CME Article

Drug eruptions with novel targeted therapies – immune checkpoint and EGFR inhibitors

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Summary

Given the increasing use of novel targeted therapies, dermatologists are constantly confronted with novel cutaneous side effects of these agents. A rapid diagnosis and appropriate management of these side effects are crucial to prevent impairment of the patients' quality of life and interruptions of essential cancer treatments. Immune checkpoint and EGFR inhibitors are frequently used targeted therapies for various malignancies and are associated with a distinct spectrum of cutaneous adverse events. Exanthematous drug eruptions represent a particular diagnostic challenge in these patients. Immune checkpoint inhibitors can elicit a plethora of immune-related exanthemas, most commonly maculopapular, lichenoid, and psoriasiform eruptions. Additionally, autoimmune bullous dermatoses and exanthemas associated with connective tissue diseases may arise. In cases of severe, atypical or therapy-resistant presentations an extensive dermatological investigation including a skin biopsy is recommended. Topical and systemic steroids are the mainstay of treatment. Papulopustular eruptions represent the major cutaneous adverse effect of EGFR inhibitor therapy, occurring in up to 90 % of patients within the first two weeks of therapy, depending on the agent. Besides topical antibiotics and steroids, oral tetracyclines are the first choice in systemic treatment and can also be used as prophylaxis.

Introduction

The increasing use of modern targeted therapies leads to the emergence of novel cutaneous side effects that must be diagnosed and managed appropriately.

In the last two decades, the development of modern targeted therapies has expanded available therapeutic options, especially in the field of oncology. Meanwhile, a large number of molecular targets for small molecules and monoclonal antibodies have been established. Such novel therapeutic approaches are frequently associated with novel cutaneous side effects. Exanthematous skin eruptions represent a particular challenge in this context due to the frequently necessary polypharmaceutic therapy. Benign exanthemas in late-type reactions, and the much rarer severe drug rashes caused by known medications, have already been covered in previous CME articles [1, 2]. It is, however, important to detect novel drug associated eruptions, differentiate them from other diagnoses, and manage them appropriately. Immune checkpoint inhibitors and inhibitors of the epidermal growth factor receptor (EGFR) are frequently and increasingly used in day-to-day clinical practice. Therefore, this CME article focuses on exanthemas associated with these drugs, including differential diagnoses and therapeutic options. With early diagnosis and adequate therapy, these cutaneous side effects can often be well controlled, thus avoiding impairment of the patient's quality of life as well as disruption of effective oncological therapy.

Immune checkpoint inhibitors and EGFR inhibitors are common targeted therapies, each with a specific cutaneous side effect profile.

Immune checkpoint inhibitors

Blockade of inhibitory immunological checkpoints with CPI (immune checkpoint inhibitors), referred to as immunotherapy in oncology, is increasingly used in various malignant diseases. Immune checkpoint inhibitors target either CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) or PD-1 (programmed cell death protein 1), or its ligands (PD-L1). Based on their activating effect on the immune system, CPI are associated with a novel and diverse spectrum of cutaneous immune-related adverse events (irAE). These occur in 47–60 % of patients treated with CTLA-4 inhibitors and in 30–40 % of patients treated with PD-1/PD-L1 inhibitors [3]. Cutaneous irAE usually appear within the first few weeks after initiation of treatment, sometimes directly after the first administration [3, 4]. Cutaneous irAE are thus the most common and the earliest occurring immune-related side effects.

The spectrum of possible skin reactions associated with immunotherapy is large and ranges from various inflammatory responses to bullous eruptions (Table 1) [5]. Non-specific pruritic maculopapular skin reactions are the most common forms. The eruptions may, however, also resemble well-known inflammatory dermatoses and are thus termed "lichenoid" or "psoriasiform" exanthemas. Exanthematous

Cutaneous eruptions are the earliest occurring immune-related adverse events associated with immune checkpoint inhibitor treatment.

Table 1 Overview of the most important exanthemas associated with checkpoint inhibitor immunotherapy, timing of onset and differential diagnosis.

	Average latency after treatment initiation until skin eruptions occur (weeks)
Non-bullous exanthemas	
Maculopapular exanthemas	2–6
Lichenoid exanthemas	~12
Psoriasiform exanthemas	0–4 (pre-existing psoriasis) ~12 (initial manifestation)
Connective tissue disease-associated exanthemas – Dermatomyositis – Cutaneous lupus erythematosus	 Unknown (reports from week 0) ~10
Morbus Grover-like exanthemas	3–6
Selection of important differential diagnoses: – Drug eruptions caused by other medications: antibiotics, analgetics, etc. – Infectious exanthemas	
Bullous Exanthemas	
Bullous pemphigoid	~24
Bullous lichenoid exanthemas	~12
Stevens-Johnson Syndrome/toxic epidermal necrolysis	0–4 (cases with delayed appearance have been reported)
Selection of important differential diagnoses: – Severe bullous drug eruptions caused by other medications: allopurinol, sulfonamides, anticonvulsants etc. – Bullous infectious exanthemas: Staphylococcal Scalded Skin Syndrome (SSSS), bullous impetigo, herpes simplex/zoster – Mechanical blisters (pressure/tension blisters)	

Immune-related cutaneous adverse events usually do not impair continuation of immunotherapy.

skin lesions may also occur as a sign of newly appearing or unmasked autoimmune disease such as lupus erythematosus or dermatomyositis [6]. Bullous exanthemas must be differentiated mainly from bullous pemphigoid, severe bullous drug eruption, and bullous variants of lichenoid exanthema [5, 7].

Severity is graded according to the CTCAE classification (Common Terminology Criteria for Adverse Events) (Grades I–V) [8]. Most exanthemas associated with immunotherapy are classified as mild, with less than 3 % higher grade reactions (≥ CTCAE Grade III) in mono-immunotherapy and less than 5 % in combined immunotherapy (PD-1 inhibitors plus CTLA-4 inhibitors) [5, 9, 10]. Even pronounced skin eruptions that necessitated dermatological consultation only led to interruption of the oncological treatment in 25 % of cases, of which 16 % were subsequently able to resume their treatment [11].

In several studies, cutaneous irAE seen under immunotherapy were associated with a better therapeutic response. This was especially true for vitiligo in melanoma patients. Some studies, however, indicate a similarly positive association of immunotherapy-associated exanthema with therapeutic response [12, 13].

Maculopapular exanthemas

The most common skin reactions with immune checkpoint inhibitors are non-specific maculopapular exanthemas that resemble the 'classic' maculopapular drug rashes.

Non-specific maculopapular exanthemas appear in about 10–25 % of patents within 2–6 weeks after treatment initiation, and sometimes even after the very first administration of CPI. They occur more frequently and earlier with combined therapy and with CTLA-4 inhibitors than with PD-1/PD-L1 inhibitors. These exanthemas are usually mild. The clinical appearance shows bright red macules and papules, mainly on the trunk, while the face as well as the palms and soles are spared. Pruritus and mild scaling may be present [5]. Histopathology frequently shows perivascular lymphocytic infiltration in the superficial dermis, sometimes with eosinophils and spongiosis [14]. A careful anamnesis regarding medication is essential to exclude other drugs as possible elicitors of a maculopapular drug eruption (such as antibiotics). Non-specific maculopapular skin lesions may also constitute the initial manifestation of specific exanthemas or severe drug reactions, so patients need to be monitored accordingly.

