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REVIEW ARTICLE

Cutaneous toxicities of new treatments for melanoma

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Abstract
New drugs against advanced melanoma have emerged during last decade. Target therapy and immunotherapy have changed the management of patients with metastatic disease. Along with its generalized use, drug toxicities have appeared and the skin is the target organ of a significant part of them. This revision summarizes the most common side effects and consensus management to improve the compliance of therapies and patients' quality of life. Among the BRAF inhibitors, main cutaneous side effects are photosensitivity, plantar hyperkeratosis, and the appearance of verrucal keratosis or squamous cell carcinoma. Special attention must be paid to the development of new primary melanomas or changes on nevi during BRAF inhibitor therapy. The most common cutaneous side effects of immunotherapy are rash, pruritus, and vitiligo. It remains controversial the possible role of these toxicities as markers of response to therapy.

Keywords Melanoma · Target therapy · Immunotherapy · Toxicity · Nivolumab · Pembrolizumab

Introduction

In recent years, the therapeutic arsenal for the treatment of metastatic melanoma has undergone a revolution. The development of target therapy (BRAF and MEK inhibitors) and immunotherapy (anti-CTLA4 and anti-PD-1) has substantially changed the life expectancy of patients with metastatic disease. Both BRAF inhibitors (vemurafenib [1] and dabrafenib [2]) alone or in combination with MEK inhibitors (trametinib [3] and cobimetinib [4]), as well as immune-checkpoints inhibitor therapy anti-CTLA4 (ipilimumab [5]) and anti-PD-1 (nivolumab [6] and pembrolizumab [7]) have shown increased survival in patients with metastatic melanoma. Moreover, some of these drugs will be soon used as adjuvant therapy in melanoma-free disease patients at high risk of recurrence [8, 9]. While the benefits of these new drugs are beyond doubt, their adverse effects should not be underestimated. The skin is the target organ of a significant part of this toxicity. This review summarizes the various cutaneous toxicities of anti-melanoma treatments and discusses its appropriate management.

Cutaneous toxicities of BRAF inhibitors

If we consider together the different forms of cutaneous toxicities of BRAF inhibitor (BRAF-i) therapy, we could state that skin toxicities are the most common side effect of this therapy [10]. An easy way to classify them is dividing them between tumoral and non-tumoral adverse events (Table 1) [11]. Most of the skin toxicity from BRAF-i therapy occurs between weeks 8 and 36 of the treatment [12].

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Table 1 Cutaneous toxicities of new treatments for melanoma

I: Cutaneous toxicities of BRAF inhibitors
I.1. Non-tumoral cutaneous toxicities
Photosensitivity and radiation sensitivity
Skin rash
Acantholytic dermatoses
Granulomatous rash
Plantar hyperkeratosis
Alopecia/hair changes
Panniculitis
Keratosis pilaris
Xerosis
Other specific dermatosis
Sweet syndrome
toxic epidermal necrolysis
DRESS syndrome
Cutaneous sarcoidosis
Hidradenitis suppurativa
I.2. Tumoral cutaneous toxicities
Cutaneous squamous cell carcinomas
Verrucal keratosis
Development of new primary melanomas and nevi changes
II. Cutaneous toxicity of BRAF inhibitor/MEK inhibitor combination therapy
Pustular eruption
III. Immunotherapy cutaneous adverse events
Rash
Pruritus
Vitiligo
Bullous pemphigoid
Psoriasis exacerbation/psoriasiform reactions
Other
DRESS syndrome
Sweet syndrome
Stevens–Johnson syndrome/toxic epidermal necrolysis

Non-tumoral cutaneous toxicities

The clinical clues for the differential diagnosis of BRAF-i non-tumoral cutaneous toxicities are summarized in Fig. 1.

Photosensitivity and radiation sensitivity

Photosensitivity is a typical side effect of vemurafenib, whereas it is rarely present with dabrafenib, due to their different chemical structure. Its frequency was seen up to 52% of patients treated with vemurafenib in the Phase 2 trial [13].

Physiopathology: vemurafenib reduces the minimum erythematous dose against UVA and it causes a striking UVA-dependent phototoxicity [14, 15].

Diagnosis: clinical history of appearance of sunburn within minutes of sun exposure on the most exposed areas of the body: face, ears, and outer side of the arms and neck [16] (Fig. 2).

Management: photosensitivity is an adverse effect that may reduce the quality of life of the patient, but it is easily manageable with proper photoprotection, use of UVA-tailored sunscreens, and ultraviolet-dense clothing. Patients should be instructed about photoprotection including the following main points: to limit their sun exposure, wear UVA protective clothing, and use a hat as well as a sunscreen active against UVA. It is important to remind patients of the risk of sunburn from exposure through a car glass or window and white clothes. UVA-specific properties such as constant intensity regardless of daylight and season should be also communicated to patients. Photosensitivity disappears quickly once the drug is discontinued [17].

