four cases with nivolumab (n=1) and pembrolizumab (n=3) developed non-bullous pemphigoid (NBP), severe pruritus with eczematous patches or urticarial plaques[92]. A patient with metastatic RCC developed bullous pemphigoid subsequently with a single dose of 480 mg iv of nivolumab therapy[96].

Treatment: Bullous pemphigoid was the most common extensive blistering skin disorder in which treatment with systemic prednisolone was effective in the majority of reported cases. Other reported treatments include daily topical clobetasol propionate[84], betamethasone 0.05% ointment[86], doxycycline and niacinamide[98], topical fusidic acid plus betamethasone valerate cream[94]. In a reported case series, the development of non-bullous pemphigoid has been treated with 300 mg omalizumab q4w and rituximab 325 mg/m2 for 4 weeks and there is complete resolution of the eruption and significant resolution after treatment with omalizumab and Rituximab [92].

Dermatomyositis

Dermatomyositis is an idiopathic inflammatory disease characterized by skeletal muscle weakness, inflammation, and various skin problems[101]. It can occur spontaneously as a drug reaction or paraneoplastic phenomenon[102]. The histopathologic and typical cutaneous changes in DM include hyperkeratosis, epidermal basal cell vacuolar degeneration, thinning of the epidermis and dermal mucin deposition and perivascular infiltrate composed of CD4+ lymphocytes[103]. Dermatomyositis eventually causes damage to both parenchyma and blood vessels, which results in the histologic appearance of perimysial, perifascicular atrophy in muscle as well as keratinocyte injury in the skin[104]. Dermatomyositis indicates persistent skin changes and includes a heliotrope rash, macular violaceous erythema (shawl sign, v-neck rash, holster sign), and an erythematous rash that may be distributed all over the joints. Pruritic papules (Gottron's sign and Gottron's papules) are a characteristic rash initiated on the extensor surfaces of the small joints of the hands. Pruritic papules along with heliotrope rash seem to be a disease-specific cutaneous manifestation[105]

Pathogenesis: The histopathological findings of DM in muscle fiber include perifascicular atrophy, swelling of endothelial cells, capillary necrosis, up-regulation of major histocompatibility complex (MHC) I, and occurrence of an inflammatory cell infiltration composed of T lymphocytes, macrophages, and plasma cells[106]. The Inflammatory cell infiltration in DM is composed of CD4+T lymphocyte, including interferon-α (IFNα) producing plasmacytoid dendritic cells (pDCs), Th-1 cells produced by IFN-y and Interleukin (IL)-17 released by the Th17 cells, mainly distributed in the perivascular localization mostly in the perimysium. The production of Th17 cells by Interleukin (IL)-17, in turn, activates the release of proinflammatory Th1 cytokines such as IL-2, IL-1, IL-6, thus results in the proliferation of MHC class I expression on muscle fibers. The up-regulation of MHC I may directly cause muscle damage via stimulation of a cytotoxic T cell host response[107]. IL-15 also stimulates the activation of cytotoxic CD8+ lymphocytes which stimulates the prolif-

eration of myoblast endothelial cells[104]. The active involvement of the CD40/CD40 ligand (CD40L) system within the skin has been recently implicated in the pathogenesis of DM. There are elevated levels of CD40+ cells (which includes keratinocytes and mononuclear cells in the dermis) and CD4+ CD40L+ T lymphocytes have been reported in the skin biopsies from a patient with DM. Stimulation of CD40/CD40L system may be responsible for the up-regulation of several proinflammatory molecules, including IL-6, IL-15, IL-8 and MCP-1 causing keratinocyte apoptosis and inflammation at the basal cell layers and support an autoimmune etiology of dermatomyositis[106].

Clinical incidence : Fifteen cases of dermatomyositis were reported with anti-PD-1/PD-L1 immunotherapy out of which nine cases were associated with nivolumab[102, 108-114], four cases with pembrolizumab[114-117], one with atezolizumab[118], and one with durvalumab[119] immunotherapy. Most of the patients with DM had raised muscle enzymes (e.g., creatine kinase, aldolase) and inflammatory markers (e.g., C-reactive protein). Several auto-antibodies associated with dermatomyositis include anti-synthetase (anti-Jo-1), anti-transcription intermediary factor-1-gamma (TIF1γ)[110, 111]. A case with paraneoplastic dermatomyositis had been reported after the initiation of nivolumab therapy[109].