Lichenoid exanthemas

Lichenoid exanthemas are a common cutaneous side effect of immunotherapy. Bullous manifestations and involvement of the mucous membranes may occur.

Case report 1: A 76-year-old male patient reported severely pruritic, generalized skin lesions mainly on the extensor sides of the upper and lower limbs that had appeared a few weeks earlier (Figure 1). The trunk was only sparsely affected, and the mucous membranes were normal. Due to adenocarcinoma of the left upper lobe of the lung, the patient was treated with localized radiation and, for the last ten months, with a PD-1 inhibitor (pembrolizumab). He was also on continuous medication with enalapril, bisoprolol, aspirin, and fenofibrate for various medical conditions.

Lichenoid exanthemas are a common feature of immunotherapy-associated skin reactions. They mainly occur in association with PD-1/PD-L1 inhibitors; up to 17 % of patients show this reaction [5, 15]. Lichenoid skin lesions may be underdiagnosed, and some authors consider them to be the most common clinical and/or histopathological pattern of inflammatory cutaneous irAE [11, 16]. Lichenoid exanthemas appear weeks or even months (on average 12 weeks) after treatment initiation, and thus later than maculopapular exanthemas [17].

Clinical appearance varies. Exanthemas may consist of classic lichenoid papules with Wickham striae that can also coalesce into larger plaques, but can also
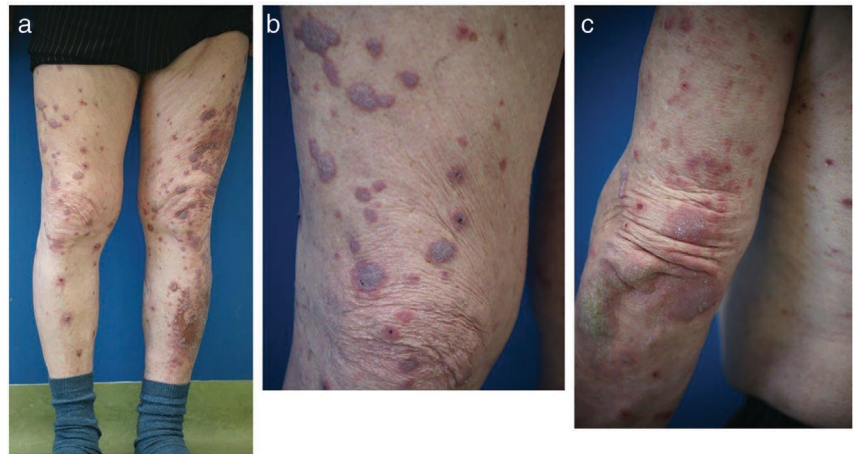
Figure 1 Symmetrically distributed violaceous papules and plaques predominantly affecting the extensor surfaces of the limbs (a, b) and arms (c). An overlying, reticulated, fine white scale is visible (b, c).

> Lichenoid drug eruption may appear several months after treatment initiation. There is no certain way to distinguish them from idiopathic exanthematous lichen ruber, either clinically or histopathologically.

present with less specific maculopapular skin lesions or resemble hypertrophic lichen ruber planus (LRP) with hyperkeratotic plaques (Figure 1). Pronounced pruritus is often reported. The skin lesions may appear localized or generalized. Bullous lesions, palmoplantar manifestations, and involvement of the mucous membranes may occur [5, 18].

Immune-mediated bullous lichenoid exanthemas, especially with involvement of the oral mucous membranes, are an important differential diagnosis to severe bullous drug reactions [7]. For a differential diagnosis, other pharmaceutical causes of lichenoid drug eruptions as well as idiopathic lichenoid LRP need to be considered. Medications that frequently cause lichenoid drug eruptions include cardiological medications (beta blockers, diuretics) as well as antimalarials and tumor necrosis factor (TNF)α blockers. As opposed to the predilection sites of classic LRP (flexor sides of the limbs), in lichenoid drug rashes the lesions more commonly appear on the extensor sides of the limbs including the backs of the hands, and in areas exposed to light. Morphology often shows a comparatively pronounced eczematous component with scaling. Diagnosis of lichenoid drug eruptions is made more difficult by the fact that they appear late – up to several months after treatment initiation – and that they clear up only slowly after the putative causal agent has been discontinued [19]. Allergological diagnostics, such as epicutaneous tests, are rarely successful [20]. If lichenoid skin lesions appear within the first few months after initiation of PD-1/PD-L1 treatment, association with the immunotherapy is probable due to the reported frequency. Premature discontinuation of essential medications for internal diseases should be avoided.

Histopathology usually cannot differentiate between immunotherapy-associated lichenoid exanthemas and idiopathic LRP [14]. The classic appearance shows irregular acanthosis and hypergranulosis with a subepithelial band-like lymphocytic epidermotropic inflammatory infiltration associated with melanophages and vacuolar degeneration, up to subepithelial fissures (bullous forms) at the dermoepidermal junction zone [14]. Occasional reports have described a comparative accumulation of CD163+ macrophages and CD4+ lymphocytes, as well as increased histological variability with spongiosis, eosinophiles, and parakeratosis, which are not typical for LRP, as indicative [14, 17].
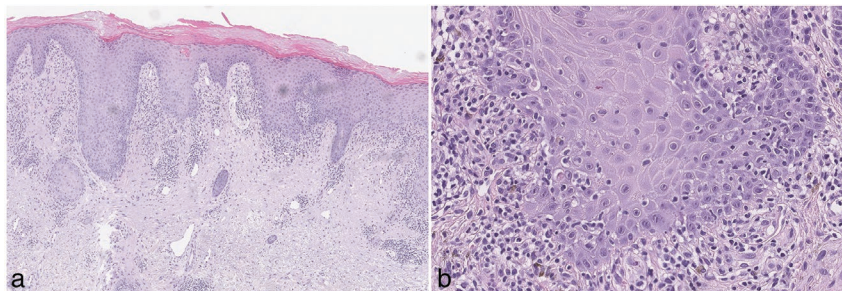
Figure 2 Histopathological features of case 1 – immunotherapy-related lichenoid drug eruption. The scaled-out image (a) shows orthohyperkeratosis with focal parakeratosis, acanthosis, and a dense band-like dermal lymphocytic infiltrate obscuring the dermoepidermal junction. Furthermore, vacuolization of basal keratinocytes and dermal melanophages indicating pigment incontinence can be seen (b).

Continuation of Case report 1: A skin biopsy showed the histological signs of lichen ruber verrucosus (Figure 2) and the patient was diagnosed with pembrolizumab-associated lichenoid exanthemas. He received topical corticosteroids (class IV), UVB phototherapy, and retinoids (acitretin). The skin lesions resolved over a period of several months until they disappeared completely. Pembrolizumab therapy was discontinued upon complete response of the tumor due to the dermatological side effect. The patient has remained tumor-free for two years.

