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REVIEW ARTICLE

Dermatologic Reactions to Immune Checkpoint Inhibitors

Skin Toxicities and Immunotherapy

Vincent Sibaud[1]

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Abstract The development of immune checkpoint inhibitors [monoclonal antibodies targeting cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1) or programmed death ligand 1 (PD-L1)] represents a major breakthrough in cancer therapy. Although they present a favorable risk/benefit ratio, immune checkpoint blockade therapies have a very specific safety profile. Due to their unique mechanism of action, they entail a new spectrum of adverse events that are mostly immune related [immune-related adverse events (irAEs)], notably mediated by the triggering of cytotoxic CD4+/CD8+ T cell activation. Cutaneous toxicities appear to be one of the most prevalent irAEs, both with anti-PD-1 and anti-CTLA-4 agents or with the newly developed anti-PD-L1 agents, which corresponds to a class effect. They are observed in more than one-third of the treated patients, mainly in the form of a maculopapular rash (eczema-like spongiotic dermatitis) and pruritus. A wide range of other dermatologic manifestations can also occur, including lichenoid reactions, psoriasis, acneiform rashes, vitiligo-like lesions, autoimmune skin diseases (e.g., bullous pemphigoid, dermatomyositis, alopecia areata), sarcoidosis or nail and oral mucosal changes. In addition, the use of anti-CTLA-4 and anti-PD-1 therapies in combination is associated with the development of more frequent, more severe and earlier cutaneous irAEs compared to single agents. In most cases, these dysimmune dermatologic adverse events remain self-limiting and readily manageable. Early recognition and adequate management, however, are critical to prevent exacerbation of the lesions, to limit treatment interruption and to minimize quality of life impairment. This review describes the variable clinical and histopathologic aspects of dermatologic irAEs induced by immune checkpoint inhibitors. Appropriate treatment and counseling are also proposed, with a step-by-step approach for optimized management by both practicing oncologists and dermatologists.

Key Points

Dermatologic reactions are among the most prevalent immune-related adverse events reported with immune checkpoint inhibitors.

They mainly manifest in the form of self-limiting maculopapular rashes and pruritus.

Early recognition and management are believed to be critical in mitigating the severity of the lesions.

1 Introduction

Immune checkpoint inhibitors [monoclonal antibodies targeting cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1) or programmed death ligand 1 (PD-L1)] represent a new class of anticancer agents. Their development represents a major breakthrough in cancer therapy, and they are already

✉ Vincent Sibaud
sibaud.vincent@iuct-oncopole.fr

[1] Oncodermatology, Institut Claudius REGAUD and Institut Universitaire du Cancer Toulouse Oncopole, 1 avenue Irène Joliot-Curie, 31059 Toulouse Cedex 9, France

registered or are undergoing evaluation in a wide range of advanced cancers.

Whether at the peripheral level (i.e., in peripheral tissue and peritumoral T lymphocytes, PD-1) or upstream (i.e., naive or memory T cells in lymph nodes, CTLA-4), immune checkpoints have a critical role in maintaining normal immunologic homeostasis. Thus, they downregulate T-cell activation and proliferation and represent negative regulators of immunity. They thereby allow for tolerance toward self-antigens, but also toward cancer cells of certain tumor types [1–4]. In the same way, PD-L1 (an immune checkpoint protein expressed on cancer cells and tumor-infiltrating immune cells) can dampen the T-cell immune response and promote tumor immune escape by binding to its receptor PD-1 on activated T cells. By activating cytotoxic CD4+/CD8+ T cells, immune checkpoint blockade therapy shifts the immune system toward antitumor activity.

Due to their unique mechanism of action, immune checkpoint inhibitors have a very specific safety profile. They entail a new spectrum of adverse events [referred to as "immune-related adverse events" (irAEs) or "adverse events of special interest"] that are mostly of a mechanism-based immune nature, mediated by the triggering of cytotoxic CD4+/CD8+ T-cell activation. Although the incidence of adverse events varies depending on the monoclonal antibodies used, the profile of these dysimmune toxicities has been found to be very similar. More than 60% of treated patients end up developing immune-related adverse effects, which can in theory affect any of the body organs [1–8]: thyroiditis, dermatitis, pneumonitis, colitis, hepatitis, hypophysitis, uveitis, polyneuritis, pancreatitis, etc. Treatment of these adverse events should be considered in a multidisciplinary approach, based on a dedicated network of organ specialists with extensive experience in the management of irAEs [3, 5, 8].

Dermatologic toxicities appear to be the most prevalent irAEs, both with anti-PD-1 (nivolumab and pembrolizumab) and anti-CTLA-4 (ipilimumab, tremelimumab) agents and with the newly developed anti-PD-L1 agents (atezolizumab, durvalumab, avelumab) [2–11]. They occur in more than one-third of the patients treated with these monoclonal antibodies (Table 1), regardless of the cancer being treated [4, 9, 11–18]. The vast majority of these cutaneous adverse events, however, are self-limiting, and immune checkpoint inhibitors present an acceptable skin toxicity profile [13–20]. Although the overall incidence is higher with ipilimumab compared to anti-PD-1 or anti-PD-L1 agents, the dermatologic toxicity profile is very similar and above all corresponds with a class effect [4, 9, 12]: maculopapular rash (spongiotic and lichenoid dermatitis), vitiligo (only among patients with melanoma), induced psoriasis, auto-immune skin diseases, etc. In addition, dermatologic toxicities are the first to occur with immune checkpoint inhibitors [2, 4, 5, 7, 11], and this does not appear to be dose dependent [10, 20, 21]. Lastly, cutaneous irAEs observed with anti-CTLA-4/anti-PD-1 used in combination (e.g., ipilimumab and nivolumab) are more frequent, more severe, and long lasting and develop earlier compared to PD-1 or CTLA-4 inhibitors prescribed as single agents [6, 7]. As the use of anti-PD-L1 antibodies is only emerging, the data for these agents still need to be consolidated.

The pathophysiologic mechanisms governing cutaneous irAEs have not been established. They are, however, clearly related to T-cell activation mediated by blockade of PD-1 (or the PD-L1 ligand) and CTLA-4 receptors. The aberrant targeting of dermal-epidermal antigens by reactivated CD4+/CD8+ T cells still needs to be identified.

Finally, it needs to be emphasized that the occurrence of some of these cutaneous reactions induced by anti-PD-1 appear to be correlated with a better therapeutic response, in terms of objective response (vitiligo) [22], progression-free survival (cutaneous adverse events all together) [20] or overall survival (maculopapular rash and vitiligo) [10]. Further prospective studies on a larger scale appear to be required, however, in order to confirm these data, particularly for cutaneous irAEs other than vitiligo.

2 Skin Rashes

2.1 Nonspecific Maculopapular Rash

2.1.1 Incidence

A pruritic maculopapular rash represents the most frequent cutaneous irAE observed with PD-1/PD-L1 and CTLA-4 inhibitors [3, 7, 9, 10, 20, 23]. Its incidence is slightly higher with anti-CTLA-4 treatment and with the therapeutic combination of anti-PD-1/CTLA-4 (Table 1) [4, 13–18]. The overall incidence (by meta-analysis) varies between 24.3% [95% confidence interval (CI) 21.4–27.6], 16.7% (95% CI 11.9–23), and 14.3% (95% CI 8.7–22.7) for ipilimumab [21], pembrolizumab, and nivolumab [12], respectively. The rate of grade ≥ 3 rash [i.e., affecting more than 30% of the body surface area (BSA)], however, remains below 3% in monotherapy [13–18].

In comparison, the risk of developing a maculopapular rash with PD-L1 inhibitors appears to be lower. It affects less than 10% of treated patients [24–28].