Treatment: The potent treatment of dermatomyositis included systemic corticosteroids, prednisone methylprednisolone, topical triamcinolone 0.1% cream to involved areas, and clobetasol 0.05% ointment. Several cases were reported, where patients received IV immunoglobulin treatment (IVIG) [102, 110, 117].

Lupus erythematosus:

Systemic lupus erythematosus (SLE) is a complex prototypic autoimmune disease associated with the presence of anti-nuclear autoantibodies (ANAs) related to chronic immune system activation. Immune irregulation is the significant characteristic of lupus erythematosus. However, it also includes the abnormal T-cell activation, hyperactivity of B-cells, inappropriate management of immune complexes, and cellular debris by the innate immune system [120].

Pathogenesis: The pathological mechanism of lupus erythematosus is unclear, but patients with systemic lupus erythematosus have shown decreased expression of PD-1 on T-cells and a higher frequency of neutrophils expressed by PD-L1. Therefore, activation of auto-reactive T-cells and over-activity of B-cells leads to the production of pathogenic autoantibodies and thus causing tissue injury[120].

Clinical incidence: A total of eleven cases of lupus erythematosus were reported with anti-PD-1 therapy. Six cases were reported with pembrolizumab[121-124] and five with nivolumab[113, 125-127] immune checkpoint inhibitors. Histological and clinical diagnosis of lupus erythematosus and lichenoid reactions in some cases is difficult to differentiate[113]. In several reported cases, the skin lesions appeared to be pruritic nummular erythematous papules and plaques[122] and annular papulosquamous plaques[121, 125]. One patient presented with fever, arthralgia, asthenia, and bullous lupus erythematosus[127].

Treatment: The symptoms of cutaneous lesions were controlled with high potency topical and systematic corticosteroid treatment (prednisolone)[121, 127]. Other treatments initiated were tacrolimus (1mg/day)[123], triamcinolone 0.1% ointment, sun protection, and hydroxychloroquine[113, 125]. In one such reported case, the skin rash of the patient resolved without treatment within one month after interruption of pembrolizumab therapy[122].

Life-threatening cutaneous drug reactions

Stevens-Johnson syndrome/toxic epidermal necrolysis (TEN):

The stevens-johnson syndrome is a mucocutaneous adverse drug reaction recognized as a complex delayed hypersensitivity reaction characterized by epidermal detachment. SJS is a very rare and severe disorder that involves mucosa and cutaneous tissue. It is characterized by flu-like symptoms including fever, anorexia, malaise followed by erythematous eruptions that arise as dusky-red, purpuric macules symmetrically dispersed over the neck, trunk, extremities, and proximal limbs. Soon after they spread to all over the body surface area and develop into flaccid blisters characterized by epidermal detachment as well as associated

with inflammation and pain of oral, ocular, and genital mucous membrane [128]. SJS is a potentially fatal syndrome associated with anti-PD-1/PD-L1 therapy which must be recognized and treated on time. It is an immune-mediated syndrome with granulysin, a cytolytic protein present in drug-specific CD81 cytotoxic granules of T lymphocytes and natural killer cells, which act as key mediators of keratinocyte apoptosis [129]. but it may involve blocking of PD-1/PD-L1 interaction

Pathogenesis: The exact mechanism underlying stevens-johnson syndrome and toxic epidermal necrolysis remains to be elucidated, but it may involve blocking of PD-1/PD-L1 interaction which results in the cessation of T-cell homeostasis within the cutaneous and mucous membrane associated with self-directed cytotoxic and inflammatory reactions. It is a rare and unpredictable reaction that involves the accumulation of drug-specific CD8+ cytotoxic lymphocytes associated with keratinocyte apoptosis[129].

Clinical incidence: Eighteen cases reported stevens-johnson syndrome/ toxic epidermal necrolysis (TEN) with anti-PD-1/PD-L1 therapy. Eleven cases were reported with pembrolizumab[128, 130-138], five cases with nivolumab[139-142], and two cases with azetolizumab[137, 143]. The clinical incidence has shown erythematous eruptions to papules and plaques to purpuric patches over the neck, trunk, and extremities, with erosions on the lips, hemorrhagic and yellow crust on lips, an erythematous maculopapular rash with erythema, oedema, vesicles, desquamation, or even ulceration.

