Published in final edited form as:

J Am Acad Dermatol. 2019 April ; 80(4): 990–997. doi:10.1016/j.jaad.2018.10.062.

Inflammatory eruptions associated with immune checkpoint inhibitor therapy: A single-institutional, retrospective analysis with stratification of reactions by toxicity and implications for management

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Abstract

Background—There is increasing recognition of distinct inflammatory eruptions associated with checkpoint inhibitors. A better understanding of their severity, therapeutic response and impact on cancer treatment is needed.

Objective—To analyze the different rashes associated with immunotherapy referred to our institution's oncodermatology clinic and inpatient consultative service, and to evaluate their therapeutic response and impact on immunotherapy.

Methods—We retrospectively reviewed patients' medical records referred to the oncodermatology clinic or inpatient dermatology service between 2016-2018 at Yale-New Haven Hospital for eruptions that developed during immunotherapy.

Results—98 patients (51 men, 47 women) treated with checkpoint inhibitors developed 103 inflammatory eruptions, with a range of mean latency of 0.2-17.7 months. A minority (25/103; 24.3%) required immunotherapy interruption, most notably immunobullous (7/8; 87.5%), lichenoid (8/26; 30.8%), maculopapular (6/18; 33.3%), and SJS-like (2/2, 100%) reactions. Only 3/16 (18.8%) interrupted cases developed a grade 2 or 3 flare on rechallenge. Most reactions (93/103; 90.3%) responded to dermatologic therapy and/or immunotherapy interruption.

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Conflicts of Interest: Dr. Kluger served on an advisor board or received consultant fees for Roche-Genentech, Corvus, Nektar, Biodesix, Iovance, Pfizer and Celldex, received research support from Bristol Meyers Squibb, Merck, Apexigen, and the NIH for immunotherapy toxicities. Dr. Leventhal served on an advisory board for Amgen.

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Limitations—This was a retrospective study from a single tertiary care center.

Conclusion—A variety of inflammatory reactions may occur from immunotherapy with differing degrees of severity. While most rashes responded to topical treatment, immunobullous and exfoliative presentations frequently interrupted immunotherapy. Increased awareness and early recognition may reduce the need for unnecessary immunotherapy interruption.

Keywords

immunotherapy; immune checkpoint inhibitor; programmed cell death 1; programmed cell death ligand 1; cytotoxic T-lymphocyte associated protein 4; dermatologic toxicities; cutaneous adverse events; immune-related adverse events

Introduction

Immune checkpoint inhibitors are a powerful new class of anti-cancer drugs that leverage the immune system to promote anti-tumoral activity. Monoclonal antibodies directed against programmed cell death 1 (PD-1; e.g. nivolumab, pembrolizumab), programmed cell death ligand 1 (PD-L1; e.g. atezolizumab, durvalumab, avelumab), and cytotoxic T-lymphocyte associated protein 4 (CTLA-4; e.g. ipilimumab) have been approved for use in multiple cancer types.¹⁻³ Sustained anti-tumoral responses can be elicited but immune-related adverse events (irAE) affecting multiple organs may be triggered as well.⁴⁻⁶ As dermatologic irAE are among the most frequently reported,^{4,7-9} dermatologists have an important role in evaluating and managing these toxicities.

Over the past several years, specific inflammatory eruptions have emerged among the cutaneous irAE including lichenoid reactions, maculopapular eruptions, immunobullous eruptions, and Stevens Johnson syndrome (SJS).⁷⁻¹³ Clinical trials have demonstrated that cutaneous irAE of any grade are more likely to develop during combination anti-CTLA-4/anti-PD-1 therapy (i.e. 40.3% of melanoma patients on nivolumab/ipilimumab) compared with monotherapy with anti-PD-1 (25.9% of melanoma patients on nivolumab) or anti-CTLA-4 antibodies (32.8% of melanoma patients on ipilimumab) alone.¹⁴ Most studies have not differentiated between the types of rashes observed.¹⁴ Profoundly lacking is detailed information about their therapeutic impact, response to treatment, and prognostic implications. This study aims to analyze the rashes associated with immunotherapy referred to the oncdermatology clinic and inpatient consultative service at our institution and evaluate their therapeutic response and impact on immunotherapy.

