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A retrospective chart review of management strategies for lichenoid eruptions associated with immune-checkpoint inhibitor therapy from a single institution

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ABSTRACT

Immune checkpoint inhibitors and their associated immune-related cutaneous adverse events are continuing to become a mainstay of cancer treatment regimens. While most rashes are mild and easily manageable, severe or persistent rashes like lichenoid dermatoses can significantly impact the quality of life and may require ICI cessation. Lichenoid dermatoses currently have no management guidelines beyond the use of topical or oral steroids.

Our study is a single-institution retrospective chart review to characterize ICI-induced lichenoid eruptions, their treatments, and associated tumor response. We utilized natural language processing and our institutional medical record to identify patients with lichenoid eruptions on ICI therapy.

One-hundred nineteen patients were identified, of which 108 rashes were characterized as lichenoid dermatitis and fifteen as lichenoid mucositis. Most patients presented with a diffuse distribution (86%, 101/117), with pruritus in lichenoid dermatoses (82%, 89/108) and pain in lichenoid mucositis (80%, 12/15). Successful treatments for lichenoid dermatitis included topical steroids (81%, 88/108), oral antihistamines (21%, 23/108), and oral steroids (15%, 16/108). Of lichenoid dermatitis patients, 21% (23/108) did not respond to treatment (7) or required oral steroids (16). Approximately 28% of patients who had lichenoid dermatitis had delay, reduction, or discontinuation of their ICI because of their irCAE. This descriptive study highlights the impact of lichenoid dermatitis on patients' ability to remain on ICI therapy and the need for more effective non-steroidal management strategies.

Abbreviations

ICI	Immune checkpoint inhibitors
PD-1	Programmed cell death 1
PD-L1	Programmed death-ligand 1
CTLA-4	Cytotoxic T lymphocyte antigen 4
irAEs	Immune-related adverse events
irCAEs	Immune-related cutaneous adverse events
LP	Lichen planus
CTCAE	Common Terminology Criteria for Adverse Events
FDA	Food and Drug Administration

Introduction

Immune checkpoint inhibitor (ICI) therapies as single agent or combination therapy represent a promising class of immunotherapy used to treat a variety of malignancies. These immuno-oncology agents target specific T lymphocyte surface molecules like programmed cell death 1 (PD-1), programmed death-ligand 1 (PD-L1), or cytotoxic T lymphocyte antigen 4 (CTLA-4) which, when functioning normally, allow tumors to evade the host immune response. ICIs function by increasing the anti-tumor T-cell host immune response, which can produce unintended consequences associated with increased

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immunosurveillance[1,2]. These side effects, termed immune-related adverse events (irAEs), are likely related to an unmasking of autoimmunity and can manifest in various organ systems[3, 4, 5]. Of the many irAEs, immune-related cutaneous adverse events (irCAEs) are the most common and first to appear[4,6]. Common irCAEs include maculopapular/morbilliform rash, pruritus, eczematous reactions, urticaria, lichenoid dermatoses, psoriasiform eruptions, and vitiligo[7].

Our irCAEs of focus, lichen planus (LP) and lichenoid dermatoses, occur most commonly after anti-PD-1/PD-LI inhibitor therapy, with an estimated incidence of 20%, or less commonly with anti-CTLA-4 drugs [6]. While most irCAEs are mild and manageable with supportive care, they can progress to severe-grade rashes and dramatically impact quality of life, necessitating cancer therapy cessation[8]. Onset for ICI-related lichenoid dermatoses typically occurs 6–12 weeks after treatment initiation and can have variable presentations and distributions[9]. Patients often present with multiple pruritic, erythematous to violaceous papules and plaques on the chest and back, with possible involvement of the extremities, palmoplantar surfaces, genitals, and/or oral mucosa[9,10] (Fig. 1). Histologically, lichenoid eruptions are characterized by a dense, band-like lymphocytic infiltrate near the dermal-epidermal junction with vacuolar degeneration and apoptotic keratinocytes[10].

Since irCAEs have only recently been characterized, evidence for effective treatment options is sparse. The Common Terminology Criteria for Adverse Events (CTCAE) does not have specific grading criteria for LP or lichenoid eruptions. Furthermore, current treatment guidelines only suggest systemic corticosteroids and/or ICI cessation for grade 3 or 4 rashes[11]. The lack of treatment guidance as well as the lack of Food and Drug Administration (FDA)-approved systemic therapy for severe-grade lichen planus can be devastating for patients achieving good tumor response with their ICI, who either have a steroid-refractory rash or cannot tolerate systemic corticosteroids and thus must discontinue their life-saving cancer therapy.

