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Clinical Cancer Research

Cytotoxic Cutaneous Adverse Drug Reactions during Anti-PD-1 Therapy

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Abstract

Purpose: Immunotherapy has experienced impressive progress in cancer treatment. Antibodies against PD-1 improved survival in different types of cancer including melanoma. They are generally well tolerated. However, skin toxicities including pruritus, rashes, and vitiligo are reported. Although frequent, they have not been characterized further yet. In this analysis, we aimed to systematically assess and characterize the adverse cutaneous reactions observed in patients with melanoma treated with anti-PD-1 antibodies.

Experimental Design: Patients with melanoma were treated with anti-PD-1 antibodies within clinical trials and an early-access program. Adverse cutaneous eruptions that emerged in our melanoma patient cohort were systematically investigated and classified using histology and gene expression profiling in comparison with maculopapular drug rash, cutaneous GVHD, and the severe drug eruption toxic epidermal necrolysis (TEN).

Results: Between February 2013 and September 2015, 68 patients with stage IV melanoma were treated at the University Hospital Zurich (Zurich, Switzerland); 15 patients (22%) developed cutaneous reactions and 10 (15%) vitiligo. The cutaneous reactions ranged from small erythematous papules with mild pruritus to disseminated erythematous maculopapular rashes (MPR) without signs of epidermal involvement to severe MPRs, including epidermal detachment and mucosal involvement. Although skin involvement varied from mild rash to bullous drug eruptions, gene expression profiling pathogenically classified all investigated cases as TEN-like reactions.

Conclusions: As predicted by the PD-1 knockout mouse, anti-PD-1 antibodies frequently cause adverse cutaneous reactions. Gene expression profiling reminds in all cases of a TEN-like pattern, suggesting that PD-1/PD-L1 interaction is required to preserve epidermal integrity during inflammatory skin reactions.
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Introduction

Antibodies against PD-1, a checkpoint in the effector phase of cytotoxic T cells, have been successfully used in cancer immunotherapy (1–3). Through the binding to PD-1, its ligands, namely PD-L1 and PD-L2, inhibit T-cell–mediated immune responses. By preventing the binding of PD-L to PD-1, the FDA-approved antibodies, pembrolizumab and nivolumab, promote T-cell–mediated cytotoxic responses, which result in tumor regression in a variety of cancers (2). In several randomized pivotal studies, pembrolizumab and nivolumab demonstrated improved overall response rates and progression-free survival compared with chemotherapy or the anti-CTLA-4 antibody ipilimumab (4–7).

Besides efficacy, the introduction of anti-PD-1 antibodies led to a new benchmark for treatment tolerability in cancer being a treatment with very few adverse events. Adverse cutaneous reactions have however been reported. These include skin exanthemas with a frequency of 10% to 25% and vitiligo in 9% to 11% of the treated patients (2, 4, 5). Hua and colleagues hypothesize that vitiligo is associated with a favorable outcome of anti-PD-1 therapy (8). Moreover, one case of bullous pemphigoid in association with pembrolizumab (9) and one case of psoriasiform exanthema under nivolumab (10) have been published. The adverse cutaneous reactions observed under the treatment with anti-PD-1 antibodies have not been characterized in detail so far.

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous drug eruptions characterized by widespread macules, papules, and/or targetoid lesions with varying degrees of epidermal necrolysis clinically presenting as skin detachment and/or bullous skin lesions with mucosal erosions (11). Common drugs inducing SJS/TEN include allopurinol, trimethoprim–sulfamethoxazole, carbamazepin, lamotrigine, nevirapine, NSAIDs, phenobarbital, and phenytoin (12). The molecular events that cause potentially fatal SJS and TEN are only partially understood, although "drug"-specific adaptive immune responses in the effector phase of TEN are well documented (13). In the skin, T-cell–mediated immune responses occurring during SJS/TEN result in a massive keratinocyte apoptosis mediated by cytolytic molecules, including FasL (14), perforin/granzyme B (15), annexin A1 (16), and granulysin (17). Histologically, SJS and TEN are characterized by full-thickness epidermal necrolysis due to extensive keratinocyte apoptosis associated with varying degrees of inflammation and epidermal infiltration by $CD8^+$ lymphocytes.