Erythematosquamous and papulosquamous exanthemas

Psoriasiform exanthemas are mainly associated with PD-1/PD-L1 inhibitors [5, 11]. They can occur either *de novo* or as an exacerbation of pre-existing psoriasis [11, 16, 21, 22]. In the latter case, exanthematous skin lesions will frequently appear within the first month of treatment, while *de novo* manifestations usually occur later, about three months after treatment initiation [21]. The clinical appearance usually shows plaque-type psoriasis; other subtypes such as palmoplantar, pustular, guttate, erythrodermic, or inverse psoriasis are rare [21–23]. Papulosquamous exanthemas occurring in association with immunotherapy may also resemble pityriasis rubra pilaris [24].

Initial appearance or exacerbation of psoriasis is a known side effect of PD-1/ PD-L1 treatment.

Bullous pemphigoid

Immunotherapy-associated bullous pemphigoid is mostly seen with PD-1/PD-L1 inhibitors and tends to occur late, on average six months after treatment initiation [25, 26]. As in the general population, bullous pemphigoid is the most common autoimmune bullous dermatosis associated with immunotherapy. It is, however, still a rare side effect, and is seen in about 0.9 % of patients [15, 25, 26]. For comparison: Its incidence in the general population is 7.6 per 100,000 per year, though this increases significantly with age [27].

Similarly to the classic form, the pre-bullous stage shows severely pruritic urticarial to maculopapular erythemas, with the typical firm subepidermal blisters appearing in the later course of the disease [28]. The oral mucous membranes may also be involved [28, 29]. Any treatment-refractory pruritic erythema associated

Compared with other cutaneous side effects, the occurrence of bullous pemphigoid associated with immunotherapy is delayed, averaging about six months after treatment initiation.

Differential diagnoses of treatment-refractory pruritic lesions associated with immunotherapy must include the pre-bullous stage of a bullous pemphigoid.

with immunotherapy may actually be a bullous pemphigoid in the pre-bullous stage – a possibility that should always be considered in differential diagnosis.

Histopathology and immunopathology mostly resemble the classic bullous pemphigoid: Histopathological examination typically shows subepidermal fissures of varying severity as well as dermal inflammatory infiltration of lymphocytes, eosinophils, and neutrophils. Direct immunofluorescence shows linear deposits of C3 and/or IgG along the dermoepithelial junction zone [14]. Auto-antibodies against BP180 are found in up to three-quarters of all patients in serological analysis, while antibodies against other components of the dermoepidermal junction zone are much rarer [30]. Negative results on auto-antibodies, however, do not rule out the diagnosis [29, 30].

As a differential diagnosis, other bullous exanthemas reported in association with immunotherapy should also be considered, such as bullous lichenoid exanthemas [7, 31], lichen planus pemphigoides [32–34], or severe bullous drug reactions [7, 35, 36]. Clinically, the firm blisters of bullous lichenoid exanthemas are only found on lichenoid plaques. They develop due to pronounced interface dermatitis with subepidermal fissures [32]. In contrast, lichen planus pemphigoides shows firm blisters not only in classic lichenoid plaques but also on skin areas without lichenoid lesions. These are caused by secondary autoantibody formation, similar to bullous pemphigoid [32].

In addition, bullous eruptions must be distinguished from diseases in the pemphigus group. These, however, can be considered a rarity in patients with immunotherapy: There are only a few individual case reports on paraneoplastic pemphigus being revealed or newly occurring in patients receiving immunotherapy [37, 38]. This may be due to the fact that paraneoplastic pemphigus is a rare disease that occurs most frequently (84 %) in hematological disorders, which are currently not an indication for immunotherapy [39]. To date, cases of classic pemphigus vulgaris have not been reported.

Connective tissue disease-associated exanthemas

Case report 2: After the second treatment cycle of combined chemo-immunotherapy with pembrolizumab, pemetrexed, and carboplatin, a 56-year-old female patient with metastasized bronchial carcinoma experienced slightly pruritic skin lesions starting in the cleavage area. After the fourth cycle, about ten weeks after treatment initiation, she noticed pronounced exacerbation spreading over the whole body (Figure 3). The mucous membranes remained normal.

Exanthematous skin lesions under immunotherapy may indicate newly occurring autoimmune connective tissue diseases (collagenoses). These side effects are rare, with cutaneous lupus erythematosus (LE) and dermatomyositis as the main examples.

Appearance of cutaneous LE, most commonly subacute cutaneous lupus erythematosus (SCLE), has been reported from two weeks to several months (about ten weeks on average) after initiation of PD-1/PD-L1 inhibitor treatment [6, 40–43]. Epidemiological data are scarce; in a small cohort of patients with PD-1/PD-L1 inhibitor treatment the incidence of drug-induced LE was estimated at 0.5 % [41]. For comparison: The incidence of SCLE in the general population is estimated at 0.6 per 100,000, with drug association likely playing a role in up to one-third of cases [44, 45]. The work of Marzano et al. [46] provides a good overview of drug-induced LE. SCLE is the most common variant, ahead of systemic LE. Drug-induced SCLE is frequently associated with diuretics, antihypertensives, proton pump inhibitors, antifungal medications, TNFα blockers, and more

Figure 3 Erythematous plaques on the chest (c), upper back (a, b) and arms with partly Erythema multiforme-like features.

recently PD-1/PD-L1 inhibitors. The clinical picture shows sometimes extensive, annular or papulosquamous plaques mostly in areas exposed to light. Vesiculobullous forms as well as forms resembling erythema multiforme have been reported. In drug-induced SCLE, antinuclear antibodies (ANA) and SSA(Ro) antibodies are frequently positive and anti-histone antibodies are negative. Internal organs are usually not affected.

Histology in cutaneous LE is characterized by interface dermatitis, perivascular and periadnexial lymphocytic infiltrations, thickening of the basement membrane, epidermal atrophy, and dermal mucin deposits [47]. The extent of the individual features varies between the clinical subtypes, with fluent transitions. Diagnosis thus requires a clinico-pathological correlation [47]. Histopathology alone cannot clearly distinguish between systemic and cutaneous LE, nor can it differentiate LE from dermatomyositis [47].

Newly occurring dermatomyositis in a patient on immunotherapy can present with pronounced skin lesions typical for this disease, including Gottron papules, heliotropic periorbital erythema, and extensive erythema on the trunk and limbs, particularly in areas exposed to light. Muscular complaints may also occur. Symptoms quite frequently start shortly after treatment initiation, sometimes even after the very first administration of CPI [48, 49]. ANA are often positive while myositis-specific auto-antibodies may be missing [48]. In many cases, myositis-specific auto-antibodies are antibodies against transcriptional intermediary factor-1γ (TIF-1γ) [49–51], which is associated with paraneoplastic dermatomyositis [52].