Acute radiodermatitis has also been reported in patients who have been concurrently treated with radiotherapy in combination with BRAF-i [18]. A multicenter study on radiosensitization in melanoma patients showed that concomitant treatment with vemurafenib induced acute radiodermatitis more frequently than treatment with dabrafenib (40 vs 26%). In line with these findings, the ex vivo analysis of chromosomal breaks in patients under vemurafenib significantly increased radiosensitivity, and even for patients switched from vemurafenib to dabrafenib, but not for patients on dabrafenib only. No toxicities were reported after stereotactic radiation treatment. In any case, the likely increased radiosensitivity induced by BRAF inhibitors seems to be well tolerable and acceptable [19].

Skin rash

In the pivotal trials of vemurafenib and dabrafenib, the appearance of non-specific rashes was described in 3–52% of patients [20]. Subsequently, different groups of dermatologists have worked to better characterize these lesions into the following categories:

Acantholytic dermatoses An important part of these eruptions is clinically and histologically indistinguishable from a well-known dermatological disease named Grover's disease [21]. It consists of small (2–3 mm in diameter), scaly, erythematous, and pruritic papules mainly distributed on the trunk and the proximal upper arms (Fig. 2). This eruption has been described in up to 42% of patients receiving dabrafenib and 38% of those treated with vemurafenib [22].

Diagnosis: clinical examination allows the diagnosis of the disease. Dermoscopy improves the recognition of acantholytic dyskeratomas [23]. Skin biopsy is not usually necessary in this condition, but if performed, acantholysis and dyskeratosis are the main histological findings.

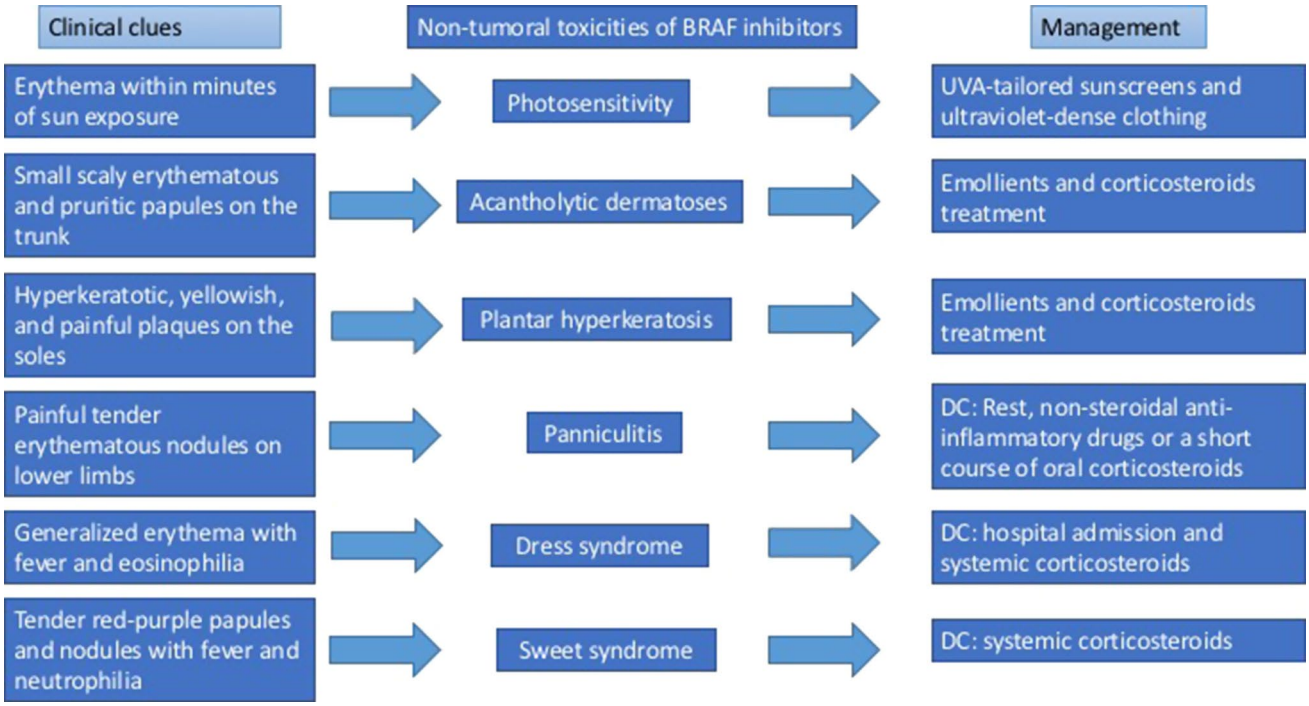

Fig. 1 Algorithm on the diagnosis and management of non-tumoral cutaneous toxicities of BRAF inhibitors. *DC* dermatology consultation

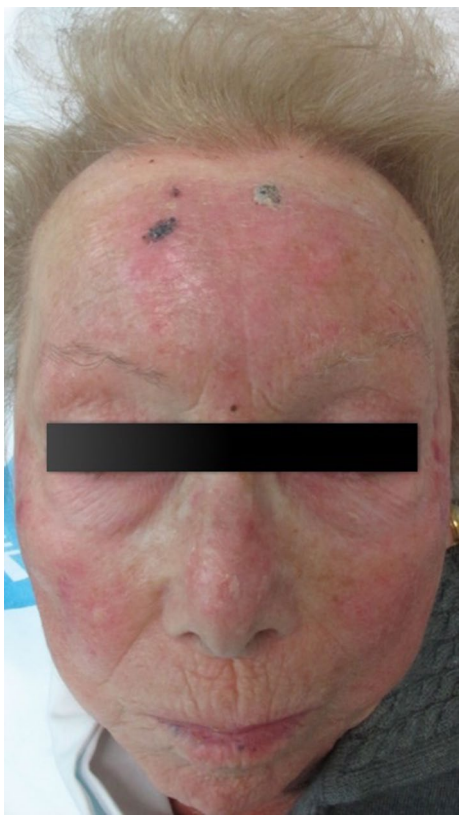

Fig. 2 Clinical picture of a patient with photosensitivity due to vemurafenib. The patient presents facial erythema that respects the headline

