The Clinical and Histopathological Features of Cutaneous Immune-related Adverse Events and Their Outcomes

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Abstract

Background: Immune checkpoint inhibitors (ICIs) cause a variety of inflammatory eruptions. A better understanding of the rash types, histopathological findings, severity, and clinical courses is necessary for appropriate managements of these eruptions. Only a few reports reviewed ICI-induced inflammatory eruptions with detailed histopathological findings. Methods: In this study, we retrospectively reviewed 42 patients who were histopathologically diagnosed with cutaneous immune-related adverse events (irAEs) following ICI therapy between 2014 and 2020 at the Department of Dermatology of Kyushu University Hospital. Results: Of the 42 patients (24 males, 18 females), maculopapular rash (33/42, 78.6%), erythema multiforme (2/42, 4.8%), lichenoid reaction (3/42, 7.1%), psoriasiform reaction (1/42, 2.4%), bullous pemphigoid (1/42, 2.4%), scleroderma-like reaction (1/42, 2.4%), and Stevens-Johnson syndrome (1/42, 2.4%) were observed. The clinical and histopathological findings of these eruptions were equivalent to typical cases of common drug eruptions. The onset of maculopapular rash was relatively early (more than half of events occurred within 1 month), whereas lichenoid reactions and autoimmune diseases occurred relatively late (4–8 m¬¬onths). With appropriate treatment and/or interruption of ICIs, most rashes were improved (40/42, 95.2%). Conclusions: The ICI-induced inflammatory eruptions shared similar clinical and histopathological features with classical inflammatory eruptions, but a variety of inflammatory eruptions may occur with different degrees of severity. Dermatologists play an important role in providing specialized care for cutaneous immune-related adverse events.

Introduction

Immune checkpoint inhibitors (ICIs) have emerged as key anti-tumor drugs that leverage the immune system to promote anti-tumor activity. Monoclonal antibodies directed against programmed cell death 1 (PD-1; e.g., nivolumab, pembrolizumab), programmed cell death ligand 1 (PD-L1; e.g., avelumab, atezolizumab, durvalumab), and cytotoxic T-lymphocyte associated protein 4 (CTLA-4; e.g., ipilimumab) have been approved for treating multiple solid tumor types, including melanoma, Merkel cell carcinoma, head and neck squamous cell carcinoma, non-small cell lung cancer, urothelial carcinoma, renal cell carcinoma, and gastrointestinal cancers. Sustained anti-tumor responses can be elicited, but immune-related adverse events (irAEs) affecting multiple organs may also be triggered.[1–3] Cutaneous irAEs are the most frequent and usually the earliest irAEs arising in patients receiving ICIs. Dermatologists play an important role in evaluating and managing these cutaneous toxicities.

Cutaneous irAEs include a diverse group of inflammatory eruptions. Nonspecific maculopapular rash, pruritus, and lichenoid reactions are the most prevalent subtypes.[4–6] Other frequent cutaneous irAEs include erythema multiforme, psoriasiform reactions, bullous pemphigoid, dermatomyositis, and oral mucosal changes.[7, 8] Severe inflammatory eruptions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been also reported.[7–11] Vitiligo-like depigmentation occurs frequently in patients who receive anti–PD-1 agents for melanoma.[7, 8]

Clinical trials have demonstrated that cutaneous irAEs are more likely to develop during combination anti–CTLA-4 and anti–PD-1 therapy (i.e., 40.3% of patients with melanoma receiving nivolumab and ipilimumab) than during monotherapy with anti–PD-1 (25.9% of patients with melanoma receiving nivolumab) or anti–CTLA-4 (32.8% of patients with melanoma receiving ipilimumab).[12] Previous studies identified different rash types of irAEs and reported their characteristics, therapeutic impact, and response to treatment.[4, 5] However, no report has described the clinical and histopathological findings of cutaneous irAEs in Asian populations. This study analyzed cutaneous irAEs to better characterize the features of each rash.

Materials and Methods

We conducted this retrospective study in accordance with the concepts enshrined in the Declaration of Helsinki. This study was approved by the Kyushu University Institutional Ethics Committee (30-363; November 27, 2018).