Apart from primary induction due to the medication, it is also possible that latent auto-immune processes may be revealed (unmasked) by this treatment. This appears especially plausible in cases of dermatomyositis with a paraneoplasia-associated auto-antibody profile. There has been one report on exacerbation of anti-TIF-1γ antibody-positive paraneoplastic dermatomyositis, which had previously remained subtle and undiagnosed, after initiation of immunotherapy [53].

Continuation Case report 2: Skin biopsy (Figure 4) as well as laboratory analyses were performed for further assessment. The patient showed ANA at high titers (1 : 1280) and SSA antibodies but negative dsDNA antibodies. There were no clinical or laboratory indications of organ involvement. After clinico-pathological
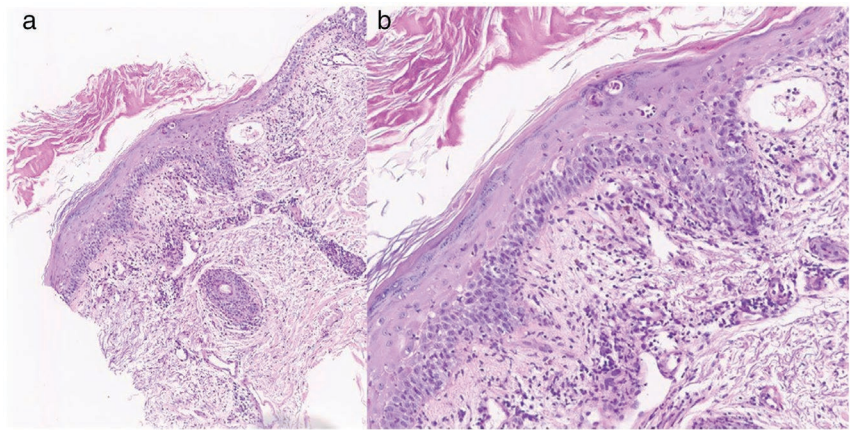
Figure 4 Histopathological features case 2 – immunotherapy-related subacute cutaneous lupus erythematosus. A superficial lymphocytic dermal infiltrate with vacuolar interface dermatitis, apoptotic keratinocytes in the overlying epidermis, and a papillary dermal edema is visible.

correlation, SCLE due to pembrolizumab therapy (CTCAE III) was diagnosed. Systemic treatment with prednisolone at 1 mg per kg body weight was initiated and topical steroid treatment commenced. This led to resolution of the skin lesions, and the prednisolone was tapered off over a period of several weeks. The immunotherapy was discontinued due to the dermatological side effects.

Severe cutaneous drug reactions

Severe bullous drug reactions such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) have been reported as very rare side effects of immunotherapy [7, 11, 35, 54]. They typically present with rapidly progressive, coalescing, dark red macules and atypical cockades with blistering, positive Nikolski phenomenon, and hemorrhagic-erosive involvement of the mucous membranes [35]. Frequently, in cases of first-time use the causative medication was initiated within the last four weeks. With CPI treatment, as well, most of the reactions occurred after the first or second administration [35]. The long half-life of substances like pembrolizumab may explain why reactions occur three weeks after first administration or shortly after the second dose. Individual case reports on delayed severe bullous drug reactions after immunotherapy have also been published. In these cases, non-specific maculopapular exanthemas preceded the bullous lesions [35, 36]. Reschke et al. [7], however, suggested that some of the SJS/TEN case reports from the literature should rather be categorized as bullous lichenoid drug eruptions. Due to a number of histopathological and clinical overlaps, it can be quite difficult to differentiate SJS/TEN from the much more common bullous lichenoid exanthemas. However, the latter present with slower clinical progression, less severe involvement of the mucous membranes, and a better prognosis. Histopathology in SJS/TEN shows cytotoxic interface dermatitis with varying epidermal necrosis and sparse lymphocytic dermal infiltration [14]. On the other hand, acanthosis, hypergranulosis, and a more prominent lichenoid lymphocytic infiltration favor the diagnosis of lichenoid drug eruption [7, 14].

Bullous lichenoid exanthemas are an important differential diagnosis for severe bullous drug reactions (SJS/TEN) with immunotherapy. These side effects are very rare.

For differential diagnosis, a careful anamnesis of medications is essential to identify other possible causes for SJS/TEN such as allopurinol, sulfonamides, or

aromatic anticonvulsants. Bullous autoimmune dermatoses and staphylococcal scalded skin syndrome (SSSS) need to be excluded [7].

There are only a few individual case reports on other severe cutaneous drug reactions with immunotherapy such as DRESS syndrome (drug reaction with eosinophilia and systemic symptoms) or AGEP (acute generalized exanthematous pustulosis) [57, 58]. Other well-conducted case reports and case series are needed before these can be categorized as rare immunotherapy-associated drug reactions.

Other exanthematous skin reactions

Morbus-Grover-like exanthema with pruritic papules and papulovesicles mainly on the trunk has been reported in association with CPI treatment, frequently occurring within the first 3–6 weeks after treatment initiation [5, 59].

Succulent erythematous plaques and fever in temporal connection with immunotherapy may indicate Sweet Syndrome. Cases were usually reported in patients on ipilimumab treatment (a CTLA-4 inhibitor) [60–62].

Immune checkpoint inhibitors are increasingly used in patients with allogenic stem cell transplants, for example in recurrent or treatment refractory Hodgkin's lymphoma. This appears to be associated with an increased risk of graft-versus-host disease (GvHD), especially of severe acute GvHD, and needs to be considered in these patients [63, 64]. Acute GvHD on the skin frequently presents with pruritus and a generalized maculopapular exanthema originating from painful palmoplantar and retroauricular erythema. Accompanying symptoms often include hepatopathy and gastrointestinal involvement (tenesmus, watery diarrhea, vomiting), which may facilitate differentiation from classic drug rashes and chemotherapy side effects such as hand-foot syndrome. It is also necessary to exclude infectious causes including viral exanthemas in these patients [65].

> In patients with allogenic stem cell transplants and immunotherapy, maculopapular exanthema may indicate acute GvHD. This is often accompanied by hepatopathy and gastrointestinal symptoms.

Apart from these exanthematous effects, immunotherapy may also have other cutaneous irAE such as sarcoid-like reactions [66–68], vitiligo, particularly in patients with malignant melanoma, or pruritus.

Diagnostic procedure

If immunotherapy-associated exanthema is suspected, the first diagnostic step is to exclude alternative causes such as drug rash caused by other medications, or infectious exanthema. Occurrence of skin reactions within the first weeks or months after initiation of immunotherapy supports a CPI-associated origin once differential diagnoses have been excluded (Table 1).

Maculopapular exanthema may also be a precursor of more specific exanthemas or severe cutaneous drug reactions. Severe, treatment-refractory, or atypical exanthemas therefore always require a comprehensive dermatological investigation including skin biopsy (histology and direct immunofluorescence) and case-specific laboratory analyses. The appearance of known warning signs for severe cutaneous drug reactions (fever, swelling of face and lymph nodes, eosinophilia, involvement of the mucous membranes, grayish skin with increased sensitivity to pain, epidermal detachment, erosions) necessitates rapid assessment [69].