2.1.2 Clinical Presentation

The lesions most often start after the first few treatment cycles (sometimes as of the first cycle). Their onset is slightly earlier

Table 1 Overall incidence of dysimmune dermatologic toxicities in patients treated for advanced melanoma (phase I–III studies) [4, 12–17]

Treatment-related skin select adverse events (% ≥ grade 3)	Pembrolizumab, anti-PD-1	Nivolumab, anti-PD-1	Ipilimumab, anti-CTLA-4	Nivolumab + ipilimumab
All	Data missing	34–42% (≤ 2%)	43.5–58.5% (≤ 3%)	58.5–71.5% (4–9.5%)
Rash (not otherwise specified)	13–21% (≤ 2%)	13–21.5% (≤ 1%)	14.5–26% (≤ 2%)	28.5–55% (3–5%)
Pruritus	14–21% (≤ 1%)	17–19% (≤ 1%)	24.5–35.5% (≤ 1%)	33–47% (≤ 2%)
Vitiligo	9–11%	7.5–10.5%	1.5–8.5%	6.5–11%

CTLA-4 cytotoxic T lymphocyte-associated antigen-4, *PD-1* programmed cell death protein 1

with ipilimumab or when immune checkpoint inhibitors are prescribed in combination (5 weeks with anti-PD-1 vs 3–4 weeks with anti-CTLA-4 antibodies, and 2 weeks with the combination of ipilimumab and nivolumab, on average) [4–6, 10, 12, 20, 29]. Delayed eruptions have, however, also been reported [12, 30]. The lesions can also worsen after each cycle of treatment [21].

The clinical presentation is relatively nonspecific, characterized by a morbilliform, maculopapular rash that remains most often of low grade (grades 1 and 2) [12, 19, 20]. It occurs mainly on the trunk and to a lesser degree on the upper limbs and spreads peripherally to the extremities [12, 23, 29] (Figs. 1 and 2). The face is commonly spared [9, 12]. The lesions mainly consist of faint erythematous macules associated with flat-topped, minimally scaly papules which can be confluent. Prominent eruptions on photoexposed sites have occasionally been reported (Fig. 2) [11, 12, 19]. Lesions are usually itchy [30], although sometimes the lesions develop in an asymptomatic manner [29]. Though common, such dermatologic adverse events are often self-limited and quite manageable [12].

This nonspecific maculopapular rash can also represent the initial manifestation of a more characteristic skin disorder induced by immune checkpoint inhibitors, including lichenoid reactions, psoriasis (de novo or flare of known psoriasis), Grover's disease, bullous pemphigoid, or much more rarely life-threatening cutaneous drug reactions (see corresponding sections). It is therefore absolutely paramount to perform an exhaustive dermatologic evaluation (including a skin biopsy in particular) for any atypical, severe, persistent, recurrent or poorly tolerated rash [3, 9].

2.1.3 Histopathologic and Biological Findings

Histopathologic studies carried out in this context have remained relatively scarce [29–33]. The most common feature is an eczema-like spongiotic dermatitis with associated superficial perivascular T-lymphocyte infiltrate which can extend to epidermis, patchy necrotic keratinocytes and scattered to florid eosinophils [3, 9, 11, 29, 31, 32, 34]. Histopathologic aspects can be very reminiscent of a dermal hypersensitivity reaction [11]. Immunohistochemical studies individualize a predominantly CD3/CD4-positive [21, 29, 33–35], a mixed CD4+/CD8+ [30] or a prominent cytotoxic CD8-positive lymphocytic infiltrate [31, 34] (Fig. 3). Less frequently, a lichenoid reaction can also be encountered [9, 23, 31–36] (Fig. 4), as well as other characteristic histopathologic aspects (e.g., psoriasis, Grover's disease, bullous pemphigoid, and granulomatous sarcoid-like dermatitis) (see corresponding sections).

A concomitant increase in the peripheral blood eosinophil count has been reported with ipilimumab-induced skin rash [29]. In our experience, it can be also noted with anti-PD-1 agents.

2.1.4 Management

The clinical severity of the eruption needs to be thoroughly measured prior to any therapeutic decision. This is assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE criteria) (version 4.02), taking into account the extent of the lesions (grade 1, < 10% of the BSA; grade 2, 10–30% of the BSA; grade 3, > 30% of the BSA) and above all the negative impact on health-related quality of life, such as limitation of instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, daily shopping, and preparing meals) or self-care activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, and taking medications) (Fig. 5).

In the vast majority of cases, immune checkpoint inhibitors can be maintained [1, 4, 12, 20], and treatment withholding (either temporarily or permanently) is only rarely needed. Early recognition, diagnosis, intervention and adequate monitoring, however, are required for maintaining dose intensity and mitigating the severity of cutaneous adverse events [4, 29]. Moreover, appropriate counseling and management are critical to minimize deterioration in quality of life. It should be also noted that these cutaneous irAEs, which most often can be managed