In this study, we aimed to systematically assess and characterize the adverse cutaneous reactions observed in patients with

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Translational Relevance

Antibodies against PD-1 have revolutionized cancer immunotherapy. This article describes relevant skin toxicities emerging upon treatment with antibodies against PD-1, such as nivolumab and pembrolizumab. Skin toxicities were classified using histology and gene expression profiling in comparison with mild maculopapular drug rashes and severe drug eruptions, such as toxic epidermal necrolysis (TEN). Although the clinical picture was variable, ranging from mild to severe, gene expression profiling resembled in all cases to severe cytotoxic SJS/TEN–like patterns. This suggests that the PD-1/PD-L1 interaction is involved in the preservation of epidermal integrity during inflammatory skin reactions. We advocate a careful examination of the skin of patients treated with immunotherapy in the near future, as these adverse cutaneous reactions can imply a loss of epidermal integrity.

advanced melanoma treated with anti-PD-1 antibodies using gene expression profiling and compared the data with other clinical types of drug eruptions.

Patients and Methods

Patients with advanced melanoma were treated with either the anti-PD-1 antibody pembrolizumab (2 or 10 mg/kg) or with nivolumab (3 mg/kg) within clinical trials (clinicaltrials.gov NCT01704287, NCT01721746, and NCT02156804; refs. 4, 7) and an early-access program. The first 68 patients with melanoma treated with pembrolizumab or nivolumab at the University of Zurich (Zurich, Switzerland) were systematically investigated for adverse skin reactions by board-certified dermatologists experienced in immunotherapy and familiar with associated adverse events (S.M. Goldinger and/or R. Dummer).

Complete and accurate skin examinations were performed before and during immunotherapy. Previously selected untreated skin eruptions of eight patients emerging during therapy were biopsied and analyzed by histology. The decision to take a biopsy was based on whether the lesion was new (i.e., not apparent prior treatment start), on the severity (grade 2 or greater), on the localization and distribution (favoring multiple and disseminated lesions), and on the clinical characteristics (palpable or scaling presentation). In general, the most infiltrated lesion was chosen and biopsied provided patient's consent and that the lesion was in a region of the body that allowed proper wound healing. Expression of PD-1 on skin-infiltrating T cells (eBioscience) and PD-L1 (Immunobiology Yale, Yale University, New Haven, CT) on keratinocytes at the foci of lymphocytic epidermal infiltration was assessed by IHC.

Gene expression analyses of five of these eight skin biopsies during anti-PD-1 therapy with pembrolizumab were in addition analyzed and compared with expression profiles of skin biopsies from patients with maculopapular rashes (MPR; $n = 8$), SJS/TEN ($n = 5$), and cutaneous GVHD ($n = 9$). RNA was isolated from patients' skin ($n = 5$) and from healthy control skin ($n = 4$) using a Qiagen RNeasy Kit (Qiagen) following the manufacturer's instructions, and total RNA was converted into cDNA by standard reverse transcription using a RevertAid RT Reverse Transcription Kit (Thermo Scientific). Quantitative PCR was performed using Power SYBR Green PCR Master Mix (Applied Biosystems). Primer sequences were obtained from http://pga.mgh.harvard.edu/primerbank/. The real-time PCR included an initial denaturation at 95°C for 10 minutes, followed by 40 cycles of 95°C for 30 seconds, 56°C for 1 minute, and 72°C for 1 minute and one cycle of 95°C for 1 minute, 56°C for 30 seconds, and 95°C for 30 seconds. Moreover, we performed gene expression arrays (Affymetrix) on the skin of patients with MPR ($n = 8$), patients with SJS/TEN ($n = 5$), patients with GVHD ($n = 9$), and healthy donors ($n = 8$) as controls. Healthy skin was obtained from healthy individuals undergoing plastic surgery. All human skin biopsies were collected with informed written consent upon the approval of local ethical committees and were conducted according to the Declaration of Helsinki Principles (KEK nr. 647). On the basis of the results of the gene expression arrays, we selected a set of genes that could be used as a specific signature for TEN as opposed to MPR and GVHD (Fig. 2A). Using quantitative RT-PCR, we determined the expression levels of the gene set specific for SJS/TEN in the skin of patients with an adverse cutaneous reaction occurring during anti-PD-1 therapy.