A growing body of clinical evidence endorses several targeted biologic and immunomodulatory therapies for certain corticosteroid-refractory irCAEs[1,12]. While mild lichenoid dermatoses can typically be managed with topical steroids, recent anecdotal evidence suggests the use of immunomodulators (i.e., cyclosporine, methotrexate) and acitretin with or without systemic corticosteroids for refractory or severe-grade rashes[13]. More evidence supporting these nonsteroidal treatment options is still required.

Interestingly, recent evidence has suggested a possible increased tumor response in patients on ICIs who develop irCAEs. This has been demonstrated in multiple studies on melanoma patients who develop irCAEs, especially vitiligo[14, 15, 16]. While less frequently reported, it has also been suggested that ICI-induced lichenoid and spongiotic eruptions may represent a robust immune response and improved oncologic outcomes[17].

Fig. 1. Erythematous to violaceous papules and plaques.

While several case series and literature reviews have covered the clinical presentation and characterization of ICI-induced lichenoid eruptions, a large-scale retrospective chart review focusing on management strategies has not yet been performed. Our study seeks to better characterize ICI-associated lichenoid dermatoses, elucidate successful treatment options, and investigate the relationship between lichenoid eruptions and oncologic outcomes.

Methods

A single institution retrospective chart review was performed for all patients with ICI-induced lichenoid eruptions between 10/19/2015 and 5/25/2021. Natural language processing was used to identify patients on ICIs who had the words “lichen” or “lichenoid” in their electronic medical record including clinical notes and pathology reports. Manual review was used to select patients who had a lichenoid eruption attributable to their ICI. Demographic, malignancy, treatment, and rash data were recorded. Protocol was approved by the institutional review board (IRB) with a waiver of consent.

Data analysis was done using Fisher tests via The GraphPad application.

Results

After selection and screening, 119 patients (68 male, 51 female) with lichenoid eruptions following ICI therapy were identified. The median age was 67 years (range, 33–81). Demographic data is shown in Table 1. Patients were being treated for a variety of malignancies including but not limited to melanoma, cutaneous squamous cell carcinoma, and non-small cell lung carcinoma (Table 1). Eighty-four percent of the patients were Caucasian, with smaller percentages of Hispanic, African American, and Asian patients. The checkpoint inhibitors used were pembrolizumab (37%, 44/119), nivolumab (32%, 38/119), atezolizumab (8%, 10/119), and others highlighted in Table 1.

Of the 119 total patients, 108 had a lichenoid dermatitis, 15 had a lichenoid mucositis, and two had other lichenoid dermatoses including lichenoides pemphigoides and were not included in the data analysis (Table 2). Six of the patients had both lichenoid dermatitis and lichenoid mucositis and were recorded individually in each group. Of the patients with lichenoid dermatitis, 91% (98/108) had a diffuse presentation and 82% (89/108) reported pruritus. The median number of days to onset was 77 (range 1–1521). To note, 44% (48/108) of patients were able to continue their immunotherapy, while 37% (40/108) of patients’ ICIs were discontinued, ten of which were because of their irCAE. The majority of patients with lichenoid dermatoses were successfully treated with topical steroids (81%, 88/108). Other successful treatments included oral antihistamines (21%, 23/108), oral steroids (15%, 16/108), and acitretin (8%, 9/108). Remaining treatments are listed in Table 2. Of the 108 cases of lichenoid dermatitis, 67% (72/108) resolved, 20% (22/108) improved, and 6% (6/108) remained stable. Only one patient reported rash progression. The median number of days to resolution was 188 (range: 14–1830).

Of the patients with lichenoid mucositis, 80% (12/15) presented with a diffuse presentation and 80% (12/15) reported pain. The median number of days to onset was 121 (range: 32–511). To note, 33% (5/15) of patients were continued on their ICI, while 47% (7/15) of patients had to discontinue their immunotherapy, five of which were because of their irCAE. Many patients with lichenoid mucositis were successfully treated with topical steroids (40%, 6/15). A smaller percentage of cases were successfully treated with oral steroids (27%, 4/27) and acitretin (13%, 2/15). Remaining treatments are listed in Table 2. Of the 15 cases

Table 1
Demographics ($n = 119$).