We identified 42 patients who underwent skin biopsy and received a diagnosis of cutaneous irAE at the Department of Dermatology of Kyushu University Hospital between November 2014 and August 2020. The patients were referred to us for the evaluation of eruptions that developed during treatment with ICIs (nivolumab, pembrolizumab, ipilimumab, atezolizumab, avelumab, and durvalumab). Excluded patients were [1] those with inflammatory eruption attributed to another drug type other than ICIs (e.g. nonsteroidal anti-inflammatory drugs, antibiotics) and [2] those with an irAE of vitiligo alone or pruritus without inflammatory eruption. All skin biopsy samples were subjected to hematoxylin-eosin staining, and the diagnosis was confirmed by at least three experienced dermatopathologists.

The medical records were reviewed and analyzed for patient demographics, underlying malignancies, and medications. The grade of rash, the duration from the start of treatment to reaction, the presence or absence of pruritus and mucosal lesions, blood eosinophil counts, and the presence or absence of other irAEs were also analyzed according to the rash type, and the treatment of rash, response of rash, and impact of the rash on immunotherapy (none, temporarily interrupted, or discontinued) were analyzed according to the grade of rash. The rash grade was determined using Common Terminology Criteria for Adverse Events, version 5.0 as follows: a grade 1 rash covered <10% of the body surface area (BSA) with or without symptoms; a grade 2 rash covered 10–30% of the BSA with or without symptoms affecting instrumental activities of daily living (ADLs) or covered >30% of the BSA with or without mild symptoms without limiting self-care ADLs; a grade 3 rash covered >30% of the BSA with moderate or severe symptoms limiting self-care ADLs; and a grade 4 rash represented life-threatening consequences requiring urgent intervention including intensive care.

Results

Demographics, underlying malignancies, and medications

Forty patients with biopsy-proven cutaneous irAEs (24 males, 18 females) met the eligibility criteria. Patient demographics, underlying malignancies, and the ICIs administered are summarized in Table 1. The most frequent cancer types were lung cancer (n = 17) and melanoma (n = 12). Other malignancies (n = 13) included Merkel cell carcinoma (n = 1), cutaneous squamous cell carcinoma of the head and neck (n = 3), sebaceous carcinoma of the head and neck (n = 1), esophageal squamous cell carcinoma (n = 2), gastric adenocarcinoma (n = 1), renal cell carcinoma (n = 4), and urothelial carcinoma (n = 1).

Cutaneous irAEs were most commonly associated with the anti–PD-1 antibodies nivolumab (19/42, 45.2%) and pembrolizumab (10/42, 23.8%), followed by combination anti–PD-1 and anti–CTLA-4 therapy with

nivolumab and ipilimumab (5/42, 11.9%). The anti–PD-L1 antibodies atezolizumab (4/42, 9.5%) and avelumab (2/42, 4.8%) and anti–CTLA-4 antibody ipilimumab (2/42, 4.8%) were associated with fewer cutaneous irAEs.