> For pronounced, treatment-refractory, or atypical exanthemas, skin biopsies and case-specific laboratory investigations are recommended to improve etiological characterization.

If exanthemas mainly appear in areas exposed to light, the patient must be examined for other skin reactions that may indicate connective tissue disease. Histological and laboratory analyses including ANA, SSA-/SSB, dsDNA, anti-histone and myositis antibodies as well as determination of creatinine kinase levels in case of muscle complaints, are recommended in these cases.

> If exanthema appears mainly in light-exposed areas, connective tissue disease-associated exanthema needs to be considered.

In cases of bullous skin reactions or skin lesions with pronounced, treatment-refractory pruritus, bullouse autoimmune dermatoses need to be excluded – especially bullous pemphigoid and its pre-bullous precursor. This requires a skin biopsy and serological evaluation including indirect immunofluorescence and determination of BP-180/BP-230 auto-antibodies.

Treatment

General principles on treating cutaneous irAE

Therapeutic management needs to be adapted to the severity of the cutaneous side effect according to the CTCAE classification, thus the grade of severity must routinely be evaluated and documented accordingly [4, 70]. The CTCAE classification version 5 offers detailed grading for various cutaneous side effects. Extent of the affected body surface, severity of associated symptoms, and patients' impairment of daily activities and quality of life are the most important criteria for grading [8]. Table 2 summarizes relevant criteria for immunotherapy-associated exanthemas and the corresponding therapeutic measures. While the CTCAE classification constitutes a valuable support tool for non-dermatologists, from a dermatological point of view a more precise characterization of cutaneous irAE according to the variants of immunotherapy-associated exanthemas described above is to be desired. This permits better assessment of the further course of the disease, and a more targeted choice of treatment. The diagnosis of SJS, for example, is described as a Grade III reaction in the CTCAE classification (Table 2) – a fact that definitely appears worthy of discussion from a dermatological point of view. SJS has completely different prognostic and therapeutic consequences than a maculopapular exanthema with the same grade of severity according to CTCAE.

> Most cutaneous irAE are mild (Grade I/II), they can be managed very well with early and appropriate topical treatment, and they do not usually require discontinuation of immunotherapy.

The majority of cutaneous irAE, especially the most common maculopapular, lichenoid, and psoriasiform reactions, are rather mild (Grade I/II); they can be managed very well with early and appropriate topical treatment, and they do not usually require discontinuation of immunotherapy [11, 21].

For mild symptoms, temporary use of topical glucocorticoids (medium and high potency) is the basic recommended treatment. Discontinuation of immunotherapy and, if appropriate, systemic glucocorticoids are required for persistent and severe (Grade ≥ III) exanthemas (Table 2). Decisions on continuation of immunotherapy must be taken on an individual basis and by an interdisciplinary team. This decision needs to consider the present response to oncological treatment, the therapeutic goal (palliative or curative), the patient's impairment of quality of life due to the cutaneous irAE, and the response to topical and systemic dermatological treatment. In cases of severe cutaneous adverse reaction, immunotherapy must always be discontinued [54].

> Topical glucocorticoids for mild exanthema and systemic glucocorticoids for severe exanthema constitute the mainstay of treatment for cutaneous irAE. Discontinuation of immunotherapy is required in case of persistent and severe exanthema (Grade ≥ III).

A classic drug rash will usually resolve rapidly after withdrawal of the causative medication. In contrast, immune-related cutaneous adverse events may show a protracted and sometimes recurrent course even after withdrawal of the medication, due to the persistent immune-mediated effects [17, 28]. Maintenance therapy may be required, and relapses with increased disease activity may occur after further administrations of immunotherapy [11].

> Persistent immunological effects of immunotherapy may frequently cause a protracted course of cutaneous irAE, even after discontinuation of immunotherapy.

Specific treatment measures

In cases of specific dermatological manifestations, appropriate therapeutic options for the relevant dermatosis can be employed. This underscores the importance of

Table 2 CTCAE grading (severity) scale for cutaneous drug eruptions and implications for the therapy of cutaneous immune-related adverse events associated with immune checkpoint inhibitors.

	Grade I (mild)	Grade II (moderate)	Grade III (severe)	Grade IV (life-threatening)	Grade V (death)
Symptoms	– Skin eruptions < 10 % of BS – no/mild concomitant symptoms	– Skin eruptions 10–30 % of BS or maculopapular/papulo-pustular exanthema > 30 % of BS without/with mild concomitant symptoms (pain, pruritus) – asymptomatic erythroderma – impaired IADL	– Skin eruptions > 30 % of BS with moderate to severe concomitant symptoms (pain, pruritus) – Erythroderma with mild concomitant symptoms (pruritus, pain) – SJS (skin detachment < 10 % of BS) – impaired BADL	– Skin eruptions > 30 % of BS with associated fluid/electrolyte imbalance – Treated in intensive care or burn unit – SJS-/TEN overlap (skin detachment 10–30 % of BS) – TEN (skin detachment > 30 % of BS)	–
Treatment of cutaneous irAE [4]	– General measures (gentle skin care, avoiding UV exposure and skin irritation) – Topical glucocorticoids (low potency) – Continue immunotherapy	– General measures (gentle skin care, avoiding UV exposure and skin irritation) – Topical glucocorticoids (medium to high potency) – Continue immunotherapy with weekly monitoring; if no improvement: Treat as in Grade III	– Topical glucocorticoids (high potency) – 0.5–1 mg/kg prednisolone; if improved: reduce dosage over a period of 2–4 weeks* – Temporary discontinuation of immunotherapy; re-evaluate continuation if CTCAE ≤ Grade I/mild Grade II and prednisolone dose ≤ 10 mg	– Topical glucocorticoids (high potency) – 1–2 mg/kg prednisolone; if improved: reduce dosage over a period of at least 4 weeks* – Terminate immunotherapy	–

Abbr.: BADL, basic activities of daily living (such as body care, eating); BS, body surface; CTCAE, Common Terminology Criteria for Adverse Events; IADL, instrumental activities of daily living (such as cooking, shopping, housework, use of transport); irAE, immune-related adverse event; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

*In verified cases of SJS/TEN: short-term systemic corticosteroid treatment < 1 week, consider early administration of ciclosporin (3–5mg/kg for 10 days).

Appropriate targeted and immunomodulatory treatment approaches may be employed for specific dermatological manifestations. These include phototherapy or retinoids for psoriasiform and lichenoid exanthema as well as dapsone or doxycycline for bullous pemphigoid.

characterizing exanthemas as clearly as possible. Since the patients have underlying malignant disease, immunmodulatory and targeted therapies are prefered. The idea is to mitigate any possible negative effect of broad immunosuppression on the antitumor efficacy of immunotherapy. The same concerns apply to the use of biologicals in this patient cohort, so due to the limited experience available they should only be used in treatment-refractory cases [22, 35, 71]. However, study data indicate that application of systemic glucocorticoids for treatment of irAE, at least, is not associated with an impaired prognosis [72].