Results

Between February 2013 and September 2015, 68 patients were treated with either pembrolizumab (2 and 10 mg/kg; every 3 weeks) or nivolumab (3 mg/kg; every 2 weeks) in different clinical trials (clinicaltrials.gov NCT01704287, NCT01721746, and NCT02156804; refs. 4, 7) and an early-access program. Of the first 68 patients with stage IV melanoma treated with pembrolizumab ($n = 54$) or nivolumab ($n = 14$) at the University Hospital of Zurich (Zurich, Switzerland), 15 patients (22%) developed a cutaneous inflammatory reaction, and 10 (15%) developed vitiligo. Clinically, the adverse cutaneous reactions ranged from small erythematous papules with mild pruritus to disseminated erythematous MPRs without major clinical signs of epidermal involvement to severe MPRs, including epidermal detachment and mucosal involvement (Table 1). Histology performed on selected lesional skin biopsies of eight patients at the onset of the adverse cutaneous reaction revealed different manifestation grades of apoptotic keratinocytes and even focal full-thickness necrosis of the epidermis in two cases in the histology (Table 1). In particular, a 77-year-old patient presented with a generalized unspecific MPR predominantly affecting the trunk with focal areas of epidermal detachment a few days after the first pembrolizumab infusion (Fig. 1A, <10% of the body surface area). Histology showed epidermal damage with apoptotic keratinocytes, subepidermal lymphocytic infiltrates, and dermo-epidermal cleavage (Fig. 1B). One week later, mucosal involvement and genital ulcerations developed. Taken together, these features led to a diagnosis of SJS, and pembrolizumab therapy was discontinued.

Skin biopsies from six patients were also analyzed by IHC and revealed in all cases an accumulation of $CD8^+$ cells at the dermo-epidermal junction and some $CD8^+$ exocytosis within the epidermis, as well as keratinocyte apoptosis suggestive of a cytotoxic etiology. Expression of PD-1 on skin-infiltrating T cells and keratinocytes at the foci of lymphocytic epidermal infiltration was also assessed by IHC (Fig. 1C and D). Despite topical steroids, the lesions of this patient subsequently evolved into persistent polygonal flat erythematous papules, clinically suggestive of

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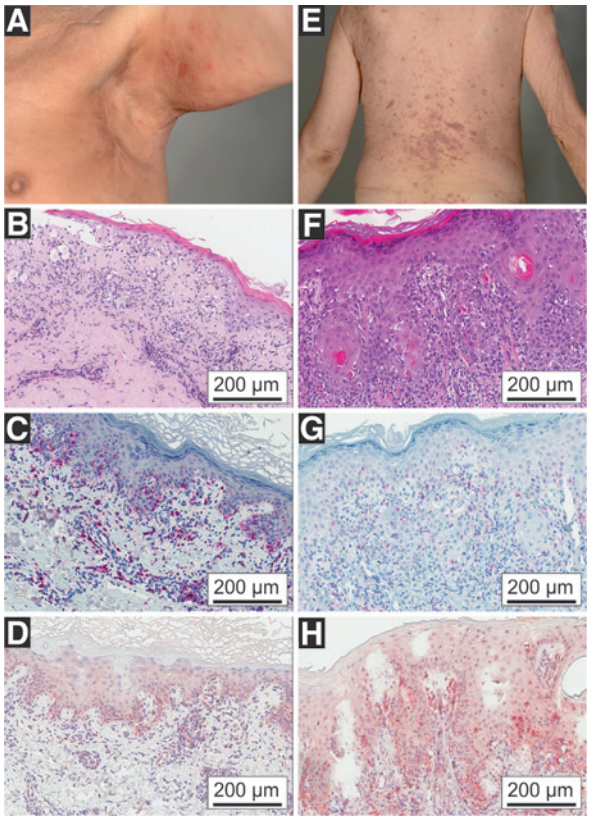

Figure 1.
Clinical and histologic presentation of a patient with metastatic melanoma developing a severe adverse cutaneous reaction (ACR) upon treatment with pembrolizumab. A–D, SJS. E–H, lichen planus. A, clinical features of SJS. B, histology of SJS (hematoxylin–eosin stain). C, PD-1 stain of SJS. D, PD-L1 stain of SJS. E, clinical features of lichen planus. F, histology of lichen planus. G, PD-1 stain of lichen planus. H, PD-L1 stain of lichen planus.

lichen planus (Fig. 1E). Accumulation of cytotoxic $CD8^+$ lymphocytes in the junction zone and in the epidermis, causing apoptotic cell death of keratinocytes, classical for lichen planus, was confirmed by histology (Fig. 1F). PD-L1 expression on keratinocytes was clearly detectable by IHC in the proximity of T cells (Fig. 1G and H).