Clinical presentations, histopathological diagnoses, and grade of rash

Diagnoses were rendered via clinicopathological correlation. Of the 42 cutaneous irAEs identified via skin biopsy, the most common rash type was maculopapular rash (33/42, 78.6%), namely scattered edematous macules and/or red papules. The diagnosis of maculopapular rah was also renderd in cases with scattered papules, even there was a possibility of a fused taget lesion forming an erythematous plaque. The irAE of maculopapular rash was similar to typical exanthematous drug eruptions secondary to antibiotics, nonsteroidal anti-inflammatory drugs, and other treatments. The distribution of maculopapular rash was trunk-predominant (n = 14), extremity-predominant (n = 8), trunk alone (n = 6), or extremities alone (n = 5). Histopathologically, vacuolar degeneration at the dermal-epidermal junction and perivascular infiltration of lymphocytes were observed. Eosinophilic infiltration was not evident in some cases (n = 6). Other rash types included erythema multiforme (2/42, 4.8%), lichenoid reaction (3/42, 7.1%), psoriasiform reaction (1/42, 2.4%), bullous pemphigoid (1/42, 2.4%), scleroderma-like reaction (1/42, 2.4%), and SJS (1/42, 2.4%). Histopathologically, erythema multiforme shared similar features as maculopapular rashes (vacuolar degeneration at the dermal-epidermal junction, perivascular infiltration of lymphocytes, and infiltration of eosinophils). Lichenoid reactions had lichen planus-like clinical features, including pink-to-violaceous scaly papules. Oral ulcers and leukoplakia were observed in one case, and nail dystrophy were not evident in our patients. Psoriasiform reactions were similar to typical psoriasis vulgaris, including plaque psoriasis with well-defined, reddish-pink papules and plaques with silvery scales. Histopathologically, we observed epidermal hyperkeratotic parakeratosis and acanthosis without a granular layer, elongation of rete ridges, and dermal papilla. Perivascular infiltration of lymphocytes, eosinophils, and neutrophils at the upper dermis was also observed. In cases of bullous pemphigoid, broken bullae with erythematous macules appeared together with histopathological subepidermal bullae and eosinophilic infiltrate. An additional direct immunofluorescence test was performed, and linear deposits of IgG and C3 were identified. Overall, cutaneous irAEs shared clinical and histopathological features with classical inflammatory eruptions. Clinical presentations and histopathological features are summarized in Table 2, and examples of typical findings are presented in Figure 1.

Of the 42 rashes, 27 (64.3%) were grade 1, 12 (28.6%) were grade 2, and 3 (7.1%) were grade 3, and no grade 4 rash was observed. The grade 3 rashes included maculopapular rashes and SJS. No patients died of cutaneous irAEs.

Rash characteristics

Table 3 summarizes the patient demographics, associated ICIs, rash characteristics, and other irAEs according to the rash type.

Maculopapular rash was the most common inflammatory eruption in each ICI class (anti–PD-1 antibody, 21/29; anti–PD-L1 antibody, 5/6; anti–CTLA-4 antibody, 2/2; and combined anti–PD-1 and anti–CTLA-4 therapy, 5/5). However, no obvious correlation was found between ICI classes and rash types.

Maculopapular rash was the most common type in patients with lung cancer and melanoma (n = 14 and n = 10, respectively). Overall, no specific trends were observed between tumor types and rash types.

The duration from the start of ICI treatment to cutaneous reaction varied according by rash type. Maculopapular rash, erythema multiforme, and SJS had a short median latency, ranging 11.0–94.5 days. Conversely, lichenoid reaction, psoriasiform reaction, bullous pemphigoid, and scleroderma-like eruption had a longer median latency, ranging 140.0–231.0 days. The longest latency of 509 days (32 cycles of nivolumab completed) was noted in a patient with maculopapular rash. The shortest latency of 0 days (6 h after administering pembrolizumab) was also noted in a patient with maculopapular rash. Pruritus was observed in 24 patients (57.1%), and there were one case of maculopapular rash and one case of lichenoid reaction with mucosal

lesions other than SJS. The mean blood eosinophil count was elevated (range, 4.5–19.8%) in patients with maculopapular rash, erythema multiforme, lichenoid reaction, psoriasiform reaction, and SJS. By contrast, the mean blood eosinophil count was not significantly elevated (range, 0.9–3.8%) in patients with bullous pemphigoid and scleroderma-like eruption.

Other irAEs, including adrenalitis, colitis, hepatitis, cholangitis, diabetes mellitus, hypophysitis, pneumonitis, thyroiditis, and parotitis, were found in patients with maculopapular rash (n = 8) and lichenoid reaction (n = 2).

Treatment and impact on immunotherapy

Table 4 summarizes the ICI classes, treatments for rash, impact on immunotherapy, and response to dermatologic therapy or interruption of immunotherapy according to the grade of cutaneous irAE.

The combined use of anti–PD-1 and anti–CTLA-4 antibodies tended to be associated with a higher grade of rash. Grade 3 rash was observed in patients receiving anti–PD-1 therapy (n = 2) and combined anti–PD-1 and anti–CTLA-4 therapy (n = 1).