Treatment: First-line treatment included systemic high-dose corticosteroids (methylprednisolone, prednisone) while other treatments like intravenous fluids and silver sulfadiazine, vancomycin, intravenous immunoglobulin (IVIG) infusion [136], lidocaine 1% solution [139], nystatin betnovate 0.1% ointment[141], infliximab [138], were initiated for the prevention of adverse events associated with anti-PD-1/Pd-L1 therapy.

Oral mucosa involvement

Oral Lichenoid Reactions:

Oral lichenoid reactions (OLRs) or oral lichenoid lesions (OLLs) are clinically and histologically similar to lichen planus[63]. Lichen planus is a severe chronic inflammatory disorder that can affect the skin and lining mucosa, including oral, oesophageal, and genital mucosa. Oral lichenoid reactions are reported to affect about 1-2% of the population, with women more commonly affected than men [10]. Oral lichen planus usually occurs on the buccal mucosa, gingivae, and tongue. Clinical presentations of oral lichenoid reactions vary from white striated reticular patterns to white and red confluent plaques, ulcerations, and erosions. A case was reported with pembrolizumab-induced oral graft versus host disease (GVHD) or lichen planus like lesion [144].

Pathogenesis: While the etiology of oral lichenoid reactions is unknown, but it is supposed to be an immunologically T-lymphocyte mediated reaction to the keratinocytes present on the basal surface of the skin or mucosal membrane [63].

Clinical presentation : Eighteen cases of oral lichenoid reactions were reported with anti-PD-1/PD-L1 immunotherapy. Cases associated with various drugs are as follows, four with pembrolizumab[145, 146], fourteen with nivolumab[146-150]. The time from initiation of anti-PD-1/PD-L1 treatment to the development of oral lichenoid reactions ranges from two weeks to four years with the dosing regimen of pembrolizumab: 200 mg /2mg/kg I.V., every 3 weeks, nivolumab = 200 mg I.V. every 15 days, 480 mg every 4 weeks, 240 mg I.V. q2w, 3 mg/kg I.V. q2w. Oral lichenoid reactions occur in patients within the age of 26-93 years (mean=62). The disease arises on the buccal mucosa, soft palate, ventral and dorsal aspect of the mouth and tongue, labial mucosa, gingivae, and the hard palate. Clinical and histological findings of the disease include the occurrence of a white striated reticular pattern to red confluent plaques erosion, wickham striations ulcerations, or erosions.

Treatment: Patients responded well to the topical steroid therapies (prednisone, methylprednisone) [148] when prescribed for oral irAEs. Other treatments have also been evolved which include betamethasone cream [147], dexamethasone 0.1 mg/ml solution [149], fluocinonide 0.05% gel, Oracort dental paste, triamcinolone acetonide 0.1% paste [146].

Conclusion

In current times, the use of immune checkpoint inhibitors for the treatment of various cancers has increased rapidly. Thus, it has become essential to understand various irAEs associated with their use and monitoring of these irAEs in patients undergoing immunotherapy. There is an extensive range of cutaneous adverse reactions observed with PD-1/PD-L1 immune checkpoint inhibitors and they account for the most significant share of immune-related adverse events that range from mild to life-threatening complications such as stevens-johnson syndrome/ toxic epidermal necrolysis (TEN). The time of occurrence of these reactions usually varies from days to several months. The most common cutaneous adverse reactions observed are lichenoid reactions, granulomatous skin reactions, pruritus, pigmentary disorders such as vitiligo. The blocking of the PD-1/PD-L1 signaling pathway is involved in the pathophysiology of numerous autoimmune skin diseases like bullous pemphigoid, psoriasis, vasculitis, and dermatomyositis. The management of skin toxicity from anti-PD-1/PD-L1 treatment involves topical and systemic corticosteroids, immunosuppressive drugs, antihistamines, UVB-NB therapy. Furthermore, adequate management of the cutaneous adverse events and recognition in early stages could lead to the prevention of worsening of the lesions, reduction in morbidity and thus, enhances the chances of continuing PD-1/PD-L1 therapies without limiting the treatment.

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