Methods

After approval from the institutional review board, medical records of patients treated by the oncdermatology clinic and inpatient consultative service at Yale New Haven Hospital from January, 2016 to January, 2018 were obtained from the electronic health record data system. Patients referred to dermatology for eruptions that developed during treatment with the following FDA-approved checkpoint inhibitors were identified: nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, and ipilimumab. The medical records were reviewed and analyzed for patient demographics, medical history, medications, clinical morphology of

skin lesions, presence or absence of pruritus, grade of rash, latency, skin biopsy, direct immunofluorescence (DIF) and indirect immunofluorescence (IIF) studies if performed, clinical diagnosis as documented in the dermatology note, treatment of rash, response of rash, date of cycle 1, impact of rash on immunotherapy (none, temporarily interrupted, discontinued), evolution of rash on retreatment with immunotherapy if applicable, and other immune related adverse events (irAE).

Grade of rash was determined by Common Terminology Criteria for Adverse Events (CTCAE), version 4: grade 1 rash covered <10% body surface area (BSA); grade 2 covered 10-30% BSA with or without symptoms impacting functional activities of daily living (ADL); grade 3 covered >30% BSA with or without symptoms impacting self-care ADL; and grade 4 represented life-threatening (e.g. exfoliative dermatitis) rash requiring hospitalization or intensive care.⁴

Results

Demographics and setting

In this cohort, 98 patients (51 males, 47 females) developed 103 inflammatory eruptions during treatment with immunotherapy and were referred to dermatology at our tertiary care center from 2016-2018. 88/103 (85%) rashes were evaluated in the outpatient oncodermatology clinic, while 15/103 (15%) rashes were evaluated by the inpatient consultative service. The most frequently associated cancer types were lung cancer (n=44), melanoma (n=33), and renal cell carcinoma (n=7). Other malignancies (n=19) included acute myelogenous leukemia, gastrointestinal, gynecological, head and neck, glioblastoma, genitourinary, Hodgkin's lymphoma, and Merkel cell carcinoma.

Rashes were most commonly associated with the anti-PD-1 agents pembrolizumab (35/103 rashes) and nivolumab (33/103), followed by combination anti-CTLA-4/PD-1 therapy with ipilimumab/nivolumab (17/103). The anti-PD-L1 agents atezolizumab (8/103) and durvalumab (5/103), and anti-CTLA-4 monotherapy with ipilimumab (5/103) were associated with fewer inflammatory eruptions referred to dermatology.

9/98 (9%) patients had a pre-existing dermatosis that was quiescent prior to immunotherapy but that subsequently flared during treatment; psoriasis was the most common (7/9).

Table 1 summarizes the demographics, rash characteristics, associated immunotherapy class, and other irAE.

Rash diagnosis, latency, and grade

Diagnoses were rendered clinically (50/103) or by clinicopathological correlation (53/103). Inflammatory reactions were categorized as lichenoid (26/103, 25%), maculopapular or exanthematous (18/103, 18%), psoriasiform (17/103, 17%), eczematous (12/103, 12%), immunobullous (8/103, 8%),^{15,16} prurigo simplex/nodularis (7/103, 7%), Grover's-like (4/103, 4%), acneiform (4/103, 4%), granulomatous (3/103, 3%),¹⁷ SJS-like (2/103, 2%) or pityriasis-rosea (PR)-like or pityriasis rubra pilaris (PRP)-like erythroderma (single cases each).¹⁸

Among the most prevalent cancer types, the most common reactions were lichenoid (n=10), maculopapular (n=9) and psoriasiform (n=7) in patients with lung cancer, and lichenoid (n=8), eczematous (n=7) and psoriasiform (n=6) in patients with melanoma. Overall no trends were observed between tumor and rash type.