In our study, 20 of 42 (47.6%) rashes were treated with systemic steroids, namely prednisolone at doses of <0.4 (7/20, 35.0%), 0.4–1.0 (7/20, 35.0%), and >1.0 mg/kg (6/20, 30%). In two cases, steroid pulse therapy (intravenous methylprednisolone 1000 mg/day for 3 consecutive days) was used. Both patients were receiving combination therapy with anti–PD-1 and anti–CTLA-4 antibodies, and both rashes were maculopapular rashes. In the case of psoriasiform reaction (n = 1), topical active vitamin D was added to topical steroid and systemic antihistamine.

Interruption of ICI therapy occurred in multiple rash types because of the eruption severity. In total, 7 of 42 cases (16.7%) resulted in temporary interruption, and 19 of 42 cases (45.2%) resulted in permanent discontinuation. Most patients who developed extracutaneous irAEs required temporary treatment interruption (2/10) or permanent discontinuation (7/10) regardless of the rash grade of rash.

In total, 40 of 42 (95.2%) rashes (including those that were exacerbated on subsequent ICI administration) improved with appropriate dermatologic therapy, interruption of immunotherapy, or both. Only 2 of 42 (4.8%) rashes did not respond to dermatologic treatment and interruption of immunotherapy.

Discussion

This study summarized data on 42 cases of irAEs. Several retrospective studies and reviews summarized the clinical and histopathological features of cutaneous irAEs, but none of these studies examined Asians. Our study is the first report of a detailed examination of the clinical and histopathological findings of cutaneous irAEs in a relatively large cohort experienced in Japan. The most common cutaneous irAEs was maculopapular rash, but ICIs caused virtually every type of skin rash, including erythema multiforme, lichenoid reaction, psoriasiform reaction, autoimmune diseases such as scleroderma-like reaction and bullous pemphigoid, and severe drug eruptions such as SJS. Interestingly, cutaneous irAEs shared clinical and histopathological features with classical inflammatory eruptions. Although not observed in our study, there have been reports of sarcoidosis,[13]Grover's disease,[14–16] granuloma annulare,[17] dermatomyositis,[18, 19]Sjögren's syndrome,[20] pityriasis rubra pilaris,[21] or acute generalized exanthematous pustulosis[22, 23] induced by ICIs.

The incidence of ICI-induced inflammatory eruptions is the highest among irAEs, with anti–PD-1 and anti-CTLA-4 antibodies causing events in 20–30 and nearly 50% of patients, respectively.[7, 8]However, most events are self-limiting (grades 1–2). In this study, 39 of 42 (92.9%) rashes were grades 1–2, covering less than 30% of the BSA, and grade 3 or higher rashes accounted for 7.1% of all rashes. These findings are consistent with previous reports.[4, 7, 8, 24] In this study, one case of grade 3 cutaneous irAEs was attributable to combination treatment with anti–PD-1 and anti–CTLA-4 antibodies, and the combination therapy tended to cause more severe inflammatory eruptions than anti–PD-1 or anti-CTLA-4 antibody monotherapy. Thus, combination therapy may increase the grade of rash and the frequency of cutaneous irAE.

Cutaneous irAEs may occur first among all irAEs,[7, 8]and the onset of rash varies by rash type. In our study, maculopapular rash, erythema multiforme, and SJS had a relatively early onset, with most of them occurring within 3 months after the first ICI dose. Conversely, lichenoid reactions and autoimmune diseases such as bullous pemphigoid and scleroderma-like reactions occurred relatively late, emerging 4–8 months after treatment initiation. Previous case reports and reviews indicated that maculopapular rash often develops 3–6 weeks after the first use of ICIs,[7, 8, 24, 25] lichenoid reactions occur after 6–12 weeks,[5, 7, 8, 25–27] and bullous pemphigoid appears after approximately 14 weeks,[5, 27] roughly consistent with our results. Although previous reports suggested a relatively early onset of psoriasiform reactions,[28, 29] this event occurred approximately 26 weeks after treatment initiation in our patient. Excluding the maculopapular type, only a few cases were included in each rash type, and further accumulation of cases is required.