In all cases, none of the concomitant medications taken by patients had been recently started or were known to cause SJS/TEN (Table 1). Furthermore, lymphocyte transformation tests to the concomitant medication taken by patient 1 did not provide evidence for a "drug"-specific immune response (data not shown; Table 1).

Treatment included systemic steroids (prednisone 1 mg/kg, tapered for 4 weeks), systemic steroids (over a course of 4 weeks), disinfectant agents when necessary, and rehydration of the skin. Treatment with pembrolizumab could be continued in six of eight cases and did not further affect the skin.

Gene expression profiling of RNA extracted from lesional skin of validated cases of MPR (eight cases), SJS/TEN (five cases), and cutaneous GVHD (nine cases) enabled us to identify a set of 18 genes for which the expression levels enable differentiation among the three diagnostic categories (Fig. 2A). Analysis of the level of expression of these 18 genes was performed in the lesional skin biopsies of five patients and revealed a gene expression profile reminiscent of SJS/TEN (Fig. 2B). Both SJS/TEN skin ($n = 5$) and skin of five patients presenting an adverse cutaneous reaction upon anti-PD-1 therapy had significant upregulation of *PI3*, *SPRR2B*, *GZMB*, *CXCL9*, *CXCL10*, and *CXCL11*; whereas expression of *DSC3*, *LOR*, *FLG*, and *KRT1* were similar to those in healthy skin. Differences were seen in the expression levels of *CCL27*, *NURR1*, *GNLY*, *FASLG*, and *PRF1*, which were all upregulated in the skin of the five anti-PD-1 patients, but not in SJS/TEN skin (Fig. 2B).

Taken together, our clinical, histologic, immunohistologic, and gene expression analyses provide evidence that the adverse cutaneous reactions observed in patients treated with anti-PD-1 antibodies are reminiscent of SJS/TEN and point to a role for PD-1 in regulating cytotoxic T-cell responses in the skin.

Discussion

The cross-talk between cancer cells and immune cells of the tumor microenvironment is crucial for the outcome of antitumor immune responses and immunotherapy. In various cancers, these interactions often result in a local immunosuppression, resulting in the escape of tumor cells from immunosurveillance. The use of checkpoint inhibitors, such as antibodies to PD-1, leads to significant clinical benefits by inducing advanced and metastatic tumor regression. Although anti-PD-1 antibody therapy is safe and well tolerated in patients with melanoma (2, 18–20), adverse cutaneous reactions have been reported (2, 4, 9, 10, 21). Here, we report and describe adverse cutaneous reactions during anti-PD-1 immunotherapy with pembrolizumab. In 22% of the patients, which is more than reported in clinical trials (4, 7, 21), we observed inflammatory skin lesions ranging from mild MPRs, typically associated with scaling and/or lichenoid lesions to very severe SJS-like skin lesions that slowly improved and resulted in a chronic lichen planus.

Clinical and histologic features of the lesions strikingly resemble the findings reported in mice with a disrupted PD-1 gene (22). These mice develop a lupus-like inflammatory syndrome with proliferative glomerulonephritis, arthritis with sometimes granulomatous inflammation and skin lesions, reported as "dermatitis-like lesions, necrotic lesions, and erythema" (22). The histologies of the skin of these mice present features compatible with lichen planus, including acanthosis, hypergranulosis, and apoptotic keratinocytes, together with a lymphocytic infiltrate of the grenz zone of the basal membrane resulting in a vacuolization and, sometimes, split formation (22).