For severe lichenoid exanthemas including bullous forms, specific treatments include retinoids or phototherapy – the latter with the exception of melanoma patients [18, 31]. For psoriasiform exanthemas that cannot be managed adequately by topical glucocorticoids or vitamin D3 analogs, phototherapy and retinoids are indicated as well. Apremilast and methotrexate are proven options as a subsequent therapeutic step [21, 22].

Protracted cases of SCLE occurring while on immunotherapy can be treated with hydroxychloroquine, and dermatomyositis with intravenous immunoglobulin [42, 46, 48, 49].

Discontinuation of immunotherapy often becomes necessary in cases of bullous pemphigoid or lichen planus pemphigoides. The decision if treatment should be continued must be taken individually [11, 26]: In mild cases, continuation of immunotherapy is possible with accompanying topical corticosteroids and frequent dermatological examinations [28, 29]. In severe cases, systemic glucocorticoids and discontinuation of immunotherapy are mandatory [25, 28]. Maintenance treatment is often indicated; immunomodulatory substances such as dapsone or doxycycline are appropriate medications [11, 26, 32]. Omalizumab has also been used successfully, especially in patients with increased total IgE [26, 73]. There are also some individual case reports on the use of rituximab, with varying success [29, 74, 75]. With continued maintenance treatment, reduction of the systemic steroid dose and re-introduction of immunotherapy may be feasible [26].

In confirmed cases of SJS/TEN, it is recommended to start medication with ciclosporin (3–5 mg/kg BW for 10 days) as early as possible, and limit systemic steroid treatment to just a few days [76, 77].

Inhibitors of the epidermal growth factor receptor (EGFR)

Case report 3: On the fifth day of treatment with the EGFR inhibitor erlotinib for metastasized lung cancer, a 73-year-old male patient developed a papulopustular exanthema on the upper back, the upper chest, and the face (Figure 5). He also reported mild pruritus.

EGFR inhibitors (EGFRI) are used for a broad range of oncological disease such as lung cancer, breast cancer, and gastrointestinal cancer as well as squamous cell carcinoma of the skin and the head and neck region. The EGFR pathway can be inhibited either in the extracellular or the intracellular space – extracellularly via parenteral administration of monoclonal antibodies, and intracellularly with oral 'small molecules'.

EGFR is an important regulator of cutaneous homeostasis, and any intervention in the EGFR pathway may cause the typical range of cutaneous side effects.

EGFR is expressed in many parts of the skin, especially in the basal keratinocytes, the outer hair root sheath, the sweat glands, and the sebaceous glands [78]. EGFR inhibition leads to impaired differentiation of keratinocytes and epithelial cells in the skin appendages. This has been histopathologically shown in both affected and healthy skin [79, 80]. EGFR inhibition also resulted in an increased expression of pro-inflammatory cytokines and chemokines as well as a decrease of

Figure 5 Follicular papulopustular eruption with emphasis on seborrheic and UV-exposed areas on the upper back, chest (a) and face (b, c).

antimicrobial peptides [79, 81]. The latter fact may explain the increased susceptibility to cutaneous superinfections seen with EGFRI treatment, especially infections caused by *Staphylococcus aureus* [82]. EGFR is thus an important regulator for cutaneous homeostasis, and interventions in the EGFR pathway are associated with a typical range of cutaneous side effects.

Papulopustular exanthemas are the most common cutaneous side effects of EGFR inhibitors. After several weeks of treatment, about 30 % of patients also develop xerosis cutis with a tendency towards asteatotic eczema. Other cutaneous side effects include pruritus, increased photosensitivity, and hair disorders (trichomegaly, alopecia, hirsutism) [83]. One particularly distressing side effect is painful paronychia, which occurs in 17 % of patients around two months after treatment initiation, especially on the big toes [84, 85]. Initially, the nail affection is sterile, but bacterial and fungal superinfections are common [85]. The typical temporal course of cutaneous side effects with EGFRI is depicted in Figure 6.

Exanthemas in the framework of severes cutaneous adverse reactions are a rarity with EGFRI treatment. Very few individual case reports exist on severe bullous drug reactions (SJS/TEN) with osimertinib [86–88], afatinib [89, 90], and cetuximab [91, 92].
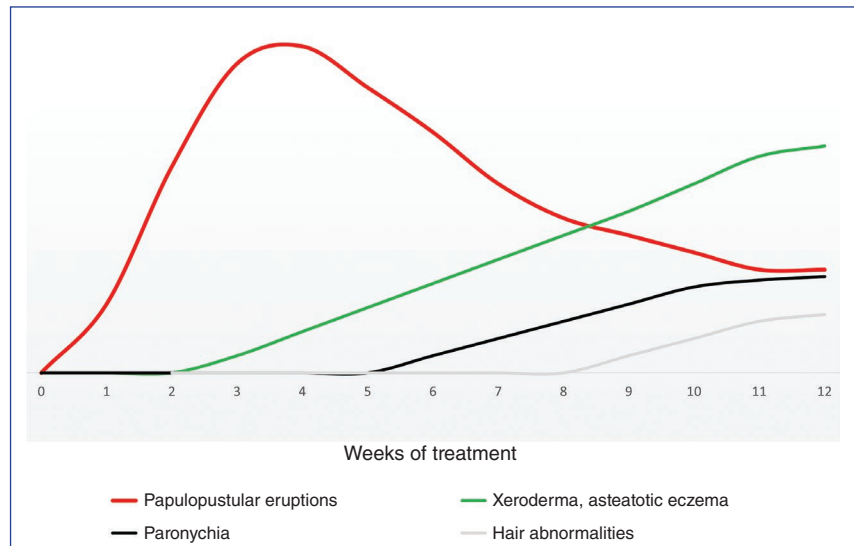
Papulopustular exanthemas

Papulopustular exanthemas are the most common cutaneous side effect of EGFRI. Severity is also graded according to the CTCAE criteria (Table 2) [8]. Papulopustular exanthemas occur more frequently (70–90 %) with monoclonal antibodies and afatinib (a second-generation tyrosine kinase inhibitor with irreversible and broad inhibition of the entire ErbB receptor family), and they are also more severe (Grade III/IV exanthemas in 10–15 %) [93]. With other tyrosine kinase inhibitors, especially third-generation substances (such as osimertinib), skin reactions appear to occur less frequently and to be milder [94, 95].

Clinically, follicular papules and pustules will appear within two weeks of treatment initiation (Figure 5). Seborrheic areas and those exposed to UV radiation are affected while regions with previous radiation therapy remain spared [96]. Despite the frequently used term "acneiform rash", the eruption, as opposed to classic acne, lacks the typical blackheads while dysesthesia and pruritus are common [83]. With continued therapy, the papulopustules will become

Papulopustular exanthema is the most common cutaneous side effect of EGFRI. Asteatotic eczema, paronychia, and hair disorders may also occur.

Papulopustular exanthemas occur in up to 90 % of patients with EGFRI treatment, especially with monoclonal antibodies and afatinib.