Management: these mild dermatoses may disturb the patient, but they do not require discontinuation of the treatment. These cutaneous manifestations can be managed with emollients and, in some cases, topical corticosteroids treatment.

Granulomatous rash Recently, two completely different cases of granulomatous rash during treatment with vemurafenib and the combination of dabrafenib and trametinib have been described [24]. In these cases, skin biopsy is needed for confirmation of the diagnosis.

Plantar hyperkeratosis

BRAF-i induces hyperkeratosis at friction zones of the soles (Fig. 3), presenting as hyperkeratotic, yellowish, and painful plaques on the heel and metatarsal region. Pain usually improves within 4–6 weeks leaving only hyperkeratosis of the area that resembles callosities. This side effect was underreported in clinical trials of vemurafenib and dabrafenib. In studies where this side effect has been analysed, it has been reported in up to 60% of patients receiving vemurafenib [25] and 22% of those receiving dabrafenib [26]. The development of hyperkeratosis in less common locations such as the vulva, gums, or nipples has also been reported in some patients treated with vemurafenib.

Diagnosis: clinical examination.

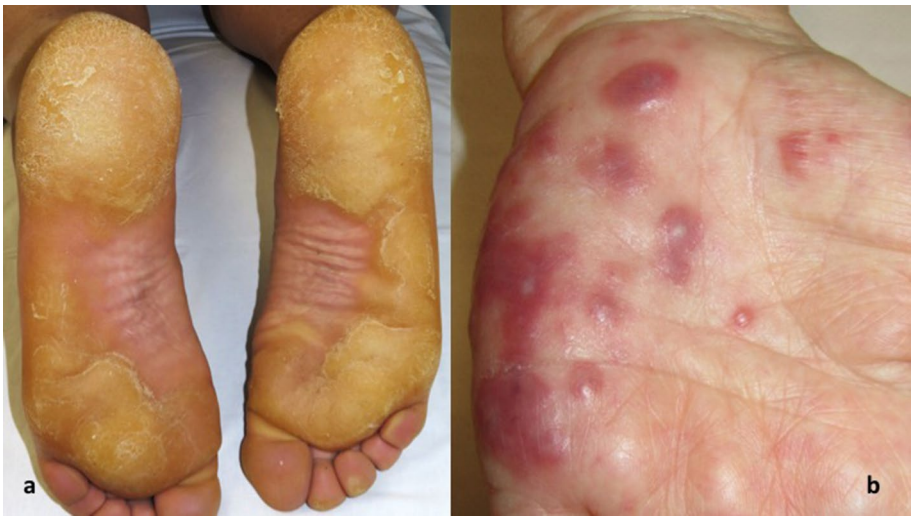

Fig. 3 **a** Plantar hyperkeratosis caused by BRAF inhibitor therapy. **b** Development of tender erythematous nodules on the palms suggestive of Sweet syndrome (Sweet is an eponymous)

Management: treatment with topical ointment or topical corticosteroids is usually efficient to mitigate the symptoms.

Alopecia/hair changes

Hair changes have been described with the generic term of alopecia (hair loss) in 8–36% of patients treated with vemurafenib and dabrafenib. Other frequent hair alterations associated with BRAF-i are diffuse hair loss with hair thinning and curling, and greying and wire-like hair. However, total alopecia has not been reported.

Physiopathology: a recent study reported that 66% of hair changes due to Vemurafenib were acute telogen effluvium [27]. Histopathology confirmed an interruption of the anagen phase and the increased number of hair follicles in telogen and catagen. The authors suggest that BRAF-i interrupts the anagen phase in the matrix cells of hair bulb, leading to anagen hair follicles into apoptosis-driven regression followed by telogen.

Diagnosis: trichological examination is usually sufficient for the diagnosis of hair alterations associated with BRAF-i. However, if other concurrent alterations of the hair are suspected, such as androgenetic alopecia, the diagnosis and specific treatment (i.e., topical minoxidil) do not differ from the management of other patients.

Management: given the new evidence in the physiopathology of this side effect, it has been suggested a new therapeutic approach with the use of clobetasol propionate foam 0.05% daily [27].

Panniculitis

Panniculitis has been reported in melanoma patients treated with both BRAF-i. In a recent case series study, it has been described in 13% of patients treated with vemurafenib, 3% with dabrafenib, and 10% with the combination dabrafenib–trametinib [28].

Diagnosis: diagnostic of this toxicity is based on the clinical examination and biopsy of the lesions. Clinically, the lesions present as painful, tender erythematous nodules usually located on both lower limbs but were also noted on upper limbs, abdomen, back, and buttocks. It could be associated with arthralgia. Histologically, it has been reported predominantly lobular panniculitis with neutrophilic infiltrate [29] and also panniculitis with septal and lobular involvement [30].