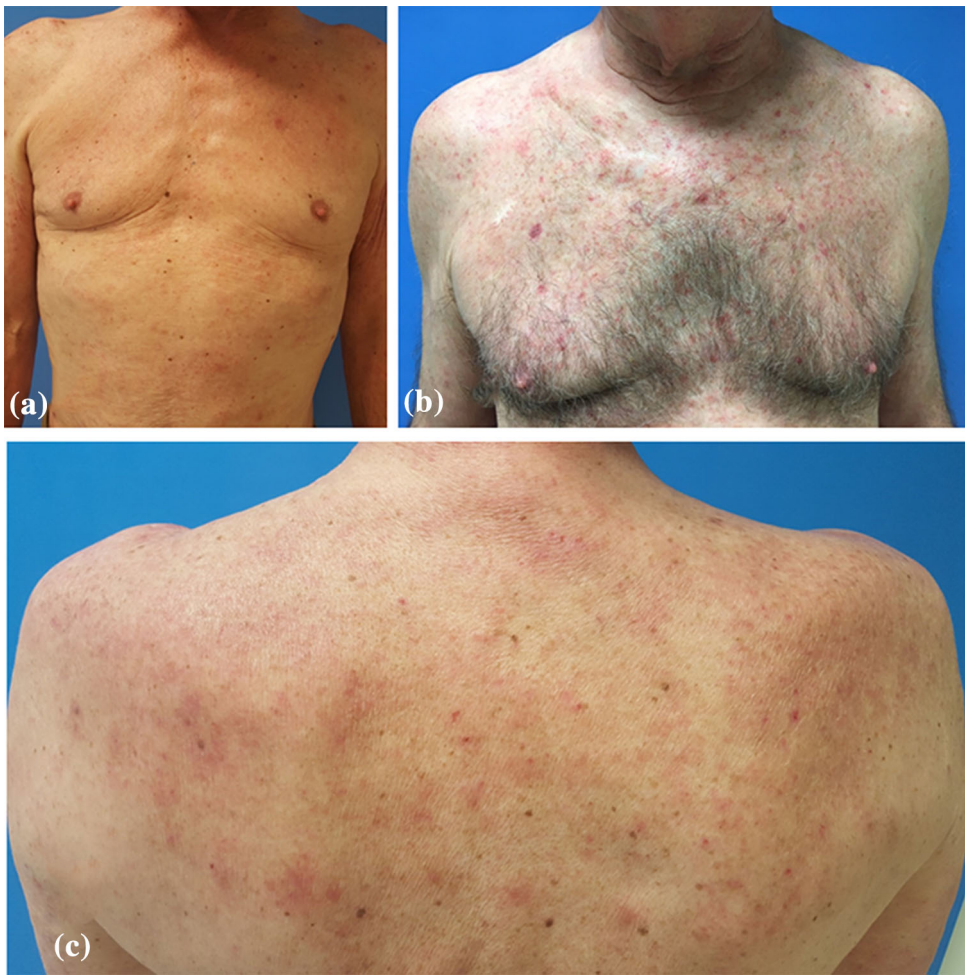

Fig. 1 **a–c** Pruritic maculopapular rash involving the trunk

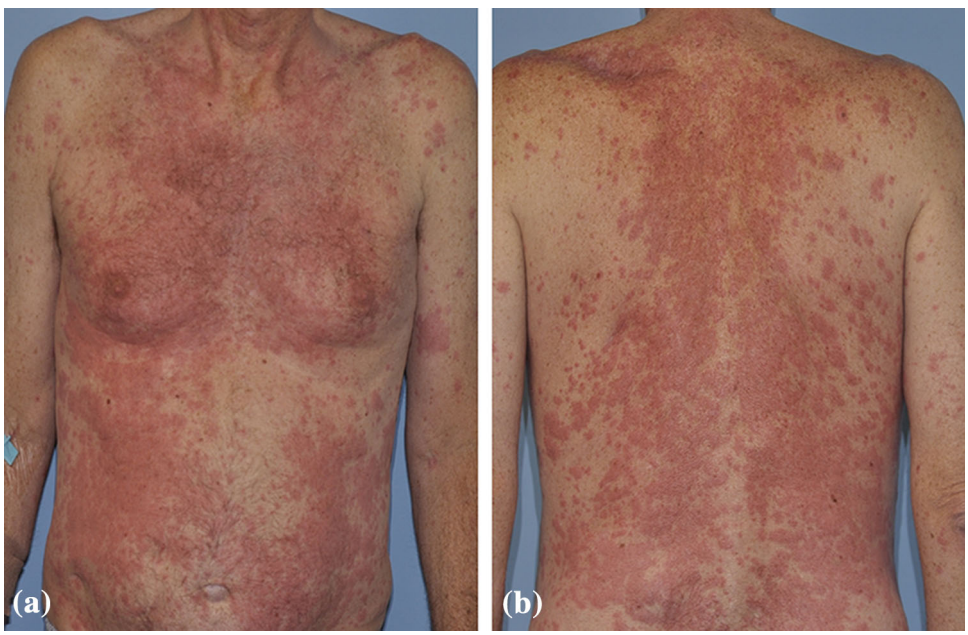

Fig. 2 **a**, **b** Grade 3 maculopapular rash, predominantly on photoexposed areas (photo courtesy of M. Lacouture, MD, Memorial Sloan Kettering Cancer Center, NY, USA)

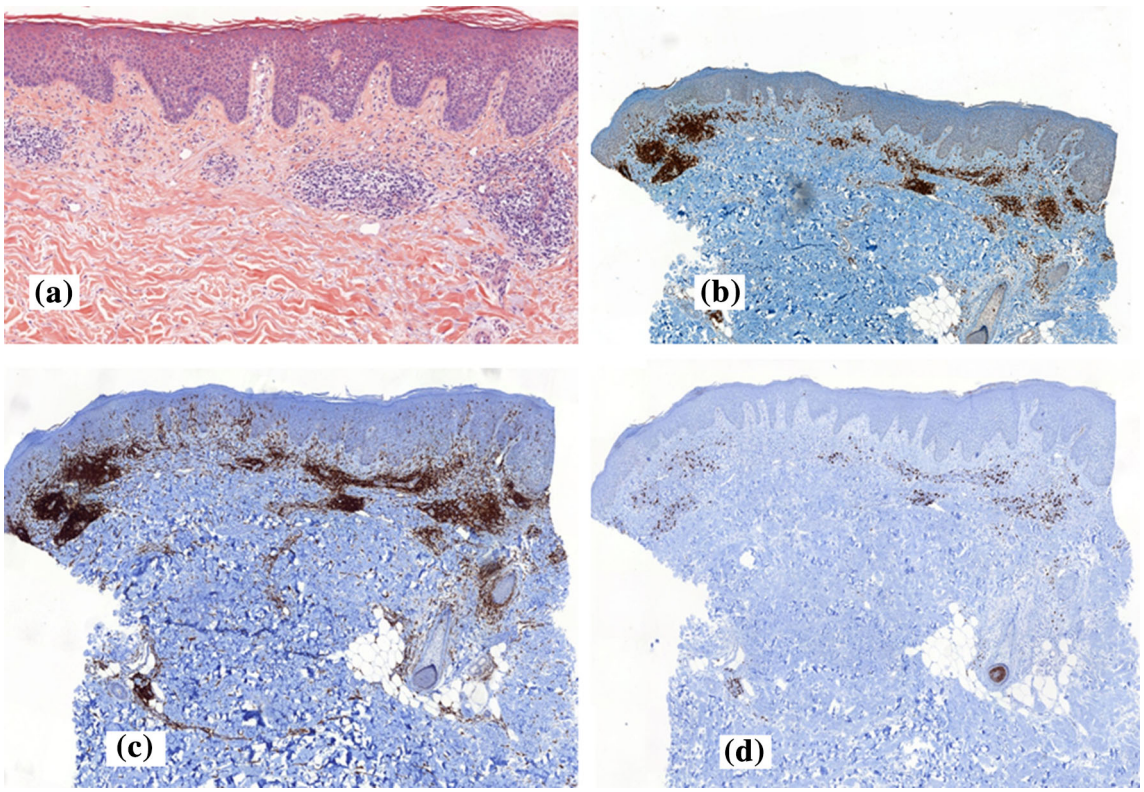

Fig. 3 **a** Eczema-like changes combining a superficial perivascular T-cell infiltrate, a marked spongiosis, a patchy exocytosis and eosinophils (hematoxylin–eosin stain, 10× magnification); **b**–**d** immunostaining reveals a predominantly CD3-positive (**b**)/CD4-positive (**c**) lymphocytic infiltrate, with a weak CD8 staining (**d**) (× 5 magnification)

by tailored treatments, are often long lasting, regressing only slowly even when systemic corticosteroids are prescribed [4].

The management strategy mainly includes prescription of systemic antihistamines, high- to very-high-potency topical steroids (e.g., betamethasone or clobetasol propionate, cream or ointment) and/or topical moisturizers [4–9, 12, 20]. The use of systemic corticosteroids (0.5–1 mg/kg/day) is, in principle, restricted to the management of persistent and severe reactions (i.e., ≥ grade 3). It is, however, uncommonly required in clinical practice; its introduction should be considered collectively and in a multidisciplinary approach, and only after a thorough dermatologic evaluation including a skin biopsy. In particular, the absence of a more specific skin disorder, which may require specific management (see corresponding sections), needs to be ascertained. The same reasoning should be applied for any atypical or persistent lesions. In this regard, we have recently proposed a modified management algorithm [9] for use by practicing oncologists (Fig. 5). According to the product safety information of these products, immunotherapy should theoretically be suspended when systemic corticosteroids are prescribed, and should be resumed when the steroid dose is ≤ 10 mg/day of prednisone equivalent. It has been recently reported, however, that the use of systemic corticosteroids or other immune-modulating drugs in patients treated with anti-PD-1 agents does not seem to interfere with anticancer immune response [4].

2.2 Lichenoid Reactions

A certain number of these maculopapular rashes in fact correspond with lichenoid reactions, with lichenoid interface dermatitis and variable degrees of basal vacuolar changes. This is seen particularly with anti-PD-1/PD-L1 agents [9, 12, 23, 30–36]. The diagnosis is generally made after a histologic analysis, and it is likely that the incidence has remained greatly underestimated. According to some authors [23, 30], it represents the most prevalent identified histologic feature in patients treated with anti-PD-1 therapy. It does not correspond strictly to our own experience, with a higher incidence of eczema-like dermatitis with spongiosis.