Mean latency to onset varied according to rash type. Maculopapular, PR-like, PRP-like and SJS- like eruptions had the shortest mean latency, ranging from 0.2-1.4 months. Conversely, lichenoid, eczematous, psoriasiform, immunobullous, acneiform, prurigo simplex/nodularis and granulomatous reactions had a longer mean latency, ranging from 4-18 months. One of the SJS- like reactions initially manifested with clinical and histopathologic features of AGEF, then 2 weeks later developed positive Nikolsky's sign and sloughing of mucosal and cutaneous surfaces consistent with AGEF/SJS-like phenotype.

Of 103 rashes, 53 (51%) presented as grade 1, 30 (29%) as grade 2, 18 (17%) as grade 3, and only 2 developed grade 4 toxicity. Immunobullous (median grade 3), SJS-like (median grade 4), and PRP-like erythrodermic (grade 3) eruptions presented at a higher grade, followed by maculopapular eruptions (median grade 2). Low-grade eruptions rarely progressed to a grade 3 or 4 rash, however, few cases of lichenoid, maculopapular, bullous pemphigoid and AGEF/SJS- like reaction progressed from a grade 1 or 2 presentation to grade 3 or 4. No patients died due to dermatologic toxicity.

Morphology of rash

The predominant morphology of the 5 most common rash types are described below. 75% of eruptions had associated pruritus, regardless of grade. Table 2 summarizes the morphological descriptions and severity of the different rash types.

Overall, checkpoint inhibitor-associated rashes shared clinical features with classic dermatologic eruptions. Lichenoid reactions had lichen planus-like characteristics, including violaceous scaly papules, oral and/or genital ulcers, leukoplakia, hypertrophic plaques and nail dystrophy. Maculopapular eruptions were similar to typical exanthematous drug eruptions secondary to antibiotics. Psoriasiform eruptions were similar to multiple subtypes of psoriasis, including plaque psoriasis with well-defined red-pink papules/plaques with silvery scale over extensor extremities, seborrheic plaques on the face and scalp, pustules, inverse plaques, palmoplantar involvement, and widespread guttate papules. Eczematous reactions presented with erythematous scaly macules/papules and ranged from localized patches/plaques, nummular plaques, dyshidrotic vesicles, and asteatotic eczema. Immunobullous disorders similarly mimicked the diversity of presentations that can be observed with autoimmune blistering disorders, including tense vesicles/bullae but also urticarial lesions, oral erosions, dyshidrosiform vesicles, and annular configurations.¹⁶

Histopathologic analysis

Biopsies were obtained in 53/103 (51%) rashes and evaluated by Yale dermatopathologists. Additional DIF and IIF studies were performed if vesicles or bullae were present or if patients had refractory pruritus. The most commonly biopsied rashes were lichenoid, immunobullous, psoriasiform, maculopapular and eczematous reactions. Lichenoid interface

dermatitis was the most frequent histopathologic diagnosis (16/53 biopsies, 30%). Histopathologic features of the different rash types are summarized in Table 3

Treatment of rash

Treatment of the eruptions varied according to the severity. 93/103 (90%) of rashes in our study were treated with topical corticosteroids. 21/103 (20%) required systemic corticosteroids. Immunobullous (8/8), SJS-like (2/2), PRP-like erythroderma (1/1), maculopapular (4/18), and lichenoid reactions (3/26) had the highest associated use of systemic corticosteroids. Other treatments included acitretin, phototherapy with narrowband UVB, and intralesional kenalog for lichenoid reactions; phototherapy with narrowband UVB, acitretin, and methotrexate for psoriasiform eruptions; doxycycline with or without niacinamide, omalizumab, methotrexate and dapsone for immunobullous eruptions;^{15,16} and infliximab for the 2 SJS-like eruptions, both of which had associated colitis. Management of pruritus, the most frequently associated symptom, was an integral component of dermatologic care and included topical corticosteroids, topical camphor-menthol, antihistamines, gabapentin, pregabalin, and aprepitant.