Management: adequate rest and elevation of the affected region is the mainstream of the treatment. It is possible to add non-steroidal anti-inflammatory drugs or a short course of oral corticosteroids. Most patients responded to conservative medical management without the need to reduce or to stop BRAF-i [31].

Others

Keratosis pilaris is a common, harmless skin condition characterized by diffuse keratotic papules centred around the hair follicles. They usually appear on the upper arms, thighs, and buttocks, sometimes with redness or swelling. A significant pruritus may accompany the eruption.

It has been described in roughly 33% of patients in the first weeks of treatment. Diagnosis is based on the clinical observation of the typical follicular papules. Topical preparations, including retinoids and those containing keratolytic agents such as urea, alpha-hydroxy acids, or salicylic acid provide comforting relief.

Xerosis is also common with or without pruritus. Emollients, oral antihistamines, and topical corticosteroids may be used in severe cases or when eczema evolves or is worsened due to the BRAF-i treatment.

Other specific dermatosis such as Sweet syndrome [32], toxic epidermal necrolysis [33, 34], DRESS syndrome (Drug reaction with eosinophilia and systemic symptoms) [35], cutaneous sarcoidosis [36], and hidradenitis suppurativa (acne inversa) [37] have been reported in patients treated with BRAF-i. In these cases, physical examination and skin biopsy are needed to confirm the clinicopathological diagnosis. Specific treatment depends upon the final diagnosis and severity of the symptoms, which can require the discontinuation of the BRAF-i treatment.

Tumoral cutaneous toxicities

Cutaneous squamous cell carcinomas

The appearance of well-differentiated squamous cell carcinomas (SCC) and cutaneous keratoacanthomas (KA) during treatment with BRAF-i in monotherapy is the most known side effect of these drugs. In clinical trials, they were found in 21–31% of patients treated with vemurafenib when MEK inhibitors were not associated [1, 20]. Later, in the open drug safety study, its incidence dropped to 14% probably due to a better treatment of precursor lesions such as actinic keratosis (AK) [38]. The incidence of SCC is lower with dabrafenib, affecting 6–11% of patients in monotherapy [39].

The typical appearance of these lesions is pink papules with a central keratotic area and raised margins [40] (Fig. 4a). They can be located in areas with chronic sun damage as well as in covered areas. Their average onset is at 8 weeks after starting vemurafenib, while, with dabrafenib, the main risk of appearance is later, at around 16 weeks. However, carcinomas can continue to appear even beyond the first year of treatment, so continuous dermatologic vigilance is essential [41].

Physiopathology: the mechanism by which these carcinomas occur is known as paradoxical MAP kinase pathway activation. It has been observed that up to 60% of carcinomas of patients treated with vemurafenib carry mutations in RAS [42, 43]. In keratinocytes with mutated RAS and wild-type BRAF, BRAF inhibitors act antagonistically as they do in the melanocytes, activating the MAP kinase pathway through CRAF (an isoform of BRAF) [44]. Therefore, BRAF-i accelerates the appearance of carcinomas in keratinocytes with underlying mutations.

Currently, the role of human papillomavirus in the development of these tumors is also being discussed [45].

Diagnosis: it is based in clinical examination, and dermoscopy is essential to differentiate AK, KA, and SCC [46]. In some cases, histopathology is required to confirm the diagnosis.

Management: SCC and KA induced by BRAF-i can be treated with simple excision [47]. In the case of AKs, topical treatment with specific drugs or cryotherapy is the treatment of choice [48]. Their appearance does not require adjustment or discontinuation of treatment with the BRAF-i. In patients who develop multiple skin cancers during treatment, the