2.2.1 Clinical Presentation

The lesions start after several weeks or months of treatment [23, 30, 34–36] and tend to be delayed in comparison to other forms of maculopapular rash [34, 36]. The clinical presentation is variable, and a wide spectrum of lesions can

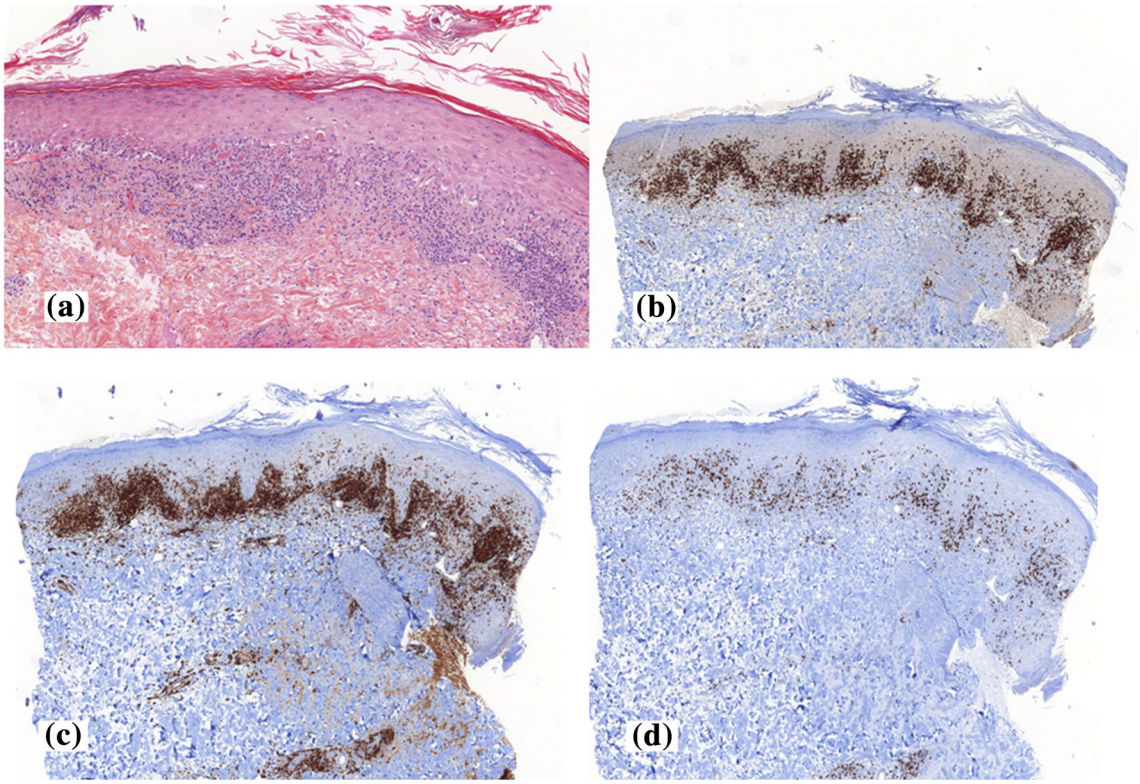

Fig. 4 **a** Lichenoid reaction with band-like T-cell infiltrate, vacuolar interface dermatitis with apoptotic keratinocytes, hyperkeratosis, and hypergranulosis (hematoxylin–eosin stain, 10× magnification); **b**–**d** immunostaining reveals a predominantly CD3-positive (**b**)/CD4-positive (**c**) lymphocytic infiltrate, with a weak CD8 staining (**d**) (5× magnification)

be observed, which can also develop in combination. These lichenoid reactions range from typical lichen planus with flat-topped papules and visible Whickham striae to hypertrophic or papulosquamous lesions. Pruritus can be severe and debilitating [30]. Once again, lesions mainly occur on the trunk and the limbs [23, 34–36], although a spreading of the lesions is possible [12, 19, 30]. A palmoplantar involvement is not uncommon (Fig. 6) [19, 30]. Distinct inverse distribution has also been described [37], as well as lichen planus pemphigoides or lichen sclerosus atrophicus [19, 34]. Lastly, concomitant genital, oral or ungual involvement is possible and needs to be systematically searched (Fig. 6) [19, 23, 30, 36, 38].

2.2.2 Histopathologic findings

Histologically, a superficial band-like lymphohistiocytic infiltrate along the dermal–epidermal junction is seen, with patchy-to-florid vacuolar interface dermatitis and basilar/suprabasilar apoptotic keratinocytes, associated—to varying degrees—with hypergranulosis, acanthosis, spongiosis and eosinophils (Fig. 4) [12, 23, 30, 34–36]. A marked parakeratosis was identified in this setting [23, 32, 38]. Ancillary immunostaining individualizes a mixed CD4+/CD8+ or a predominantly CD4+ T-cell infiltrate [21, 29, 30, 34, 35]. Finally, lichenoid dermatitis can be also associated with spongiotic changes together with an epidermal eosinophil infiltrate, as described by Shi et al. [30].

2.2.3 Management

Treatment is based on topical steroids and, much more rarely, on oral corticosteroids, phototherapy, or acitretin [19, 30, 34–36]. In most cases, the immune checkpoint blockade therapy can be maintained [30, 31, 34, 35, 37], although the psychosocial impairment can be pronounced. Lesions that last for months after the discontinuation of immunotherapy may also be encountered.

2.3 Psoriasis

The risk of developing psoriasis with anti-PD-1/PD-L1 or anti-CTLA-4 agents is also well-established [9, 39], even though the actual incidence still needs to be determined. Exacerbation or occurrence of psoriatic arthritis and even more skin psoriasis can be observed [40–43].

Fig. 5 Proposed management algorithm for maculopapular rashes. *ADL* activities of daily living, *BSA* body surface area

2.3.1 Clinical Presentation

In the majority of cases, patients have a personal history of psoriasis. De novo psoriasis is also possible, which may occur later after several months of treatment [9, 19, 43–45]. Plaque psoriasis is the most frequent presentation, although guttate, pustular or inverse psoriasis and sebopsoriasis have been described [43]. The scalp can also be affected, as can the palmoplantar areas (Fig. 7) [46]. Psoriatic arthritis can also occur [41], even in patients with no personal or family history of psoriasis.

2.3.2 Pathogenesis

The pathogenesis has yet to be defined. However, it has been shown that the PD-1 axis downregulates T-helper cell 1 (Th1)/Th17 signaling pathway [47]. Therefore, PD-1 blockade could promote a secondary overexpression of proinflammatory cytokines mediated by Th17 lymphocytes. In this regard, Tanaka et al. recently found that these patients presented elevated serum levels of interleukin-6 [45].

2.3.3 Histopathologic Findings

The histologic features are strictly similar to those seen in classic psoriasis vulgaris (Fig. 7). On the other hand, a lower expression of PD-L1 and PD-1 by the keratinocytes has been reported for the PD-1-induced psoriasis [44].

2.3.4 Management

Management needs to be carried out using a multidisciplinary approach. In most cases, immunotherapy can be maintained and the patient managed by topical treatments (e.g., vitamin D analogs, topical corticosteroids) [9, 43]. Acitretin and UVB therapy have also been administered in some cases [43]. There are no data available regarding the efficacy and safety of anti-tumor necrosis factor alpha (anti-TNF-α) in this context. In our experience, however,

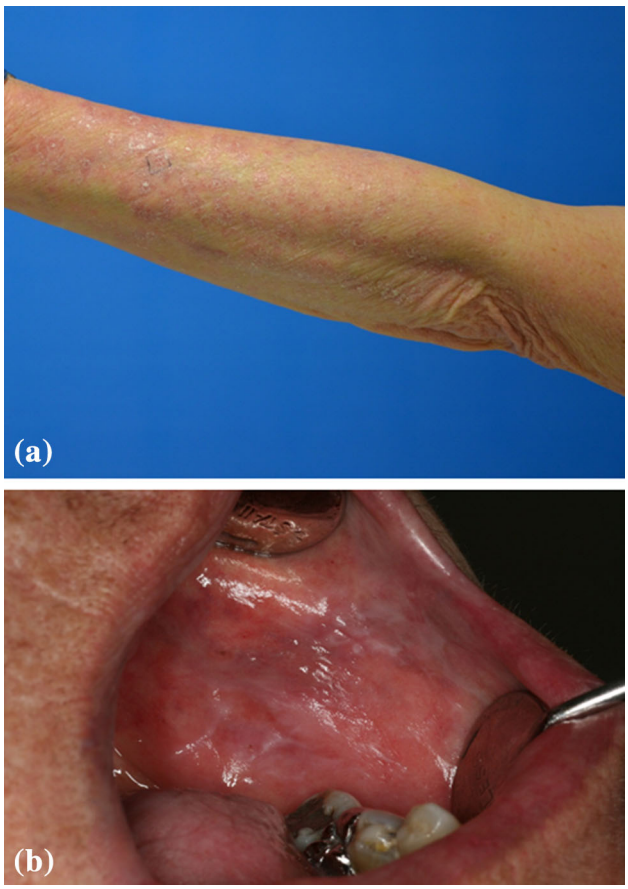

Fig. 6 Lichenoid reaction involving the skin (**a**) and oral mucosa (**b**), with visible reticular striae

we have not observed a significant improvement in patients with severe psoriasis. This corroborates the recent data of Tanaka et al., suggesting a mechanism that is not directly dependent on TNF-α in these patients [45].