The histologic analysis of these human adverse cutaneous reaction cases demonstrated signs of a cytotoxic skin eruption characterized by an accumulation of $CD8^+$ T cells at the dermo-epidermal junction and $CD8^+$ T-cell exocytosis into the epidermis with apoptotic keratinocytes. These features can also be observed in severe immune-mediated skin diseases, such as acute GVHD and SJS/TEN. Gene expression analysis of lesional skin from anti-PD-1–treated patients revealed a gene expression profile resembling SJS/TEN with an upregulation of major inflammatory chemokines, such as *CXCL9*, *CXCL10*, and *CXCL11*, of cytotoxic mediators such as *PRF1* and *GZMB* and the pro-apoptotic molecule *FASLG*, as well as an upregulation of PD-L1, which was confirmed by IHC in three cases. In contrast, the expression pattern of selected genes in the skin lesions of anti-PD-1–treated patients was different from that seen in acute GVHD and MPR. Therefore, clinical, histologic, immunohistologic, and gene

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Table 1. Patients' characteristics, clinical presentation, and histology of the adverse cutaneous reactions

	Characteristics [M/F; age (y)]	Onset (weeks after starting anti-PD-1 Abs)	Clinical presentation	Histology	Concomitant medication	Other possibly treatment related adverse reactions	Discontinuation of pembrolizumab (yes/no)	Treatment of the adverse cutaneous drug reaction
Patient 1	M; 76	1 (after 1 infusion)	MPR evolving into subepidermal blister formation including mucosal involvement with pain and pruritus, evolving into lichen planus	Four biopsies over time: 1. Lichenoid dermatitis with accumulation of $CD8^+$ cells at the dermo-epidermal junction and $CD8^+$ exocytosis and focal keratinocytic apoptosis 2. Lichenoid inflammation with vacuolization of junction zone and keratinocytic apoptosis 3. Lichenoid accumulation of cytotoxic $CD8^+$ lymphocytes in the junction zone and in the epidermis with apoptotic keratinocytes 4. Lichenoid inflammation with hyperkeratosis resembling lichen verrucosus	Phenprocoumon; spironolactone; acetylsalicylic acid; bisoprolol; metamizole[a]; rabeprazole; mirtazapine; lorazepam; torasemide, ramipril; oxycodone[a]; dalteparin[b]	None	Yes	Systemic prednisone 1 mg/kg (tapering for 4 weeks); topical steroids, including oral application for 4 weeks; topical disinfectants (panthenol, hyaluronate sodium with silver sulfadiazine; chlorhexidine) skin hydration
Patient 2	M; 66	6 (after 3 infusions)	Disseminated MPR with moderate pruritus	Lichenoid drug reaction with follicular accentuation focal spongiosis and $CD8^+$ exocytosis	Fluticasone/salmeterol; salbutamol	Vitiligo	No	Topical steroids for 4 weeks; skin hydration
Patient 3	M; 50	5 (after 3 infusions)	Disseminated MPR with main focus on the trunc and neck. No pruritus	Lichenoid dermatitis with vacuolization of junction zone and focal keratinocyte apoptosis	Pantoprazole[c]; bisoprolol[c]	Anemia (hemolysis)	Yes (due to anemia)	Topical steroids for 4 weeks; skin hydration
Patient 4	M; 82	1 (after 1 infusion)	Small erythematous papules with moderate pruritus	Lichenoid dermatitis with $CD8^+$ cells in the dermo-epidermal junction and focal full thickness necrosis	Phenprocoumon	None	No	Skin hydration
Patient 5	M; 72	51 (after 17 infusions)	Psoriasiform disseminated skin lesions predominantly on the lower extremities both sides. Mild pruritus	Two biopsies over time: 1. Focal acanthosis and spongiosis and some apoptotic keratino cytes with lichenoid aspect 2. Lymphocytic infiltration of the adnexa	Simvastatin; losartan; chondroitin sulfate	Vitiligo	No	Topical steroids for 4 weeks; skin hydratation
Patient 6	M; 78	21 (after 7 infusions)	Focal erythematous plaques on the trunk and on the neck with mild pruritus	Lichenoid drug reaction with lymphocytic infiltrate and few eosinophils	Candesartan; acetylsalicylic acid; atorvastatin	Vitiligo	No	Systemic prednisone 1 mg/kg (tapering over 2 weeks); topical steroids for 4 weeks; skin hydration
Patient 7	M; 58	9 (after 3 infusions)	Focal erythematous plaques on the lower leg with mild pruritus	Lymphocytic perivascular sleeve-like inilftrates and lichenoid inflammation with spongiosis	Lisinopril; ibuprofen; xylometazoline	Vitiligo	No	Topical steroids for 2 weeks; skin hydration
Patient 8	F; 66	60 (after 21 infusions)	Focal erythematous papule with moderate pruritus on the back	Acanthosis, papillomatosis, and lichenoid inflammation	Losartan	None	No	Skin hydration

[a]Start 8 weeks before onset.
[b]Start 1 week before onset.
[c]Start 4 weeks before onset.