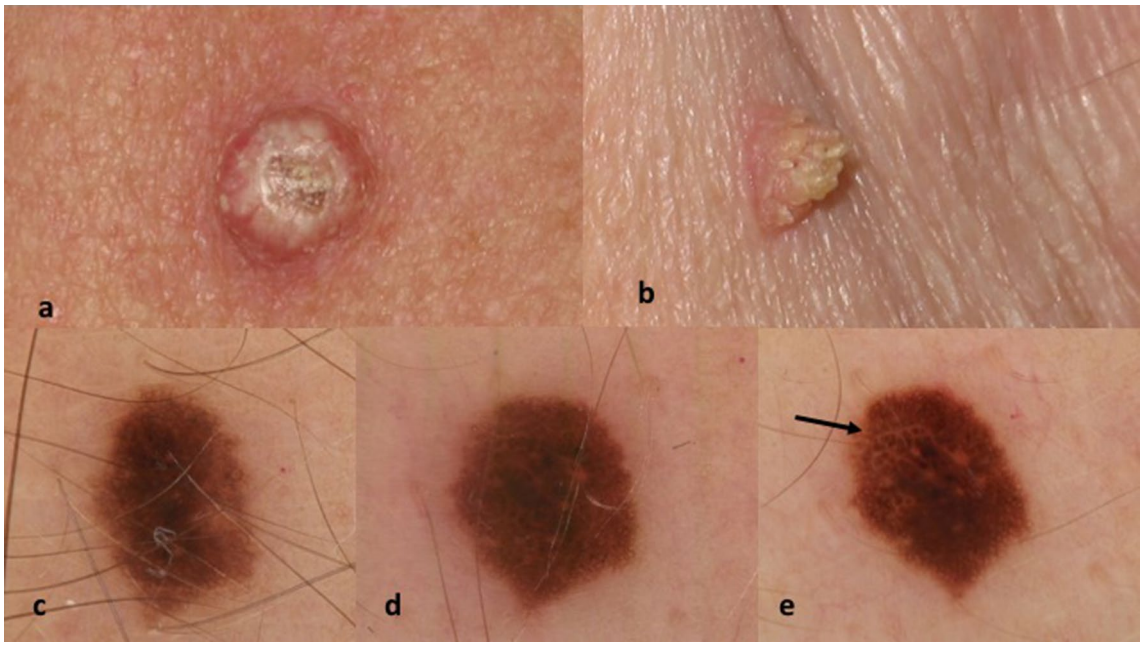

Fig. 4 **a** Clinical image of keratoacanthoma a pink tumor with a central keratotic area and raised margins. **b** Clinical picture of verrucal keratosis, a small hyperkeratotic papule resembling viral wart. **c**–**e** Nevus transformation into melanoma during dabrafenib therapy [**c** the lesions without atypical dermoscopy features before treatment; **d** nevus changes at 5 months; **e** development of a negative pigment network (arrow) suggestive of melanoma development at 7 months of treatment. The lesion was excised with the diagnosis of melanoma]

administration of acitretin, an oral retinoid, may be useful in preventing the emergence of new carcinomas [49, 50]. To date, there have been no cases of distant metastasis caused by these carcinomas. In patients with actinic damage, dermatologic consultation prior commencing BRAF-i therapy is recommended to treat precursor lesions such as AK, to avoid them progressing into SCC.

Verrucal keratosis

Much more common than SCC is the development of verrucal keratosis, also known as acantopapillomas or verrucal papillomas. These terms are used to describe lesions consisting of small hyperkeratotic papules that resemble viral warts, actinic keratosis, or small keratoacanthomas (Fig. 4b). They develop in both sun-exposed and unexposed areas. These lesions appear underreported in the pivotal trials of vemurafenib (described in 18–29% of patients). Subsequent works increase their incidence up to 79% of patients treated with vemurafenib [25] and 49% of those treated with dabrafenib [26].

Physiopathology: these lesions are also caused by paradoxical MAP kinase pathway activation.

Diagnosis: it is based in clinical examination and dermoscopy. If excised, histopathology shows papillomatosis, acanthosis, hyperkeratosis, preservation of the granular layer, and absence of koilocytes or keratohyalin granules. It can also be accompanied by moderate atypia of the basal layer [51]. It is believed that these lesions may be precursors of cutaneous SCC [52].

Management: verrucal keratosis can be treated with cryotherapy unless there are any suspicious features of malignancy. In that case, the lesion should be excised. Acitretin may be useful in the prevention of verrucal keratosis [49].

Development of new primary melanomas and nevi changes

New appearance and relevant modifications of nevi have been described previously with sorafenib [53], and it was also observed in about 10% of patients during BRAF-i, at a mean time of onset at 81 days (52–130 days) [25, 54]. Since Dalle et al. [55] reported the first five cases of second primary melanomas detected during BRAF-i treatment; more attention has been focused in the detection of these cases, highlighting the important role of the dermatologist during the follow-up. Indeed, several groups have reported clinical and dermoscopic modifications on nevi profile [21, 56–58]. The changes may include involution or evolution, with modifications in size, pigmentation, and scaly surface or hyperkeratosis (Fig. 4c-e). Changes can be found in up to 55% of lesions when sequential digital dermoscopy is performed, and most of the changes were observed within the first 6 months of treatment.

Second primary melanoma induction is now included among the adverse events of BRAF-i, reported especially in vemurafenib case series [55, 59]. The different clinical trials with vemurafenib or dabrafenib have reported that about 1–2% of patients can develop new primary melanomas [1, 39, 54]. The median time to develop a second primary melanoma has been estimated to be 14 weeks (range of 4–42 weeks), quite similar to SCC (8 weeks). Latest studies report about 15–20% of patients may develop atypical melanocytic lesions/melanomas during BRAF-monotherapy [60, 61].

Physiopathology: the pathogenesis of these new primary melanomas is still unclear. Most of the melanomas seem to be originated in a preexisting nevus and are BRAF wild type [60, 62]. Interestingly, a minority of melanomas harbouring NRAS(Q61R) mutations have been found in these works.

Immunohistochemical analysis have shown non-significant increases in staining of phosphorylated ERK, and a significant increase in phosphorylated-AKT and cyclin D1 signalling in newly developed primary melanomas compared with nevi [60, 61].

Melanoma induction raises the question of the nature of the earliest cellular events identifiable within preexisting nevi. However, contrary to keratinocytic tumorigenesis, common nevi are frequently found BRAF-mutant [63–65]. All malignant lesions reported to date were BRAF wild type, whereas there was no NRAS mutation in common nevi, but BRAF mutations were frequent [60, 62]. It would be reasonable to assume that changes on nevi during BRAF-i therapies could depend on BRAF status. They could suffer involution if they are BRAF mutated, and otherwise, they could grow or evolve if they are BRAF wild type [60]. Further studies are needed to better understand the possible and interesting pathways implicated in nevogenesis and melanomagenesis.