Rashes improved in 93/103 (90%) cases with a combination of dermatologic therapy and/or interruption of immunotherapy, including rashes with a mild flare on subsequent immunotherapy infusions. Only 10/103 (10%) rashes did not respond to dermatologic treatment and interruption of immunotherapy. Further, 2 cases of lichenoid reactions and 1 case of prurigo nodularis persisted at least 6 months after cessation of immunotherapy, through the most recent follow-up.

Table 4 summarizes the dermatologic treatments, response of rash to therapy, and associated impact on cancer therapy.

Impact on immunotherapy

Interruption of checkpoint inhibitor therapy because of the eruptions' severity occurred in multiple rash types. 16/103 (15.5%) resulted in temporary interruption, and 9/103 (8.7%) resulted in permanent discontinuation. There was a statistically significant association between high grade rash (grade 3 or 4) and interruption or discontinuation of immunotherapy ($p<0.05$), as expected.

Immunotherapy was immediately discontinued in 2 patients with grade 4 SJS-like reactions and in the 1 patient with intolerable grade 3 toxicity from PRP-like erythroderma.¹⁸ As a group, immunobullous eruptions most commonly required either temporary interruption (3/8 patients) or permanent discontinuation (4/8 patients) of checkpoint inhibitor therapy due to either grade 3 toxicity, mucosal involvement, or intolerable symptoms of pruritus.¹⁶ Less commonly, lichenoid (8/26 patients) and maculopapular eruptions (6/18 patients) resulted in interruption of treatment. Only 1/17 psoriasiform rashes resulted in interruption of treatment, but this patient had both grade 3 rash and colitis. Prurigo simplex/nodularis, Grover's-like, acneiform, granulomatous, and PR-like eruptions had no impact on immunotherapy in this cohort.

Of the 16 eruptions that resulted in temporary interruption of immunotherapy because of the severity of the rash, only 3 cases (lichenoid, maculopapular, and bullous pemphigoid) had a grade 2 or 3 flare on rechallenge with checkpoint inhibitor therapy. The others resolved or remained well controlled (grade 1) on dermatologic therapy and continued checkpoint inhibitor therapy.

Discussion

This study summarizes data on 103 inflammatory eruptions that developed during checkpoint inhibitor therapy at a tertiary care center. This relatively large cohort supports previous literature on the diversity of associated dermatologic toxicities;^{7-13,16,17,19-21} the top 5 diagnoses were lichenoid, maculopapular, psoriasiform, eczematous and immunobullous reactions. Our series adds several important findings related to severity, therapeutic response and impact on cancer treatment.

Of the distinct rash types, immunobullous reactions most frequently required treatment interruption, followed by lichenoid, maculopapular and SJS-like reactions. Overall, approximately 25% of rashes required interruption of immunotherapy, underscoring the substantial impact of cutaneous toxicity on oncologic care. This rate is similar to smaller, previously reported series.^{9,13} Importantly, it was safe to restart immunotherapy in patients whose treatment was temporarily interrupted because of a grade 2 or 3 rash; most eruptions resolved on their own or remained low grade and controlled on dermatologic therapy when checkpoint inhibitor therapy was resumed.

Interestingly, we found that 9% (9/98) of patients had a preexisting dermatosis, most commonly psoriasis that flared on immunotherapy. In addition, there was a wide range of mean latency (0.2-17.7 months) among the inflammatory eruptions; for instance, in general, granulomatous, lichenoid, psoriasiform, eczematous and immunobullous rashes had a longer latency compared to maculopapular and SJS-like eruptions. Importantly, grade 4 toxicity with SJS-like presentation may have a protracted course, requiring close observation of rashes that fail to respond to dermatologic treatment.²⁵

Dermatologists have an important role in providing specialized care to oncologic patients with toxicities from their treatments. Cutaneous irAE from immune checkpoint inhibitor therapy are among the most frequently reported and may result in interruption of cancer treatment in severe cases. With proper assessment and prompt management, a majority of inflammatory eruptions may be effectively treated without interruption of immunotherapy.