Figure 6 Cutaneous side effects during EGFR inhibitor therapy over time. Papulopustular eruptions occur within the first 2–4 weeks after therapy initiation and typically improve spontaneously over the subsequent weeks, whereas xerosis simultaneously increases. Several weeks after therapy initiation paronychia and hair abnormalities arise.

Papulopustular skin reactions in seborrheic and UV-exposed areas within the first two weeks of treatment are typical.

encrusted, partly in a hemorrhagic manner, and a slow improvement of the symptoms occurs [83]. After resolution, the affected areas frequently show erythema with teleangiectasia, xerosis cutis, and less frequently post-inflammatory hyperpigmentation [79].

Due to the close temporal correlation and the characteristic clinical appearance there is usually no difficulty with differential diagnoses. However, other drugs may also cause "drug acne", albeit less frequently (Table 3) [97]. The clinical picture in these cases also shows monomorphic papular to papulopustular skin lesions (initially without blackheads) with abrupt onset at an age untypical for acne vulgaris and sometimes spreading beyond the seborrheic areas [97]. In cases of atypical clinical appearance and further course, infectious folliculitis must be excluded via microbiological diagnostics.

Prognosis

A patient's quality of life and treatment adherence may be impaired by the burdensome symptoms, so it is essential that the patient be informed about this side effect beforehand and that prophylactic measures are initiated already at the start of therapy.

Various studies have shown that patients with EGFRI-associated papulopustular exanthema actually responded better to oncological therapy [98, 99]. Tentative approaches to find the optimal dose by increasing dosage until papulopustular reactions appeared, however, did not result in any positive effects on overall survival, and have been rejected [100, 101]. If tolerated by the patient, papulopustular exanthema is therefore not a contraindication for continued therapy. However, a patient's adherence to treatment may be impaired by the burdensome symptoms, so it is essential that the patient be informed about this side effect beforehand and that prophylactic measures are initiated already at the start of therapy.

Table 3 Common causes of drug-induced papulopustular eruptions.

Drug class	Substances
Steroids	Glucocorticoids, anabolic/androgenic steroids
Anti-tuberculosis drugs	Isoniacide, rifampicin
Neuropsychiatric therapies	Lithium, anticonvulsants (phenytoin, carbamazepine, lamotrigine), aripiprazol
Vitamins	High-dose vitamin B1, B6, and B12
Immunosuppressive treatments	Ciclosporin
Halogens	Bromine, iodine, chlorinated hydrocarbons
Targeted therapies	
EGFR inhibitors	Monoclonal antibodies (cetuximab, panitumumab), small molecules (gefitinib, erlotinib, afatinib, dacomitinib, lapatinib, osimertinib)
MEK inhibitors	Trametinib, cobimetinib
Multi-tyrosine kinase inhibitors	Sorafenib, sunitinib, regorafenib, axitinib
mTOR inhibitors	Sirolimus, everolimus, temsirolimus
Proteasome inhibitors	Bortezomib

Abbr.: EGFR, epidermal growth factor receptor; mTOR, mechanistic target of rapamycin.

Prophylaxis

The following prophylactic lifestyle and skincare measures are recommended:

▸ Use of emollient basic skin care with urea twice a day; only gentle, pH adjusted shower gels,
▸ Avoidance of mechanical, physical, and chemical skin irritation,
▸ Consistent use of sunscreen with high UV protection due to the treatment-associated, increased photosensitivity. However, sunscreen has no proven direct effect on EGFRI-mediated papulopustular exanthemas [102].

For substances associated with a high incidence of papulopustular exanthema, tetracycline prophylaxis for at least eight weeks from the initiation of EGFRI treatment can be recommended, while a "wait and see" approach may be justified for tyrosine kinase inhibitors with a low risk of exanthema.

Prophylactic use of tetracyclines (off label) is recommended in the S3 guideline of the German Cancer Society as a level B recommendation [93]. Its primary effect is a reduction of moderate/severe exanthema by 50–70 %, with only a small effect on the general incidence of exanthema [93, 103]. There were no negative effects regarding oncological treatment success, and a retrospective study even found a positive effect on overall survival with prophylactic tetracycline use [104, 105]. For prophylaxis, tetracyclines are administered at therapeutic doses from the initiation of EGFRI treatment for at least eight weeks. Tetracycline prophylaxis appears to be particularly useful in cases with substances with a high incidence of papulopustular exanthema, while in cases with tyrosine kinase inhibitors with a low risk of exanthema a "wait and see" approach may be justified.

Treatment

External treatment with antibiotics and steroids, as well as systemic tetracyclines, are the mainstays of treatment.

External treatment of papulopustular exanthema alternates between topical antibiotics (1 % clindamycin, 0.75–2 % metronidazol, 1 % nadifloxacin) and topical medium to high-potency corticosteroids. "Classic" topical acne treatments such as benzoyl peroxide, azelaic acid, or retinoids are not recommended due to their drying effect. The same applies to topical calcineurin inhibitors. If no systemic prophylactic tetracycline treatment has been administered, this should be established

(doxycycline 200 mg/day, lymecycline 300 mg/day, minocycline 100 mg/day). A response may be expected after 1–4 weeks, but there are no studies on optimum treatment duration. A pragmatic approach would be to consider discontinuation of the tetracyclines after eight weeks if the patient has responded well, or proactively continue treatment at a reduced dose (doxycycline 40 mg/day). The risk of relapses, however, will be increased since sub-antimicrobial doses are demonstrably associated with reduced efficacy [106]. For pustular skin lesions suspected of bacterial superinfection, a bacterial swab is recommended to detect tetracycline-resistant organisms. Appropriate antibiotic treatment according to the antibiogram, for example with first-generation cephalosporins, should then be established. In cases of severe exanthema (grade III/IV) and failure of tetracycline therapy, switching to low-dose isotretinoin (20–30 mg/day) and short-term systemic glucocorticoid treatment is an option. For CTCAE grade III onwards, the substance-specific summaries of product characteristics (SPC) on treatment discontinuation and dose modification need to be consulted [93, 107, 108].

Continuation Case report 3: Based on the clinical appearance and the temporal connection with initiation of erlotinib treatment, the diagnosis was "EGFRI-associated papulopustular exanthema" (CTCAE grade III). It was treated with systemic lymecycline 300 mg/day plus external clindamycin lotion and class III topical steroids. This resulted in a slow resolution of the pustular skin lesions. Erlotinib treatment was continued at a lower dose until the tumor progressed.

Conclusion

Due to the ongoing development of new targeted therapies, particularly in the field of oncology, dermatologists will continue to encounter new cutaneous side effects. Adequate diagnosis and management of these side effects are of great importance, not least because they can help ensure the success of oncological therapy by avoiding unnecessary breaks or discontinuation of immunotherapy. In view of the rapidly evolving medical literature, continuous and critical analysis of the publications is mandatory. It is not uncommon to find only single or incompletely documented case reports on rare cutaneous side effects, where the causal connection to a specific drug needs to be subsequently verified by well-documented case series and studies.