Diagnosis: as any melanoma patient that already has an increased risk of second primary melanoma development, dermatologic evaluation should include clinical and dermoscopic total body examination. Digital total body photography and digitalized dermoscopy surveillance should be used specially in those patients with multiple nevi before and during BRAF-i monotherapy. In case of patients with atypical or multiple nevi they should be preferably referred to a Pigment Lesion Unit where experienced dermatologists and dermatopathologists are able to deal with these atypical melanocytic proliferations, and close follow-up with sequential digital dermoscopy every 2 months and total body mapping every 4–6 months may be indicated.

Management: nevi that present relevant or atypical changes during BRAF-i or any melanocytic lesion suspicious for melanoma should be surgically excised. If a second melanoma is confirmed, a wide excision should be considered depending on the patient status and type

of second primary melanoma found. Any other possible treatment or staging procedure should be individualized.

The risk of developing atypical melanocytic lesions/melanoma during BRAF-i seems to decrease under combined therapies with MEK inhibitors; however, a close follow-up remains mandatory since it is unclear if combination treatment will limit the emergence of all BRAF-i-driven pathologies [66].

Cutaneous toxicity of BRAF inhibitor/MEK inhibitor combination therapy

The combination therapy with BRAF and MEK inhibitors (MEK-i) in metastatic melanoma has been shown to increase the rate of responses and mean survival compared to treatment with BRAF-i alone [4]. Remarkably, toxicities of both drugs in combination do not increase and a better safety profile is achieved with the combination therapy.

The main advantage of the dual inhibition treatment is to prevent tumor resistance due to paradoxical activation of MAPK pathway by downstreaming inhibition of MEK. That activation is also responsible for the incidence of skin tumors during treatment with BRAF-i. Therefore, combination therapy significantly reduces the presence of skin tumors, both verrucal keratosis and SCC. In a study at 52 weeks of treatment in which patients under BRAF-i presented frequencies of SCC up to 16% and warty premalignant lesions of 18%, the 10 patients under combination therapy BRAF-i/MEK-i did not develop papillomas or SCCs [41]. Similar results were obtained by another group in 44 patients with melanoma. In this study, cutaneous adverse events were significantly less frequent and occurred after longer treatment (in patients treated with BRAF-i/MEK-i combination regimen compared with patients treated with BRAF-i monotherapy [67]). Another common side effect associated with BRAF-i but that was observed only in isolated cases in the combined treatment group was Grover's disease. The significant reduction in SCC, verrucal keratosis, plantar hyperkeratosis, and Grover's disease in patients treated with BRAF and MEK inhibitors was confirmed in further studies including higher number of patients [22, 68].

More recently, the CoBRIM fase III trial comparing 247 patients treated with combination therapy (cobimetinib and vemurafenib) with 246 patients receiving vemurafenib alone (median follow-up 18.5 months) confirmed lower frequency of SCC (4 vs 12.6%), keratoacanthoma (1.6 vs 9.3%), and hyperkeratosis (10.1 vs 27.2%). Contrary, photosensitivity was higher in the combination arm (47.8 vs 37.8%) [69].

Pustular eruption

In contrast, patients receiving the combination therapy had more often pustular eruption (17–40 vs 3–8% patients in the BRAF-i alone arm) [41]. The pustular rash is the most common skin toxicity associated with treatment with MEK-i. Lesions resemble acne vulgaris, characterized by inflammatory papules, pustules, and nodules, typically affecting the areas of skin with dense sebaceous follicles (face, upper chest, and back). Interestingly, the combination of BRAF-i/MEK-i has a better safety profile than the treatment with MEK-i alone. In a study with 43 patients (13 treated with trametinib and 30 with trametinib/dabrafenib), authors found a frequency of pustular lesions of 77% in trametinib group vs 10% in patients under combination therapy [70]. In a recent study, acneiform eruption was more frequent in males and related to longer treatments [68].

A recent meta-analysis that analysed 200 studies confirms that the pustular rash is more common in the combination therapy, along with other extracutaneous manifestations such as diarrhoea, decreased ejection fraction or pyrexia [71]. These data have been confirmed in CoBRIM fase III trial where combination therapy was also associated with higher frequency of grade ≥ 3 adverse events [69].

Diagnosis: clinical evidence of cutaneous lesions was similar to acne vulgaris.

Management: pustular eruption can be managed with topical antiseptics (triclosan) and antibiotics (1% clindamycin). In more severe cases, the use of oral doxycycline 100 mg daily should be considered.

Immunotherapy cutaneous adverse events

Cutaneous toxicity of immunotherapy is milder than the one caused by target treatment. Most adverse events are immune-related. In general, cutaneous adverse events are dose-dependent, manageable, and reversible [72]. Treatment with ipilimumab is commonly associated with skin-related side effects (60–64% of patients [5, 73]) that are rarely severe (only 1–4% are grade 3/4) being rash and itching [74] the most common reactions. According to Robert et al., the rash can occur in up to 50% of patients and pruritus in up to 29.6% [5]. They commonly occur at the beginning of the treatment, with its peak at the sixth week [75].