Limitations

This was a retrospective and single-institutional study. Patients were only evaluated if they were referred to our oncodermatology clinic within the cancer center or seen by the inpatient consultative service, whereas mild eruptions that responded to topical therapy or were self-limiting were not seen. Thus our cohort may represent the more severe inflammatory eruptions at our institution, while milder rashes are probably managed by medical oncologists without a dermatology consultation, and therefore not represented in our cohort.

Conclusions

Over the course of 2 years, 103 inflammatory eruptions that developed during checkpoint inhibitor therapy were referred to oncodermatology or inpatient consultative service at our institution and stratified according to toxicity. Of the severe reactions (grade 3 or 4) that required interruption of checkpoint inhibitor therapy, immunobullous and exfoliative presentations were most frequent. Most rashes (13/16) that required temporary interruption of immunotherapy resolved or were well controlled on dermatologic therapy, but 3/16 (18.8%) developed a grade 2 or 3 flare on rechallenge. Additional prospective studies are needed to further evaluate the prognostic relevance of these specific rash types.

Acknowledgments

Funding sources: This study was supported in part by the NIH for Emily Coleman's medical student research fellowship, and Harriet Kluger's immune checkpoint inhibitor toxicity grant (R01 CA227473).

IRB approval status: Reviewed and approved by Yale University School of Medicine, approval #2000021013

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Capsule summary

- Cutaneous reactions commonly develop from immunotherapy, and a variety of inflammatory patterns have been observed.
- In this cohort, 25/103 (24.3%) rashes required interruption of immunotherapy, most commonly immunobullous and exfoliative presentations.
- There are key distinctions among the rashes that develop from checkpoint inhibitors with regards to severity and impact on cancer treatment.

Summary of patient demographics, associated immunotherapy class, rash characteristics and other irAE

Table 1:

Demographics			Immunotherapy class				Rash Characteristics		
Rash type	Pts, no. (M, F)	Age, mean, y	Anti-			Latency, mean, mo (range)	Pruritus (range)	Grade, median (range)	Other irAE, [^] no.
			CTLA-4	PD-L1	PD-1 or Both				
Lichenoid	26 (17, 9)	64	2	23	1	6.2 (0.5-20)	25	1 (1-3)	9
Maculo-papular	18 (5, 13)	61	2	11	5	1.0 (0.2-5.7)	16	2 (1-3)	7
Psoriasisiform	17 (8, 9)	67	1	12	4	5.7 (0.2-28.8)	10	1 (1-3)	8
Eczematous	12 (6,6)	66	0	9	3	5.8 (0.6-25)	12	1 (1-3)	5
Immuno-bullous	8 (4, 4)	68	0	8	0	4.5 (0.5-10)	8	3 (2-3)	2
Prurigo	7 (3, 4)	71	0	6	1	10.1 (1.8-16)	7	1 (1-3)	3
Grover's-like	4 (4, 0)	71	0	4	0	4.2 (0.2-14.4)	4	1 (1-2)	1
Acneiform	4 (3, 1)	47	0	4	0	4.3 (0.2-11)	1	1 (1-2)	1
Granulomatous	3 (0, 3)	65	0	2	1	17.7 (7-36)	0	1	0
SJS-like	2 (1,1)	62	0	0	2	1.4	2	4	2
PR-like	1 (1, 0)	75	0	1	0	0.2	1	2	0
PRP-like	1 (1, 0)	63	0	1	0	0.46	1	3	0
Total	103 (54, 49)	65	5	81	17	5.13 (0.1-36)	77	1 (1-4)	36*