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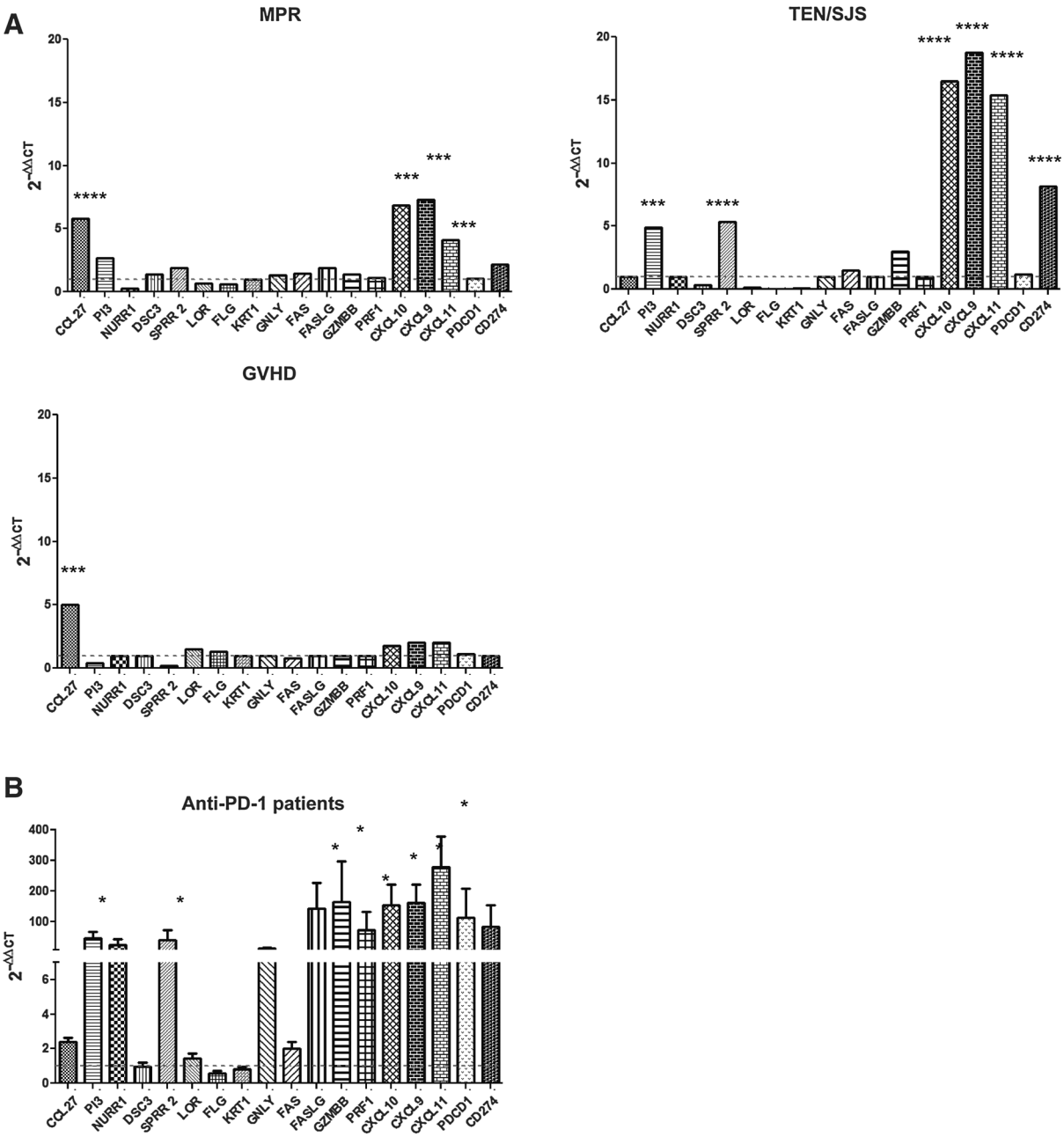

Figure 2.