Anti-PD-1 drugs produce less skin toxicity than ipilimumab, but between 3 and 9% of patients develop severe grade 3–4 skin toxicity that limits the use of the drug [76, 77]. Approximately 40% (18–50%) of patients treated with anti-PD-1 will develop some form of skin toxicity [78–80]. The most comprehensive study to date is that of Hwang et al. [80], which reviews 82 patients treated with anti-PD-1. In this study, 49% of patients developed cutaneous adverse

effects, being more frequent lichenoid reactions (17%), eczema (17%), and vitiligo (12%). The appearance of these toxicities is progressive; increasing steadily from the start of treatment, and, in some patients, (10%) can be combined. The clinical clues for the differential diagnosis of immunotherapy toxicities are summarized in Fig. 5.

Rash

In a meta-analysis by Minkis et al. [81], 24.3% of patients treated with ipilimumab presented rash (2.4% severe rash) with no relation to the dose or type of tumor. The rash is morbilliform (discrete maculopapular lesions that may merge together to form large erythematous patches), mostly seen in trunk and limbs and similar to a maculopapular drug eruption.

Anti-PD-1′s rash has been subdivided by some authors in lichenoid reactions and eczema. Lichenoid reactions are clinically seen as small papules or plaques of erythematous or purple colour with a varying degree of flaking. Most commonly appear on the trunk and do not usually have mucosal involvement. Eczema can appear similar to the "classic" eczema, with ill-defined erythematous scaly lesions, or as nummular eczema (round plaques). Usually, it is pruritic and affects several areas, more frequently the back and extremities, and less frequent the face, anterior chest, and abdomen. Other authors define the rash as a macular papular eruption similar to a skin drug reaction, which usually appears in the first cycles of treatment, affecting predominantly sun-exposed areas and respecting the mucosa [76]. It has been considered that the occurrence of rash may be associated with a better prognosis, although this should be interpreted with caution, since responders receive more treatment cycles, which makes them more likely to develop skin reactions induced by treatment.

Diagnosis: clinical examination could be sufficient to establish the diagnosis; however, a biopsy may be necessary to rule out other skin condition that may be included in the differential diagnosis. The histology of these lesions is variable, also in biopsies of lesions from the same patient [82].

Treatment: symptomatic treatment with emollients, low-to-moderate potency topical corticosteroids, and oral antihistamines can control the symptoms in most of the cases. Oral corticosteroids (0.5–2 mg/kg) for 2–4 weeks may be considered in severe cases.

Pruritus

Pruritus can be severe in around 1% of patients [83]. In our opinion, pruritus without skin lesions is probably not as common as it appeared in the first published articles [84], as in latter studies that have qualified in more detail cutaneous adverse effects; pruritus represents only 11–12% of the cases.

Diagnosis: the diagnosis is made with the medical examination and patient's history.

Management: symptomatic treatment with emollient creams, low-to-moderate potency topical corticosteroids,