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; irAEs, immune-related adverse events; AGEP, acute generalized exanthematous pustulosis; PR, pityriasis rosea; PRP, pityriasis rubra pilaris; SJS, Stevens-Johnson Syndrome; ^Other irAE included: adrenalitis, acute interstitial nephritis, colitis, hepatitis, hypophysitis, pneumonitis, thyroiditis, vitiligo, autoimmune hemolytic anemia, arthritis, aseptic meningitis, encephalitis, fatigue, pancreatitis, uveitis;

*36 total patients (2 patients had multiple rash types)

Table 2:
Summary of clinical presentations of inflammatory eruptions to checkpoint inhibitor therapy

Rash Type	Predominant Morphology, (no.)	Other presentations, (no.)	Pruritus	Grade			
				1	2	3	4
Lichenoid	pink to violaceous papules with scale (18)	oral/genital ulcers (6), leukoplakia (2), hypertrophic plaques (4), vesicles (3), koebnerization (2), inflamed seborrheic keratoses (1), dystrophic nails (1), papulopustules (1), palmoplantar (3), inverse (2), generalized papular (1)	25	17	7	2	0
Maculopapular	erythematous macules and papules (18)	erythroderma (1), photoaccentuated (1) urticarial (1)	16	3	11	4	0
Psoriasiform	Pink-red papules with silvery scale (17)	localized extensor (7), scalp and facial (4), palmoplantar pustulosis (2), inverse (2), widespread guttate/plaques (2), psoriatic arthritis (1)	10	12	4	1	0
Eczematous	Erythematous scaly macules/papules (11)	nummular plaques (4), asteatotic eczema (1), dyshidrotic (1)	12	7	3	1	0
Immunobullous ¹⁶	tense vesicles/bullae (7)	pruritic papules with erosions (2), oral ulceration (1), urticarial- predominant (1), dyshidrosiform (1), annular plaques with peripheral vesicles (LABD, 1)	8	0	1	7	0
Prurigo	linear erosions with crust (5)	prurigo nodules (1), lichen simplex chronicus (1)	7	4	1	2	0
Grover's-like	erythematous papules with scale (4)	papulovesicles (1)	4	3	1	0	0
Acneiform	inflammatory papules and pustules (3)	rosacea (2), flare of papulopustular eruption that previously developed during cetuximab (1)	1	3	1	0	0
Granulomatous ¹⁷	erythematous firm dermal papules (2)	annular plaques with papular edge (granuloma annulare, 1)	0	3	0	0	0
SJS-like	Dusky erythematous macules, moist desquamation, mucosal ulcerations, +Nikolsky (2)	Preceding erythematous plaques with pustules (culture negative) (1)	2	0	0	0	2
PR-like	pink oval macules and papules with trailing scale (1)		1	0	1	0	0
PRP-like ¹⁸	erythroderma with orange waxy keratoderma (1)		1	0	0	1	0

Summary of histopathologic diagnoses associated with inflammatory eruptions to checkpoint inhibitor therapy

Table 3:

Clinical Diagnosis	Patients (no.)	Corresponding Histologic Diagnoses (no.)
Lichenoid	16	lichenoid interface dermatitis (15), scattered foci of histiocytes and lymphocytes with epidermal collarettes (lichen nitidus-like) (1)
Eczematous	5	eosinophilic spongiosis (5)
Maculopapular	7	dermal hypersensitivity reaction (5), acute vacuolar dermatitis with eosinophils (1)
Psoriasiform	4	psoriasiform (4)
Immunobullous ¹⁶	8	subepidermal bulla with eosinophils (4), subepidermal bulla with focal interface changes (1), eosinophilic spongiosis (1), erosion of epidermis with eosinophils (1), subepidermal bulla with neutrophils (LABD, 1) DIF : linear IgG and C3 at the DEJ (5), linear IgG and C3 and IgA at the DEJ (LABD, 1) IIF : serum linear deposition of IgG at DEJ of monkey esophagus (2), serum intercellular staining of IgG and IgA on monkey esophagus with 1:10 dilution (IgA) and 1:80 dilution (IgG) dilutions (LABD, 1)
Prurigo nodularis	1	epidermal acanthosis and parakeratosis (1)
Grover's-like	2	epidermal acantholysis and dyskeratosis (2)
Acneiform	1	suppurative and granulomatous folliculitis (1)
Granulomatous ¹⁷	3	naked granulomas within the dermis with multinucleated cells (sarcoidosis-like, 2), superficial and deep perivascular and interstitial infiltrate of histiocytes and lymphocytes with focal palisading (granuloma annulare-like, 1)
SJS-like	2	epidermal necrosis with numerous apoptotic keratinocytes and lymphoplasmacytic inflammation (SJS-like, 1), subcorneal pustules and mixed infiltrate with eosinophils and necrotic keratinocytes, and lichenoid interface dermatitis with necrotic keratinocytes (AGEP/SJS-like, 1).
PR-like	1	patchy papillary dermal mixed infiltrate with plasma cells/eosinophils with red cell extravasation (1)
PRP-like ¹⁸	1	epidermal acanthosis with orthokeratosis and parakeratosis, intact granular layer and mild spongiosis, perivascular inflammatory infiltrate within the superficial dermis (1)

Table 4:

Summary of rash treatment, therapeutic response, and impact on cancer therapy

Rash Type, (no.)	Rash treatment, (no.)	Rash improved		Impact on immunotherapy		
		Yes/No	None	Held	DC	
Lichenoid (26)	topical steroids (25), systemic steroids (3), camphor-menthol (5), antihistamines (4), gabapentin (3), topical tacrolimus (3), narrowband UVB phototherapy (2), acitretin (1), doxycycline (1), intralesional kenalog (1)	23/3	18	6	2	
Maculopapular (18)	topical steroids (18), systemic steroids (4), antihistamines (1), camphor-menthol (1), gabapentin (1)	17/1	12	6	0	
Psoriasisiform (17)	topical steroids (16), systemic steroids (1), ketoconazole shampoo (4), narrowband UVB phototherapy (2), acitretin (2), antihistamines (2), topical tacrolimus (2), camphor-menthol (1), gabapentin (1), intralesional kenalog (1), methotrexate 15mg weekly (1)	16/1	16	1	0	
Eczematous (12)	topical steroids (12), systemic steroids (1), camphor-menthol (5), antihistamines (4), gabapentin (3), topical tacrolimus (3), narrowband UVB phototherapy (2)	11/1	12	0	0	
Immunobullous (8) ¹⁶	topical steroids (8), systemic steroids (8), doxycycline (2), doxycycline & niacinamide (2), omalizumab (2), dapsone (1), methotrexate (1)	8/0	1	3	4	
Prurigo (7)	topical steroids (5), systemic steroids (1), antihistamines (4), camphor-menthol (3), gabapentin (3), aprepitant (1)	6/1	7	0	0	
Grover's-like (4)	topical steroids (4), antihistamines (2), camphor-menthol (2)	3/1	4	0	0	
Acneiform (4)	topical steroids (1), doxycycline (1), clindamycin lotion (1), metronidazole cream (1)	4/0	4	0	0	
Granulomatous (3) ¹⁷	topical steroids (2)	1/2	3	0	0	
SJS-like (2)	topical steroids (2), systemic steroids (2), infliximab (1)	2/0	0	0	2	
PR-like (1)	topical steroids (1)	1/0	1	0	0	
PRP-like (1) ¹⁸	topical steroids (1), systemic steroids (1), acitretin (1)	1/0	0	0	1	

Abbreviations: DC, discontinued; UVB, ultraviolet B