Finally, several patients developing psoriatic arthritis with anti-PD-1 therapy have been successfully managed with methotrexate and low doses of corticosteroids, without treatment discontinuation [48, 49].

2.4 Life-Threatening Cutaneous Drug Reactions

Maculopapular rash can also represent the initial clinical manifestation of a more severe cutaneous drug reaction. Although it has been extremely rarely described with these monoclonal antibodies, several cases of extensive exfoliative dermatitis, Stevens-Johnson syndrome, or toxic epidermal necrolysis have nonetheless been reported [3, 19, 29, 31, 50, 51]. In this context, Vivar et al. noted a dense CD8-positive T-cell infiltrate within the dermal–epidermal–junction, together with an increase in PD-L1 expression in both lymphocytes and keratinocytes [50]. It should also be emphasized that these severe cutaneous adverse reactions can also be delayed, developing after only several cycles of treatment [50, 51]. The occurrence of erythema multiforme, acute generalized exanthematous pustulosis or drug reaction with eosinophilia and systemic symptoms (DRESS) has also been described with anti-CTLA-4 or anti-PD-1 therapies [23, 52–55].

Finally, the incidence of infusion-related reactions appears to be higher with anti-PD-L1 antibodies, especially with avelumab (about 10%, during the first or second administration) [56, 57].

2.5 Grover's Disease

The occurrence of Grover's disease has occasionally been reported with ipilimumab [58–60]. More recently, we and other authors have also noted Grover's disease with anti-PD-1 therapy [33]. The clinical presentation is polymorphic, presenting as a more or less diffuse pruritic papulokeratotic or vesicular eruption [58–60]. The diagnosis is only confirmed after a skin biopsy, and its incidence is hence probably underestimated. Suprabasal acantholysis is isolated (Darier-like form), and is associated with a predominantly CD4+ T-lymphocyte dermal infiltrate [59, 60]. A Th2-mediated immunologic mechanism has been proposed [60]. The lesions appear fairly rapidly after the initiation of the treatment [58–60], and they can last for several months after the discontinuation of immunotherapy [59, 60].

3 Pruritus

Pruritus is among the most prevalent irAEs induced by immune checkpoint inhibitors. By meta-analysis, its all-grade incidence ranges from 13 to 20% with nivolumab and pembrolizumab, respectively (with a high-grade incidence of < 3%) [12]. It is even more frequent with ipilimumab monotherapy or when used in combination (Table 1) [6, 13–18]. Contrariwise, the incidence is slightly lower with anti-PD-L1 therapy [24–28].

It typically develops concomitantly with maculopapular rash, although it can also precede it or be associated with a normal-appearing skin. The scalp is frequently involved, but the face is generally spared. An associated xerosis should be systematically probed for [4, 9, 19, 20] and treated.

It can severely affect the health-related quality of life and psychological well-being of patients. The efficacy of aprepitant (80 mg/day for 5 days) has recently been underlined in one single patient who developed severe refractory pruritus during nivolumab treatment [61].

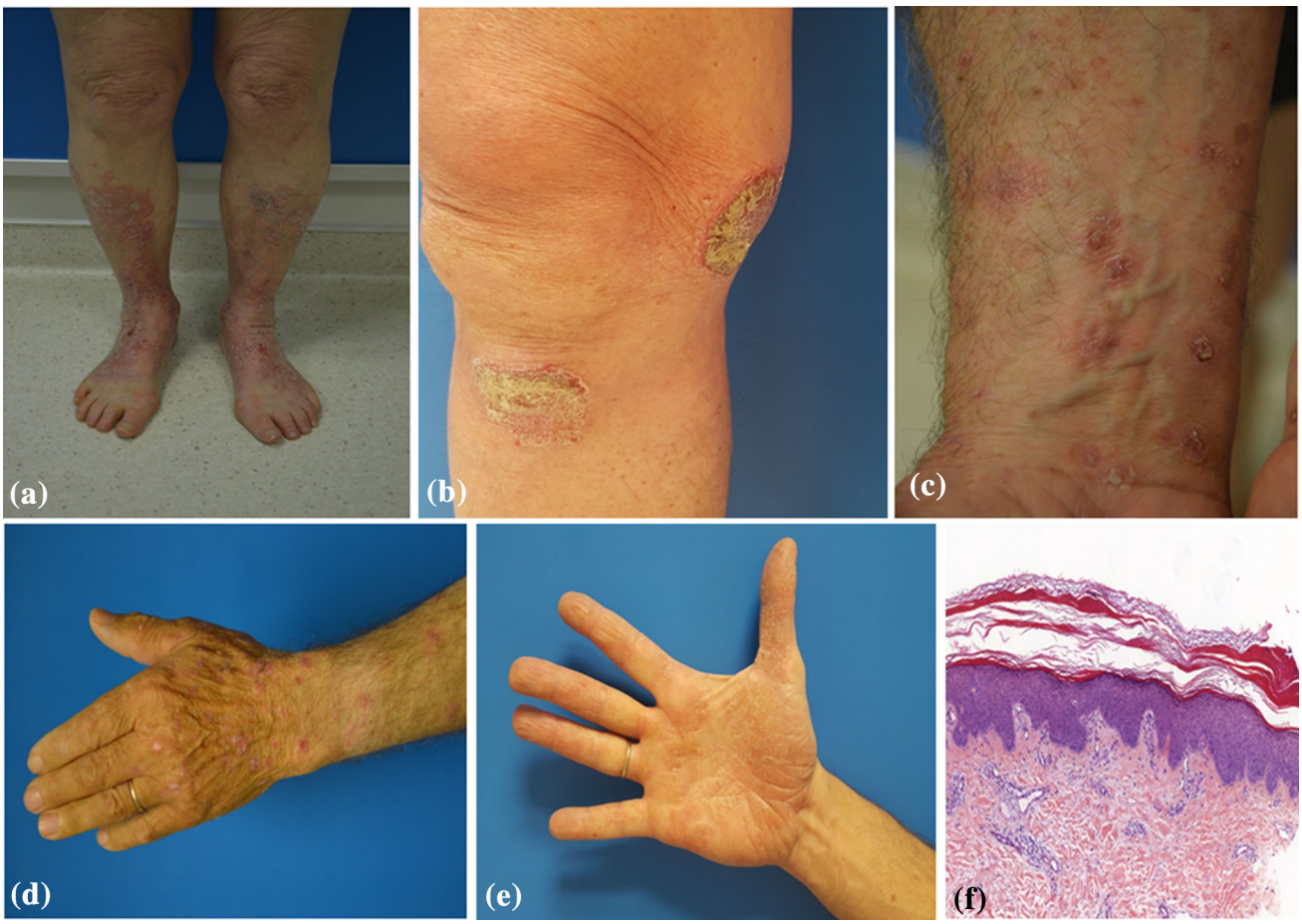

Fig. 7 **a–e** Guttate, palmar and plaque psoriasis induced by anti-PD-1/PD-L1 agents; **f** skin biopsy revealing an intense and confluent epidermal hyperkeratosis, with parakeratosis and acanthosis (hematoxylin–eosin stain, 10× magnification). *PD-1* programmed cell death protein 1, *PD-L1* programmed death ligand 1

4 Vitiligo

4.1 Incidence

Vitiligo occurs frequently in melanoma patients treated with anti-PD-1 agents [9]. Conversely, it is exceptionally described in patients treated for other types of cancer [62, 63]. By meta-analysis, its overall incidence was recently estimated to be 8.3 and 7.5% for pembrolizumab and nivolumab, respectively [12, 64]. A higher reported incidence (about 25%) has been noted in more specific dermatologic studies conducted in both prospective and retrospective ways [22, 65]. By contrast, it is slightly less common with ipilimumab (Table 1) [14, 15, 64]. Data available on vitiligo induced by PD-L1 inhibitors in patients with melanoma remain really scarce; most of the pivotal studies have been conducted in other solid cancers [24].