Cutaneous irAEs were treated according to the rash grade. More than half of grade 2 rashes were treated with systemic steroids, and patients with grade 3 or higher rashes were often treated with high-dose prednisolone ([?]1 mg/kg). In the case of psoriasiform reaction, topical active vitamin D was added to the treatment; however, there was no apparent difference in the choice of treatment by rash type. Among patients with grade 1 rash, ICIs were permanently discontinued in some patients because of irAEs in other organs. Meanwhile, ICIs can be continued and the skin rash will be improved without exacerbation following dermatologic treatments (e.g., topical steroids, oral antihistamines, moisturizers) in most cases. ICIs can be resumed after tentative interruption. Importantly, cutaneous irAEs are not dose-dependent,[8]and dose reduction may not be an appropriate management.

This study had several limitations. First, this was a retrospective, single-institutional study. Patients were evaluated only when they were referred to our dermatology department for expert advice and skin biopsy. Mild cases in which a skin biopsy was unnecessary were not evaluated. Thus, our cohort may represent more severe inflammatory eruptions at our institution. In addition, only one or two cases of minor skin rash were included. Further accumulation of cases is needed to compare the timing of onset and grade of rash.

In conclusion, we summarized the clinical characteristics and histopathological findings of 42 cases of biopsy-proven cutaneous irAEs induced by ICIs. Although various inflammatory eruptions occur in the treatment of ICIs, the inflammatory eruptions induced by ICIs share similar clinical and histopathological features with classical inflammatory eruptions. Differing from irAEs in other organs, cutaneous irAEs may be equivalent to conventional drug eruptions. Further research is warranted.

Conflict of Interest

None declared.

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Table 1. Demographics, underlying malignancy, and immunotherapy of the trial participants

Parameter	Number (%)
Age, years Range (mean ± SD)	39-85 (65.5 ± 10.3)
Sex Male Female	24 (57.1) 18 (42.9)
Underlying malignancy Cutaneous Melanoma Merkel cell carcinoma Cutaneous SCC of head and neck Sebaceous carcinoma Lung Sq NSCLC Non-Sq NSCLC Gastrointestinal Esophageal SCC Gastric adenocarcinoma Genitourinary Renal cell carcinoma Urothelial carcinoma	17 (40.5) 12 (28.6) 1 (2.4) 3 (7.1) 1 (2.4) 17 (40.5) 7 (16.7) 10 (23.8) 3 (7.1) 2 (4.8) 1 (2.4) 5 (11.9) 4 (9.5) 1 (2.4)
Immune checkpoint inhibitors Nivolumab Pembrolizumab Ipilimumab Nivolumab + ipilimumab Atezolizumab Avelumab	18 (45.0) 10 (25.0) 2 (5.0) 5 (12.5) 3 (7.5) 2 (5.0)
Total	40 (100.0)

SCC, squamous cell carcinoma; Sq NSCLC, squamous non-small cell lung cancer; Non-Sq NSCLC, non-squamous non-small cell lung cancer.

Table 2. Clinical and histopathological findings and the grade of inflammatory eruption

Rash type (n)	Clinical presentation (n)	Corresponding histopatho-logical features (n)	Grade, n	Grade, n	Grade, n	Grade, n
			1	2	3	4
Maculopapular (33)	Scattered edematous macules and/or red papules Trunk-predominant (14), Extremity-predominant (8), trunk alone (6), extremities alone (5)	Vacuolar degeneration at the DEJ (33), perivascular lymphocytic infiltration (33), eosinophilic infiltration (27), epidermal spongiosis (12), necrotic keratinocytes (13), small abscess in the epidermis (1)	22	9	2	0