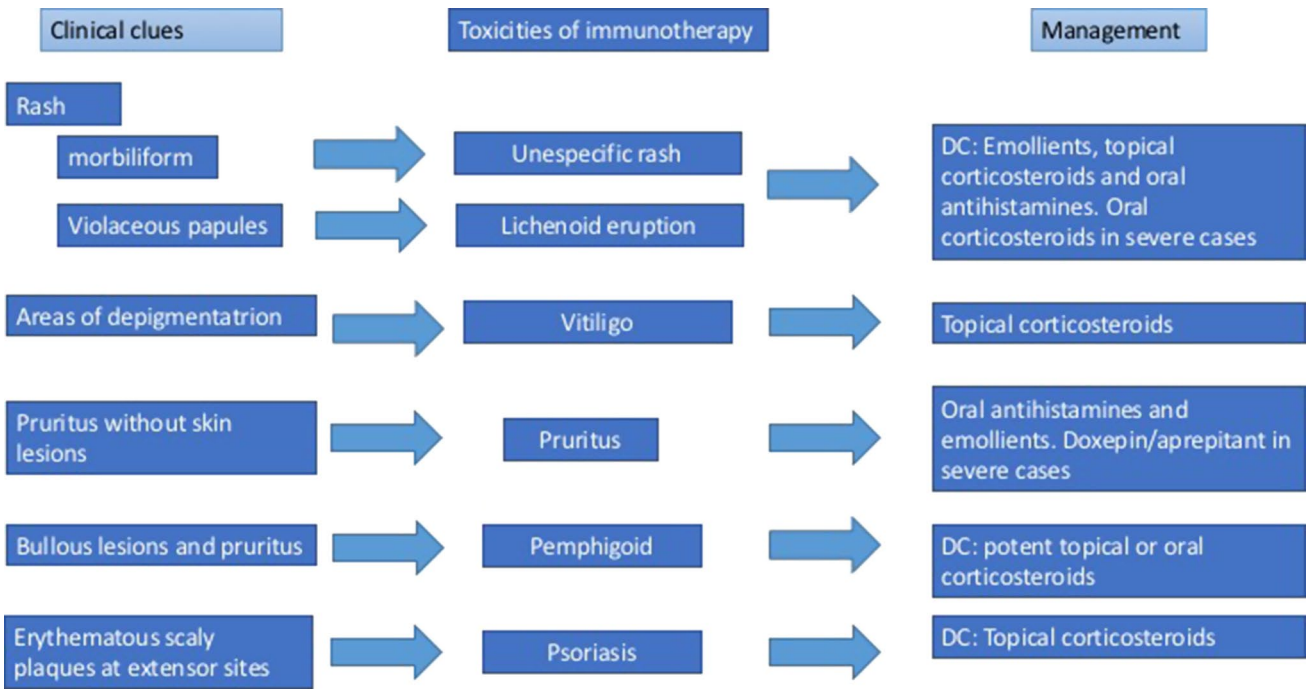

Fig. 5 Algorithm on the diagnosis and management of immunotherapy cutaneous toxicities. *DC* dermatology consultation

and oral antihistamines. Refractory cases can be managed with Doxepin or Aprepitant [84].

Vitiligo

Vitiligo is the third most common cutaneous adverse reaction of anti-PD-1 drugs. Approximately 4% of melanoma patients develop vitiligo. In patients undergoing anti-PD-1 treatment, this percentage increases to 28% (8–28%). It appears almost exclusively in patients under treatment for melanoma [85], not in those receiving treatment for other cancers, and it is more frequent associated with other toxicities, such as lichenoid reactions and eczema, rather than isolated. It is hypothesized that the appearance of vitiligo is a good prognosis marker, since 70% of patients who develop vitiligo during Anti-PD-1 treatment respond to therapy [86]. Vitiligo has been also described in patients receiving ipilimumab (in 11% of patients of Phase II study) [87]. Hair repigmentation, recently reported in patients receiving Anti-PD-1/anti-PDL1 for lung cancer, has not been reported in melanoma patients [88].

Diagnosis: clinical examination.

Management: topical corticosteroids could be used to induce repigmentation. It is also important the use of photoprotection (including clothing and broad-spectrum sunscreen) to avoid sunburns.

Other

Among less frequent adverse effects, it stands out the publication of case reports of bullous pemphigoid induced by anti-PD-1 treatment [89, 90]. In addition, cases of psoriasiform reactions [91, 92] and exacerbation of psoriasis have been described in the first cycles of treatment [93]. These reactions can be explained as the PD-1 pathway contributes to the suppression of skin reactions mediated by Th17/Th1; therefore, by inhibiting suppression with an anti-PD-1 drug, psoriasis would exacerbate [94, 95].

Other described rare skin reactions with immunotherapy are: widespread erythema, acneiform eruption [80], DRESS syndrome, photosensitivity, sensitivity/skin toxicity in previously irradiated areas, ulcerations pyoderma gangrenosum-like, acneiform rash, and eruptive keratoacanthomas [96]. Isolated cases of Sweet syndrome [97], Grover´s disease [98], Stevens–Johnson syndrome/toxic epidermal necrolysis, and erythema nodosum-like panniculitis have been also described [99]. With the increasing survival of patients treated with anti-PD-1 and its future use in adjuvant setting, it is also expected a rise in cutaneous adverse effects, since its incidence increases with drug exposure time.

Conclusions

Target therapy and immunotherapy have meant an important advance in the survival of patients with metastatic melanoma. Compliance, safety, and quality of life of patients should be kept as primary goals especially for long-time survivors and even more in the case that these drugs may be widely used as adjuvant therapies. Targeted therapy with BRAF-i carries important cutaneous adverse effects such as photosensitivity, and the development of SCC and second primary melanomas. It is presumed that generalization in the use of combination therapy with BRAF-i and MEK-i will imply a significant reduction in this toxicity. However, there will always be patients who do not tolerate or have contraindications for MEK-i and will receive BRAF-i monotherapy. Especially, in these patients, dermatologic follow-up with digital dermoscopy equipment will be fundamental for the early detection of second melanomas.

The more extensive use of immunotherapy as well as the improvement in patients' survival will also mean an increase in the cutaneous toxicities of these treatments. In our opinion, a close collaboration between dermatologists and oncologists is crucial to obtain a better understanding of the pharmacodynamics of new drugs and optimal management of the patients.

Compliance with ethical standards

Disclosure of potential conflicts of interest Dr. Aram Boada has received speaker honorarium from Roche, Novartis, and BMS. Dr. Susana Puig has been consultant of Amgen, ISDIN, La Roche Posay, Leo Pharma, Almirall, Piere Fabre, BMS, and has received research grants from Leo Pharma, Almirall, and Novartis. Dr. Josep Malvehy has been consultant of Amgen, Novartis, BMS, Glaxo, Piere Fabre, Merk, MSD, Sanofi, Sunpharma, Incyte, Almirall, Leo Pharma, ISDIN, and has received research grants from Amgen, Novartis, Roche, BMS, Glaxo, Pierre Fabre, Merk, MSD, Sanofi, Sunpharma, Incyte, Almirall, and Leo Pharma. The remaining authors have no conflict of interest to declare.

Ethical standards The manuscript does not contain clinical studies or patient data.

Informed consent Informed consent was obtained from all individual for whom identifying pictures are included in this article.

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