Immune checkpoint inhibitor-induced vitiligo potentially corresponds to a cross-reaction against antigens shared by melanoma cells and normal melanocytes (e.g., MART-1, GP100, TRP1–2 or tyrosinase) [10, 22, 65].

4.2 Clinical Presentation

Vitiligo develops progressively after several months of treatment [22, 23, 65, 66], with most often a bilateral and symmetrical distribution [22, 23]. A spreading of the lesions can be also observed [10, 22]. The occurrence of these lesions can be preceded by an inflammatory phase [22]. Focal or localized vitiligo, sometimes surrounding cutaneous metastases or lymph node dissection scar, is also possible [22, 66]. Regression of melanocytic nevi can also occur (Fig. 8) [11]. A concomitant depigmentation of the eyelashes (Fig. 8), eyebrows or scalp hair is not uncommon [19], which can also occur in an isolated manner. Based on a short series, Larsabal et al. recently proposed that these vitiligo-like lesions differ from vitiligo, both at the clinical level (e.g., more localized and unsymmetrical lesions; predominance in chronically UV-exposed areas; no associated Koebner phenomenon, i.e., with a relative sparing of

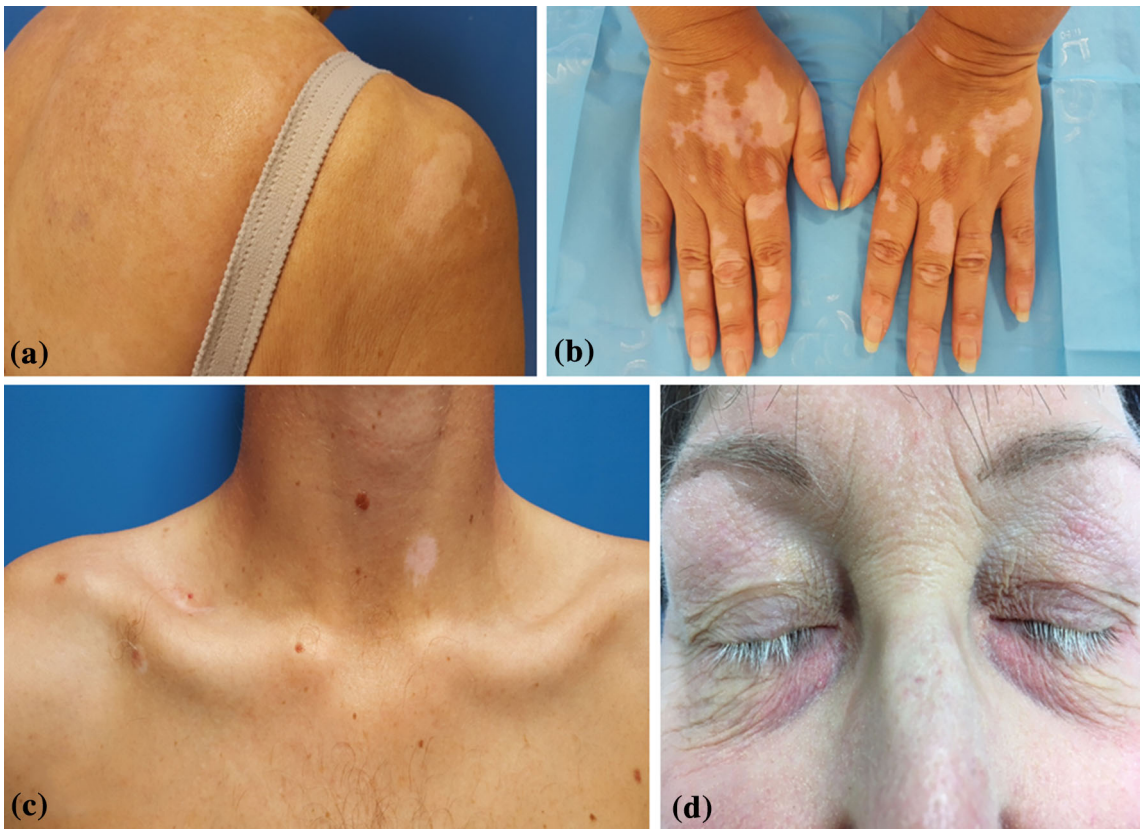

Fig. 8 **a** Patchy lesions of vitiligo; **b** bilateral lesions involving the dorsal aspect of the hands; **c** regression of melanocytic nevi; **d** typical depigmentation of the eyelashes

anatomic sites undergoing repetitive frictions) and histologically (particularly, overexpression of CXCR3 by the CD8+ T-lymphocyte infiltrate), and are suggestive of a distinct pathophysiologic mechanism [66].

Such vitiligo-like lesions most often persist after treatment discontinuation [10]. Patients therefore need to be informed, particularly in an adjuvant setting. Interestingly, recently a single case of nivolumab-induced vitiligo repigmentation developing in association with melanoma relapse has been reported [67]. Moreover, development of vitiligo in patients treated for advanced melanoma with nivolumab has been associated with both an objective response and a prolonged overall survival [22, 65]. Therefore, vitiligo occurrence may represent a positive prognostic factor [10, 20, 22, 65].

5 Autoimmune Skin Disorders

Patients exhibiting a preexisting autoimmune disorder were initially excluded from the pivotal studies, which limits the available data. It is nonetheless well-established that the PD-1/PD-L1 signaling pathway is involved in the pathogenesis of several autoimmune diseases [68], and it is now also clear that anti-CTLA-4 and anti-PD-1 agents can reactivate underlying autoimmune disorders (e.g., Crohn's disease, rheumatoid arthritis, Sjögren's syndrome, myositis, autoimmune thyroiditis, autoimmune thrombocytopenic purpura) [40–42]. Moreover, these monoclonal antibodies can also induce the development of de novo autoimmune skin diseases (e.g., bullous pemphigoid, psoriasis, vasculitis, Sjögren's syndrome, dermatomyositis).

5.1 Bullous Pemphigoid

Anti-PD-1 (nivolumab, pembrolizumab) or anti-PD-L1 (durvalumab, atezolizumab) agents have been shown to result in a higher risk of developing immune-related bullous pemphigoid [23, 69–74]. Worsening of a preexisting bullous pemphigoid is also possible, and this can also occur after treatment with anti-CTLA-4 antibodies [75].