Rash type (n)	Clinical presentation (n)	Corresponding histopathological features (n)	Grade, n	Grade, n	Grade, n	Grade, n
EM (2)	Erythematous macules with target lesion or iris formation, scattered on the trunk and proximal extremities (2)	Vacuolar degeneration at the DEJ (2), perivascular lymphocytic infiltration (2), eosinophilic infiltration (2), epidermal spongiosis (1), necrotic keratinocytes (1)	0	2	0	0
Lichenoid (3)	Pink-to-violaceous papules and plaques with scales, predominantly on the extremities (3), oral ulcer and leukoplakia (1)	Dense lymphocytic infiltration at the DEJ (lichenoid infiltration) (3), infiltration of a few eosinophils (3), necrotic keratinocytes (3), acanthosis (2), thickened granular layer (2), orthohyperkeratosis (2), and epidermal spongiosis (2)	3	0	0	0

Rash type (n)	Clinical presentation (n)	Corresponding histopathological features (n)	Grade, n	Grade, n	Grade, n	Grade, n
Psoriasiform (1)	Plaque psoriasis on the trunk and extremities, with no pustulosis, scalp lesions, or arthritis (1)	Parakeratosis, acanthosis, diminished granular layer, elongated rete ridges, intraepidermal bullae containing neutrophils, mild vacuolar degeneration at the DEJ, and perivascular infiltration of lymphocytes, eosinophils, and neutrophils in the upper dermis (1)	0	1	0	0
BP (1)	Broken bullae with erythematous macules on the chest and abdomen (1)	Subepidermal bulla containing eosinophils, perivascular infiltration of lymphocytes and eosinophils (1), linear deposition of IgG and C3 at the DEJ on DIF (1)	1	0	0	0
Scleroderma-like (1)	Skin sclerosis of the fingers (1)	Increased thick collagen bundles packing sweat glands (1)	1	0	0	0

Rash type (n)	Clinical presentation (n)	Corresponding histopathological features (n)	Grade, n	Grade, n	Grade, n	Grade, n
SJS (1)	Erythematous macules scattered on the trunk and proximal extremities, mucosal ulcerations, the Nikolsky sign (1)	Epidermal necrosis with numerous necrotic keratinocytes, acantholytic bullae, infiltration of lymphocytes and eosinophils, and parakeratotic hyperkeratosis (1)	0	0	1	0
Total			27	12	3	0

EM, erythema multiforme; BP, bullous pemphigoid; DEJ, dermal-epidermal junction; DIF, direct immunofluorescence; C3, complement 3; SJS, Stevens-Johnson syndrome.

Table 3. Summary of patient demographics, associated immunotherapy class, rash characteristics, and other irAEs

Rash type (n)	Demographics	Demographics	Immunotherapy class, n	Immunotherapy class, n	Immunotherapy class, n	Immunotherapy class, n	Rash characteristics	Rash characteristics	Rash characteristics	Rash characteris
	Age, years, mean	Sex, n, (male, female)	Anti-PD-1	Anti-PD-L1	Anti-CTLA-4	Combined anti–PD-1 and anti–CTLA-4	Latency to irAEs, days, median (range)	Pruritus, n	Mucosal lesion, n	Blood eos, %, median (range)
Maculopapular (33)	64.8	33 (17, 16)	21	5	2	5	24.0 (0-509)	19	1	4.5 (0.4-17.1)
EM (2)	74.0	2 (2, 0)	2	0	0	0	94.5 (49-140)	1	0	5.2 (5.1-5.3)
Licehnoid (3)	67.0	3 (1, 2)	3	0	0	0	169.0 (120-255)	1	1	5.2 (3.3-7.9)
Psoriasiform (1)	58.0	1 (1, 0)	0	1	0	0	185.0	1	0	11.6

Rash type (n)	Demographics	Demographics	Immunotherapy class, n	Immunotherapy class, n	Immunotherapy class, n	Immunotherapy class, n	Rash characteristics	Rash characteristics	Rash characteristics	Rash characteris
BP (1)	65.0	1 (1, 0)	1	0	0	0	231.0	1	0	3.8
Scleroderma (1)	73.0	1 (1, 0)	1	0	0	0	140.0	0	0	0.9
SJS (1)	69.0	1 (1, 0)	1	0	0	0	11.0	1	1	19.8
Total (42)	65.5	42 (24, 18)	29	6	2	5	78.9 (0-509)	24	3	5.0 (0.4-19.8)

irAEs, immune-related adverse events; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; eos, eosinophil; EM, erythema multiforme; BP, bullous pemphigoid; SJS, Stevens-Johnson syndrome.