Gene expression profiling. A, the mRNA expression levels of 6,564 different genes were measured in lesional skin of MPR; $n = 8$), TEN/SJS ($n = 5$), and GVHD ($n = 9$) patients and skin of healthy donors ($n = 8$) using the Affymetrix Human Transcriptome Array 2.0. The relative expression levels were normalized to healthy skin and indicated as fold change ($2^{-\Delta\Delta C_t}$). B, the mRNA expression levels of selected genes were measured in lesional skin of patients developing a skin drug eruption under anti-PD-1 therapy ($n = 5$). The relative expression levels were normalized to healthy skin ($n = 4$) and indicated as fold change ($2^{-\Delta\Delta C_t}$). Statistical analyses were performed using the Student t test. *, $P \leq 0.05$; **, $P \leq 0.01$; ***, $P \leq 0.001$; ****, $P \leq 0.0001$.

expression analyses strongly suggest that, at least in some patients, anti-PD-1 antibody can induce SJS/TEN–like adverse cutaneous reactions.

The intensity of the immune-mediated tissue damage varies and is interindividual, a possible explanation could be the genetic predisposition and variation based on SNPs in genes related to immune functions. These genetic background alterations can cause differences in the susceptibility to develop cutaneous drug reactions.

The exact pathomechanism of the adverse cutaneous reactions occurring upon pembrolizumab and nivolumab therapy remains to be elucidated. Although vitiligo can be considered as a successful (re)-activation of T cells with a repertoire specific to melanocyte antigens, the induction of a cytotoxic response to

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keratinocytes was not expected and is indicative of the activation of T cells with non-melanoma–derived self-antigen specificity (ies). Interestingly, both vitiligo and/or cutaneous reactions emerging during nivolumab treatment in patients with melanoma have recently been reported to be associated with overall survival (23). As a consequence, cutaneous reactions during anti-PD-1 treatment could potentially be used as biomarkers in the therapy. Although larger prospective analyses are still needed to validate this association, detection and diagnosis of cutaneous reactions during anti-PD-1 therapy gain further importance in this context. By inhibiting T-cell activation and sustaining Tregs (24), the PD-1/PD-L pathway plays a major role in peripheral tolerance, including transplant (25) and feto-maternal tolerance (26). The concept of a tolerogenic role for PD-1/PD-1L has emerged from observations that PD-1–deficient mice develop autoimmune pathologies (27), including lichenoid reactions (22). One could hypothesize that, at the steady state, PD-1/PD-L interactions are crucial for the homeostasis of T cells in the skin and for preventing severe skin-directed inflammatory reactions from occurring. In line with this, it has been recently reported that in a mouse model that PD-L1 expressed on keratinocytes presenting self-antigens, regulates autoreactive $CD8^+$ T-cell activity and prevents the development of cutaneous autoimmune disease (28). The reason for which cutaneous adverse events in anti-PD-1–treated patients can vary from vitiligo to SJS-like reactions remains unknown, and larger series of subjects would be required to assess this. A detailed characterization of the T cells causing damage to healthy tissues in patients treated with anti-PD-1 antibodies, as well as complementary skin investigations in patients without adverse skin reactions, would be of interest for a better understanding and, ultimately, the prevention of such severe forms of adverse cutaneous reactions.

Disclosure of Potential Conflicts of Interest

S.M. Goldinger is a consultant/advisory board member for Bristol-Myers Squibb, MSD, Novartis, and Roche. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: S.M. Goldinge, L.E. French, R. Dummer
Development of methodology: S.M. Goldinger, R. Dummer
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.M. Goldinger, P. Stieger, S. Micaletto, E. Contassot, R. Dummer
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.M. Goldinger, B. Meier, E. Contassot, L.E. French, R. Dummer
Writing, review, and/or revision of the manuscript: S.M. Goldinger, B. Meier, L.E. French, R. Dummer
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.M. Goldinger, P. Stieger, L.E. French, R. Dummer
Study supervision: S.M. Goldinger
Other (laboratory experiments): B. Meier

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