Bullous pemphigoid blisters can appear rapidly or only after several months of treatment (Fig. 9) [72]. They are most often preceded by pruritus and a nonspecific maculopapular eruption [69, 72, 73]. Mucosal involvement is unusual [69, 71]. Direct immunofluorescence reveals linear deposits of immunoglobulin G (IgG) and complement component 3 (C3) at the basal membrane zone. While anti-BP230 antibodies can sometimes be detected [69], analysis by enzyme-linked immunosorbent assay most often picks

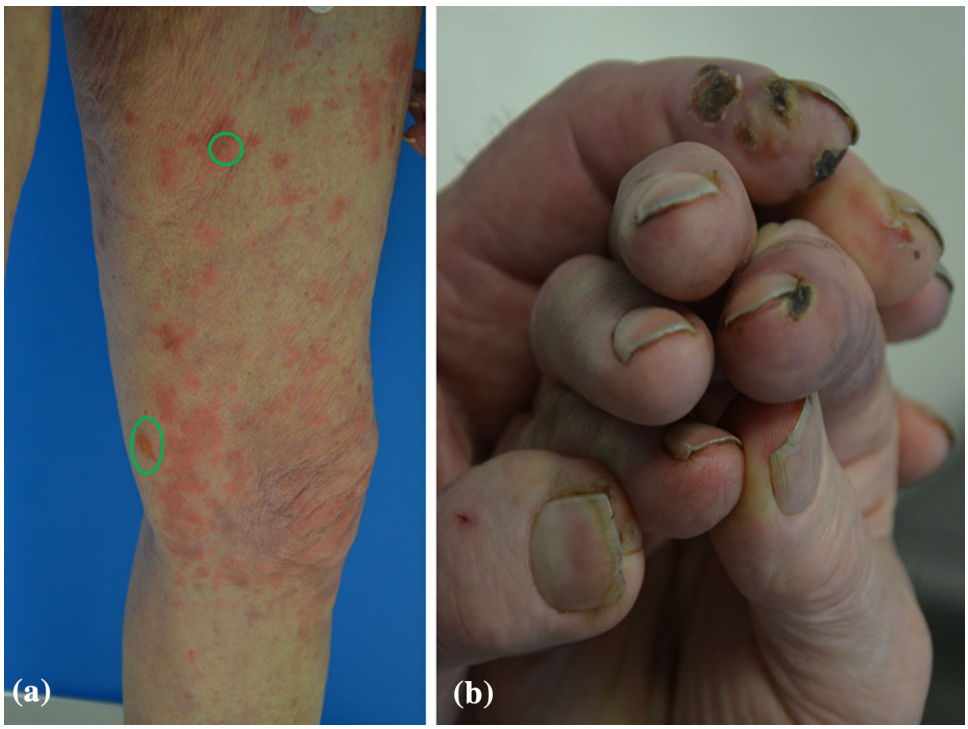

Fig. 9 **a** Bullous pemphigoid combining maculopapular rash and blisters (see green circles); **b** Vasculitis with digit necrosis and apparent livedo

up antibodies targeting the hemidesmosome component BP180 [69–73]. The mechanism underlying immunotherapy-induced bullous pemphigoid has not been characterized, although the reaction could be secondary to T-cell activation against this antigen, which may also be expressed on the surface of certain types of cancer cells [69, 70].

A careful management is required, relying mainly on topical or systemic corticosteroids. More recently, the use of rituximab or omalizumab has been proposed [71, 72]. Treatment interruption is often required, and immunotherapy is resumed on a case-by-case basis, depending on the control of the bullous lesions and according to the oncologic setting [70–74]. The persistence of lesions several months after the discontinuation of anti-PD-1 treatment has also been reported [69]. Lastly, it has been suggested that the development of bullous pemphigoid in this setting may be associated with a better clinical outcome [69, 73].

No case of pemphigus vulgaris has been recorded. Detection of anti-desmoglein or anti-plakin antibodies, however, has been described in a few patients receiving nivolumab treatment [71, 76]. In addition, one case of dermatitis herpetiformis has been noted with ipilimumab [11].

5.2 Dermatomyositis

Several cases, with fairly classic cutaneous findings of dermatomyositis, have been reported with ipilimumab treatment [77, 78]. The lesions can appear rapidly, as of the first cycle of antibody treatment [77]. Additional cases have also been observed with anti-PD-1 therapy (ongoing publication). The immunologic profile is yet to be determined, with anti-Jo1 antibodies apparently being negative in this setting [77, 78]. Polymyositis, without any skin involvement, is also described with anti-CTLA-4, anti-PD-1 and anti-PD-L1 antibodies [40, 41, 79, 80].

5.3 Vasculitis

We have observed exceptional cases of severe vasculitis with anti-PD-1, with livedo and digital necrosis associated with a very high titer of antinuclear antibodies (Fig. 9). A similar setting has been reported, without detectable immunologic findings [81] or with the presence of anti-SSA antibodies and cryoglobulin [80].

5.4 Sjögren's Syndrome

The occurrence—or worsening—of Sjögren's syndrome, which can potentially be severe, has been reported sporadically with anti-PD-1 (together with arthritis, sicca syndrome, and positivity of antinuclear and anti-SSA antibodies) [40, 41, 80]. It needs to be pointed out that changes in the expression of PD-1/PD-L1 have previously been reported in Sjögren's syndrome [68], particularly with regard to the periglandular lymphocytic infiltrate.

The occurrence of isolated sicca syndrome with salivary hypofunction, without joint involvement or associated immunologic findings is, on the other hand, much more

common in clinical practice [82]. It can be severe and can occur abruptly [83]. It develops secondary to T-lymphocyte infiltration, with sialadenitis and a variable Chisholm score (see corresponding sections). Ophthalmologic involvement is much less frequent [83].

6 Other Cutaneous Toxicities

6.1 Sarcoidosis

The occurrence of sarcoidosis with anti-PD-1/PD-L1 or with ipilimumab treatment is not uncommon. An exacerbation of a preexisting sarcoidosis is also possible [42, 84]. The most commonly involved sites are the lungs (e.g., pulmonary micronodular and ground-glass infiltrates, mediastinal and hilar lymphadenopathy) [85–87], and it can sometimes be mistaken for cancer progression. Other organs can be involved, such as eyes, bones, kidney, spleen, the nervous system, joints with Löfgren's syndrome, and the skin [28, 84–91].

Immune checkpoint-related cutaneous sarcoidosis mainly manifests in the form of subcutaneous embedded erythematous nodules [84, 87, 92], with non-caseating epithelioid granuloma. Other forms have been reported: papules or coalescing plaques of varying degrees [86–88], annular lesions [85], exclusive facial involvement [91], and a specific localization at previous scar sites [87, 90] or tattoo sarcoidosis [88]. They most often occur in association with pulmonary involvement, although they are sometimes isolated [85, 91].

Systemic corticosteroids generally allow for regression of the lesions, and the immunotherapy can most often be resumed. The isolated cutaneous lesions can also be treated with topical corticosteroids [89] or synthetic anti-malarial drugs [91].

Some authors consider immunotherapy-induced sarcoidosis to be a paradoxical reaction [87, 91, 92]. Indeed, an upregulation of PD-1 by the T CD4+ lymphocytes of patients with sarcoidosis has recently been shown [93].

6.2 Sweet's Syndrome

Several cases have been noted with ipilimumab [94–96] and more recently with nivolumab treatment [19]. Localized acral variants ("neutrophilic dermatosis of the hands") can also occur [94]. These lesions respond rapidly to oral corticosteroids.

Two cases of pyoderma gangrenosum have also been reported with ipilimumab [52, 97].

6.3 Acneiform Rash and Papulopustular Rosacea

An acneiform rash (or papulopustular folliculitis), mainly on the torso, can sometimes be seen with anti-CTLA-4 [54, 98], anti-PD-1 or anti-PD-L1 monoclonal antibodies [11, 23, 99, 100]. A preexisting rosacea can be also exacerbated by immunotherapy, mainly in the form of facial papulopustular rosacea [21, 98, 101].

6.4 Infrequent Toxicities

A wide range of other dermatologic reactions has been sporadically described with immune checkpoint inhibitors. They are listed in Table 2.

7 Hair and Nail Toxicities

7.1 Alopecia

In several pivotal studies, alopecia has been noted in 1–2% of the patients treated with anti-PD-1 or anti-PD-L1 agents [4, 12, 19, 27]. It corresponds to a partial alopecia (alopecia areata involving scalp hair, eyebrows or beard) or a more diffuse universalis type (Fig. 10) [105]. In our experience, it is more frequent and more severe with ipilimumab. Histologic findings reveal a non-scarring alopecia with a perifollicular T-cell infiltrate [105]. Regrown hair frequently exhibits poliosis [105].