Table 4. ICI therapy class, rash treatment, impact on immunotherapy, and therapeutic response according to the rash grade

Rash grade (n)	Immunotherapy class, n	Immunotherapy class, n	Immunotherapy class, n	Immunotherapy class, n
	Anti–PD-1	Anti–PD-L1	Anti–CTLA-4	Combined anti–PD-1 and
1 (27)	20	4	2	1
2 (12)	7	2	0	3
3 (3)	2	0	0	1
4 (0)	0	0	0	0
Total (42)	29	6	2	5

PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4.

[+]The rash treatment was as follows: 1, only topical steroids or systemic antihistamines; 2, systemic steroids (<0.4 mg/kg prednisolone) and/or topical steroids; 3, systemic steroids (0.4–1.0 mg/kg prednisolone) and/or topical steroids; 4, systemic steroids (>1.0 mg/kg prednisolone) and/or topical steroids

Figure Legends

Figure 1A . Maculopapular rash, grade 3. The patient received pembrolizumab for stage IV non-squamous non-small cell lung cancer. Histopathology reveals vacuolar degeneration at the dermal-epidermal junction, perivascular infiltration of lymphocytes and eosinophils, and necrotic keratinocytes (hematoxylin-eosin [HE]; A2: ×10 original magnification, A3: ×200 original magnification, A4, 5: ×400 original magnification).

Figure 1B . Erythema multiforme, grade 2. The patient received nivolumab for stage IV squamous non-small cell lung cancer. Histopathology reveals vacuolar degeneration at the dermal-epidermal junction and perivascular infiltration of lymphocytes and eosinophils, histopathologically resembling maculopapular rash (HE; B2: ×10 original magnification, B3: ×200 original magnification).

Figure 1C . Lichenoid reaction, grade 1. The patient received nivolumab for metastatic melanoma. Histopathology reveals the lichenoid infiltration of lymphocytes and a few eosinophils, and the epidermis exhibited acanthosis, a thickened granular layer, orthokeratotic hyperkeratosis, and spongiosis (HE; C3: ×10 original magnification, C4: ×100 original magnification).

Figure 1D . Psoriasiform reaction, grade 2. The patient received atezolizumab for stage IV non-squamous non-small cell lung cancer. Histopathology reveals epidermal hyperkeratotic parakeratosis and acanthosis without a granular layer, elongation of rete ridges and dermal papilla, mild vacuolar degeneration at the dermal-epidermal junction, and perivascular infiltration of lymphocytes, eosinophils, and neutrophils in the upper dermis (HE; D2: ×10 original magnification, D3: ×100 original magnification).

Figure 1E . Bullous pemphigoid, grade 1. The patient received pembrolizumab for metastatic melanoma. Histopathology reveals subepidermal bulla with eosinophils and perivascular infiltration of lymphocytes and eosinophils (HE; E2: ×10 original magnification, E3: ×100 original magnification). A direct immunofluorescence test revealed the linear deposition of IgG (E4).

Figure 1F . Scleroderma-like reaction, grade 1. The patient received nivolumab for stage IV gastric adenocarcinoma. Histopathology reveals increased amount of thick collagen fibers that packed sweat glands (HE; F2: ×10 original magnification, F3: ×100 original magnification).

Figure 1G . Stevens-Johnson syndrome, grade 3. The patient received nivolumab for stage IV non-squamous non-small cell lung cancer. Histopathology reveals epidermal necrosis with numerous necrotic keratinocytes, acantholytic bullae, infiltration of lymphocytes and eosinophils, and parakeratotic hyperkeratosis (HE; G2: ×10 original magnification, G3: ×100 original magnification, G4: ×400 original magnification).