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CME Questions/Lernerfolgskontrolle

1.   Welche Aussage zu lichenoiden Arzneimittelexanthemen ist richtig?
a)   Bei Auftreten eines lichenoiden Arzneimittelexanthems kann das auslösende Medikament durch eine allergologische Hauttestung mit großer Wahrscheinlichkeit identifiziert werden.
b)   Durch eine histopathologische Untersuchung kann ein lichenoides Arzneimittelexanthem sicher von einem klassischen Lichen ruber planus unterschieden werden.
c)   Im Gegensatz zum klassischen Lichen ruber planus tritt Juckreiz äußerst selten bei Immuntherapie-assoziierten lichenoiden Arzneimittelexanthemen auf.
d)   Immuntherapie-assoziierte lichenoide Arzneimittelexantheme verlaufen häufig schwer.
e)   Lichenoide Exantheme stellen eine relativ häufige immunvermittele Nebenwirkung unter Checkpoint-Inhibitor-Therapie dar.

2.   Welche Aussage zu kutanen immunvermittelten Nebenwirkungen unter Immuntherapie mit Checkpoint-Inhibitoren ist richtig?
a)   Sie stellen seltene immunvermittelte Nebenwirkung dar.
b)   Ein Auftreten von Immuntherapie-assoziierten Exanthemen bereits nach der ersten Checkpoint-Inhibitor-Gabe ist nicht möglich.
c)   Nach Absetzen der Immuntherapie bilden sich die Hautveränderungen häufig rasch und spontan zurück.
d)   Häufig sind die kutanen immunvermittelten Nebenwirkungen mild und beeinträchtigen die Therapiefortführung nicht.
e)   Exantheme im Rahmen von neu aufgetretenen Kollagenosen sind die häufigste Manifestation von Immuntherapie-assoziierten Exanthemen.

3.   Welche der folgenden autoimmunbullöse Dermatosen kommt am häufigsten unter Immuntherapie mit Checkpoint-Inhibitoren vor?
a)   Pemphigus vulgaris
b)   lineare IgA-Dermatose
c)   bullöses Pemphigoid
d)   paraneoplastischer Pemphigus
e)   Pemphigus foliaceus

4.   Eine Patientin entwickelt zwei Wochen nach Einleitung einer PD-1-Inhibitor-Therapie ausgeprägte livide Erytheme mit Betonung der photoexponierten Areale (Dekolleté, Gesicht, Handrücken). Darüber hinaus wird eine zunehmende muskuläre Schwäche in den proximalen Extremitäten angegeben. Welche diagnostische Maßnahme trägt am wenigsten zur weiteren Diagnosefindung bei?
a)   Autoimmunserologie (ANA, Myositis-Antikörper)
b)   Hautbiopsie
c)   Bestimmung der Kreatininkinase
d)   Elektromyographie
e)   Abdomensonographie

5.   Welche Aussage zu psoriasiformen Exanthemen unter Immuntherapie mit Checkpoint-Inhibitoren ist richtig?
a)   Unter PD-1/PD-L1-Inhibitor-Therapie kommt es nicht selten zu einer exanthematischen Exazerbation einer vorbekannten milden Psoriasis.
b)   Bei Auftreten einer Psoriasis unter PD-1/PD-L1-Therapie muss die Immuntherapie in der Regel abgebrochen werden.
c)   Bei Immuntherapie-assoziierten psoriasiformen Exanthemen stellen die modernen Biologika die Therapie der ersten Wahl dar.
d)   Die generalisierte pustulöse Psoriasis stellt unter Immuntherapie mit Checkpoint-Inhibitoren die häufigste Psoriasis-Verlaufsform dar.

e)   Eine Psoriasis Erstmanifestation unter Checkpoint-Inhibitor Therapie wurde bisher nicht beschrieben.

6.   Welche Aussage zur Therapie von Immuntherapie-assoziierten Exanthemen ist richtig?
a)   Eine rasche und aggressive immunsuppressive Therapie ist notwendig.
b)   Der Einsatz von systemischen Glukokortikoiden zur Therapie von immunvermittelten Nebenwirkungen geht nachgewiesener Weise mit einer schlechteren Tumorprognose einher.
c)   Bei einem Immuntherapie-assoziierten bullösen Pemphigoid stellt Rituximab die Therapie der ersten Wahl dar.
d)   Bei lichenoiden und psoriasiformen Exanthemen unter Immuntherapie sind Retinoide und eine Phototherapie kontraindiziert.
e)   Vor Wiederbeginn der Immuntherapie wird empfohlen eine Prednisolondosis von ≤ 10 mg zu erreichen.

7.   Welche der folgenden ist keine bekannte kutane Nebenwirkung unter EGFRI-Therapie?
a)   Exsikkationsekzeme
b)   Papulopustulöse Exantheme
c)   Trichomegalie
d)   Paronychie
e)   Vitiligo

8.   Welche Aussage zum Management von papulopustulösen Exanthemen unter EGFRI-Therapie ist richtig?
a)   Prophylaktische Maßnahmen sind nicht möglich.
b)   Klassische Lokaltherapeutika für die Akne vulgaris wie Benzoylperoxid oder Retinoide stellen Therapien der ersten Wahl dar.

c) Bei Auftreten eines papulopustulösen Exanthems muss eine EGFRI-Therapie sofort abgebrochen werden.

d) Topische Therapiemaßnahmen spielen in der Therapie von EGFRI-assoziierten papulopustulösen Exantheme keine Rolle.

e) Bei fehlenden Kontraindikationen kann besonders bei monoklonalen EGFR-Antikörpern eine prophylaktische Therapie mit Tetrazyklinen ab Beginn der EGFRI-Therapie angeboten werden.

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9. Welches der folgenden Arzneimittel ist höchstwahrscheinlich nicht für das Entstehen von papulopustulösen Hautveränderungen verantwortlich?

a) Glukokortikoide

b) Aripiprazol

c) Sirolimus

d) Ciclosporin

e) Ramipril

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10. Welche Aussage zur klinischen Präsentation von papulopustulösen Hautveränderungen unter EGFRI-Therapie ist richtig?

a) Komedonen treten regelmäßig mit Beginn der papulopustulösen Hautveränderungen auf.

b) Die papulopustulösen Exantheme treten meist erst nach mehreren Therapiemonaten auf.

c) Pruritus und Dysästhesien sind häufige Begleitsymptome.

d) Für die Patienten stellen sie nur selten eine Beeinträchtigung in ihrer Lebensqualität dar.

e) Im Gegensatz zur Akne vulgaris finden sich die Hautveränderungen nicht in den seborrhoischen Arealen.

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 31. Dezember 2021. Die richtige Lösung zum Thema „Lichen Planus – ein Klinikleitfaden" in Heft 6 (Juni 2021) ist: (1e, 2d, 3c, 4e, 5a, 6e, 7e, 8e, 9e, 10c).

Bitte verwenden Sie für Ihre Einsendung das aktuelle Formblatt auf der folgenden Seite oder aber geben Sie Ihre Lösung online unter http://jddg.akademie-dda.de ein.