Table 2 Sporadically reported dermatologic toxicities with immune checkpoint blockade therapy

Eruptive keratoacanthomas [103], actinic keratoses and squamous cell carcinomas [23]
Erythema-nodosum-like panniculitis [102]
Radiosensitization [54, 104]
Grover's disease [58–60]
Neutrophilic dermatoses (Sweet's syndrome, pyoderma gangrenosum) [52, 94–97]
Dermatomyositis [77–79]
Sjögren's syndrome [83]
Necrotizing vasculitis [81]
Acneiform eruption [23, 95–97], papulopustular rosacea [21, 98, 101]
Annular granuloma
Peritumoral inflammatory cellulitis [19]
Toxic epidermal necrolysis, Stevens-Johnson syndrome, AGEP, DRESS, erythema multiforme [3, 23, 50–55]
Photosensitivity [4, 11, 20, 23, 54]
Urticaria [11]
Alopecia, alopecia areata, hair repigmentation [11, 19, 105, 106]
Sclerodermoid reaction [107]
Nail changes [49, 105]

AGEP acute generalized exanthematous pustulosis, *DRESS* drug reaction with eosinophilia and systemic symptoms

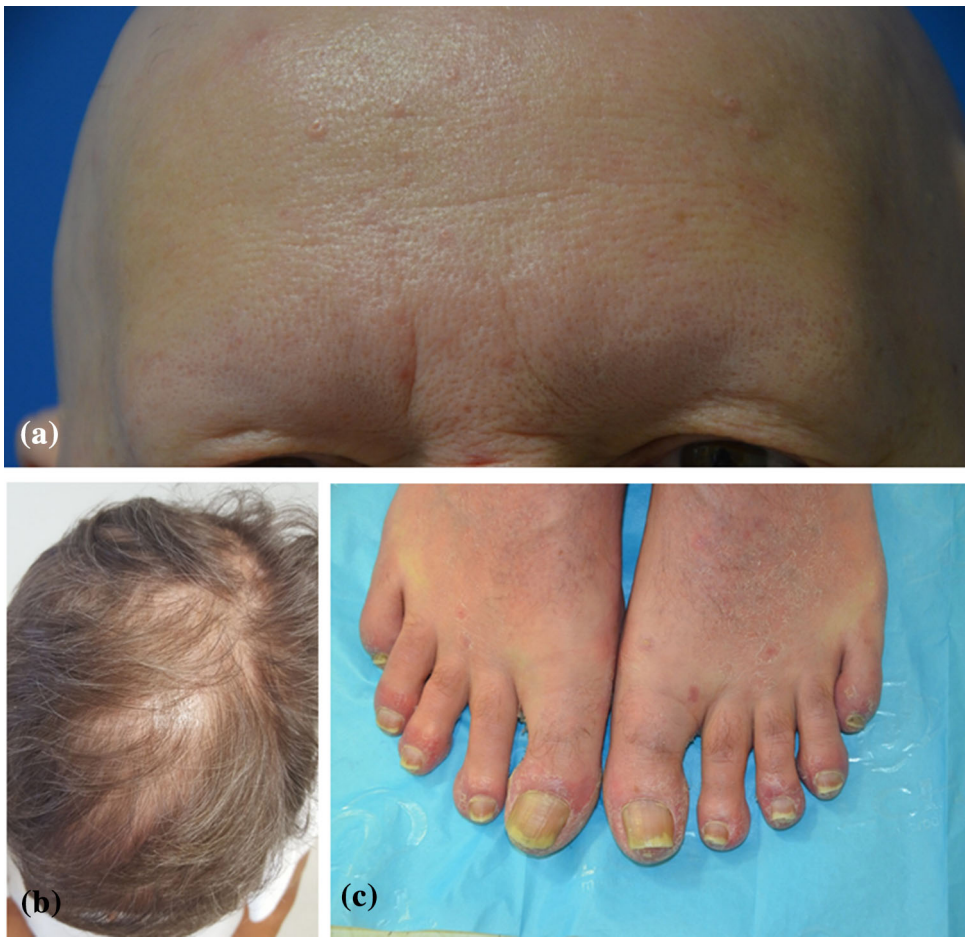

Fig. 10 **a** Diffuse alopecia universalis (involving scalp hair and eyebrows); **b** grade 1 alopecia; **c** nail changes with paronychia (in a patient with associated cutaneous lichenoid reaction)

A change in the texture of the hair has also been described sporadically [108], and it is not uncommon to encounter this in clinical practice. Likewise, depigmentation of the scalp hair, eyelashes or eyebrows is common in patients treated for melanoma, which is often associated with vitiligo lesions. By contrast, Rivera et al. have very recently reported a series of 14 patients treated with anti-PD-1/PD-L1 therapies for lung cancer who exhibited a diffuse progressive hair repigmentation [106]. This repigmentation started in the occipital and temporal areas, extending secondarily to frontal and parietal areas. Remarkably, 13 of the 14 patients remained in treatment with a partial response or a stable disease.

7.2 Nail Changes

Nail changes have only rarely been reported in the literature [105]. We have, however, observed several cases of nail dystrophy with immunotherapy, and these were sometimes associated with an onychomadesis or a proximal onychoschizia. Diffuse onycholysis and paronychia involving all finger- or toenails can also develop.

Although no histologic analyses are available to date, it is likely that these nail changes are mostly psoriatic or lichenoid in nature (Fig. 10) [49].

8 Oral Mucosal Toxicities

Patients receiving anti-PD-1/PD-L1 treatment can also exhibit oral symptoms, which are often neglected by clinicians. Xerostomia, oral lichenoid reactions and, to a lesser extent, dysgeusia, represent the main manifestations [82]. Oral involvement is clearly less frequent with anti-CTLA-4 [82].

8.1 Xerostomia

Xerostomia has been reported to occur in 4–7% and in 3% with anti-PD-1 and anti-PD-L1 agents, respectively [14, 26, 82, 100]. While it has been reported to be limited to grade 1/2 in all cases, we have personally seen severe forms in some patients that had a substantial functional impact.

Histologically, a predominantly CD4+/CD8+ T-cell infiltrate is noted, surrounding the accessory salivary glands. The detection of serum anti-SSA/SSB antibodies is typically negative, and the xerostomia in general remains isolated, aside from in the exceptional setting of Sjögren's syndrome.

8.2 Oral Lichenoid Reactions

These reactions are not uncommon in clinical practice and probably remain undiagnosed [23, 30, 34, 38]. They most often occur in an isolated manner. They can, however, be associated with skin, nail or genital lichenoid lesions [38].

Reticulated white streaks, consistent with Wickham's striae, represent the most common presentation (Fig. 6), although plaque-like, ulcerative or atrophic/erythematous lesions are also described [38]. The keratinized and non-keratinized mucosae can be affected [82]. These lesions most often remain self-limited and of low grade.

The band-like T-cell infiltrate is predominantly CD4/CD8 positive [38]. The treatment relies first and foremost on topical corticosteroids, and oral lichenoid reactions do not lead to treatment interruption.

8.3 Dysgeusia

Dysgeusia affects less than 3% of the patients treated with anti-PD-1/PD-L1 therapies [12, 14, 27].

9 Conclusion

The therapeutic use of immune checkpoint inhibitors is rapidly increasing. Of note, cutaneous toxicities represent one of the most frequent irAEs. Dermatologic safety profiles for anti-PD-1/PD-L1 and anti-CTLA-4 monoclonal antibodies appear to be very similar (class effect), yet a higher incidence is observed with the latter or when used in combination. About one-third of treated patients are faced with dermatologic adverse events, which are mostly of immunologic origin. Nonspecific macular papular rash and pruritus represent the most common manifestations, but more characteristic skin adverse events can also occur, e.g., lichenoid dermatitis, psoriasis, Grover's disease, vitiligo, sarcoidosis or autoimmune bullous disorders. In the same way, mucosal, hair and nail changes are likely to be underestimated by physicians.

Although dermatologic irAEs induced by PD-1/PD-L1 or CTLA-4 blockade therapy usually remain self-limiting and readily manageable, it is crucial to perform an exhaustive dermatologic evaluation for any severe, persistent or atypical lesions. Early recognition and appropriate management are crucial for restricting dose-limiting toxicities.

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Compliance with Ethical Standards

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