AGE*, years median (range)		67 (33–81)
SEX	Male	68 (57)
n (%)	Female	51 (43)
PRIOR IMMUNOTHERAPY**	Yes	27 (23)
n (%)	No	91 (76)
PRIMARY CANCER TYPE	Melanoma	38 (0, 1, 8, 28)
n (Stage I, II, III, IV)**	SCC – head and neck	11 (0, 0, 1, 8)
	Non-small cell lung cancer	9 (0, 0, 0, 9)
	Renal cell carcinoma	7 (0, 0, 0, 6)
	Prostate cancer	7 (0, 0, 0, 7)
	Ovarian cancer	5 (0, 1, 0, 4)
	SCC – cutaneous	4 (0, 0, 0, 3)
	Colorectal cancer	4 (0, 0, 0, 4)
	Hepatocellular carcinoma	4 (0, 1, 0, 3)
	Thyroid cancer	4 (0, 0, 0, 4)
	Urothelial cancer	3 (0, 0, 0, 1)
	Breast cancer	3 (0, 0, 0, 3)
	Angiosarcoma	3 (0, 0, 0, 2)
	Other malignancy	42 (0, 3, 3, 31)
RACE	Caucasian	100 (84)
n (%)	Hispanic	7 (6)
	African American	6 (5)
	Asian	3 (3)
	Other	3 (3)
IMMUNOTHERAPY	Pembrolizumab	44 (37)
n (%)	Nivolumab	38 (32)
	Atezolizumab	10 (8)
	Ipilimumab	2 (2)
	Cemiplimab	2 (2)
	Cetrelimab	2 (2)
	Avelumab	1 (1)
	Combination therapy***	20 (17)

* Other symptoms include hoarseness (1).
** Other treatments include topical pimecrolimus, topical calcipotriene, intravenous immunoglobulin, niacinamide, topical tacrolimus, topical clotrimazole, topical nystatin, Magic mouthwash (diphenhydramine, hydrocortisone, nystatin).
Abbreviations: CPI = immune-checkpoint inhibitor, nbUVB = narrow-band ultraviolet B light, n = number of patients R = resolved, I = improved, S = stable, P = progression.

Table 2
Characteristics and treatment of lichenoid eruptions.

PRESENTATION	Lichenoid dermatitis $n = 108$	Lichenoid mucositis $n = 15$
Days to onset, median (range)	77 (1–1521)	121 (32–511)
Distribution		
Diffuse n (%)	98 (91)	12 (80)
Focal n (%)	9 (8)	3 (20)
Symptoms		
Pruritus n (%)	89 (92)	1 (7)
Pain n (%)	17 (16)	12 (80)
Other n (%)*	1 (1)	0 (0)
ICI IMPACT		
Decreased dose n (%)	2 (2)	0 (0)
Discontinued n (%)	10 (9)	5 (33)
Delayed n (%)	18 (17)	3 (20)
SUCCESSFUL TREATMENT		
Topical steroids n (%)	88 (81)	6 (40)
Oral antihistamines n (%)	23 (21)	0 (0)
Oral steroids n (%)	16 (15)	4 (27)
Acitretin n (%)	9 (8)	2 (13)
nbUVB n (%)	4 (4)	0 (0)
Oral tetracyclines n (%)	3 (3)	0 (0)
Intralesional triamcinolone n (%)	8 (7)	0 (0)
Other non-steroidal treatment** n (%)	4 (4)	5 (33)
No treatment n (%)	2 (2)	1 (7)
OUTCOME		
Rash outcome, n (R/I/S/P)	72/22/6/1	8/1/5/1
Days to resolution, median (range)***	188 (14–1830)	153 (22–445)
Cancer progression (R/I/S/P)	31/10/23/42	3/2/3/7
Overall survival, days, median (range)	661 (69–2252)	924 (359–1399)
Time to next treatment, days, median (range)	364 (55–1357)	581 (42–1097)

* Median age at start of immune-checkpoint therapy.
** Balance is patients with unknown history of immunotherapy.
*** Combination therapy of nivolumab + ipilimumab, nivolumab + pembrolizumab, pembrolizumab + ipilimumab.
Abbreviations: i= improved n = number of patients p = progressed r = resolved s= stable SCC = squamous cell carcinoma.

of lichenoid mucositis, 53% (8/15) resolved, 7% (1/15) improved, and 33% (5/15) remained stable. Only one patient reported rash worsening. The median number of days to resolution was 153 (range: 22–445).

Regarding tumor response data, 38% (44/117) of patients experienced complete or partial response of their malignancy, 21% (25/117) had stable disease, and 39% (46/117) experienced malignancy progression. The median overall survival for all patients was 691 days (range, 69–2252). The median time to next treatment for all patients was 359 days (range, 42–1357).

In the melanoma patients from our study, the overall survival and time to next treatment, defined as time from start of ICI to start of next systemic therapy, were 673 days and 646 days, respectively. The time to next treatment for nivolumab and combination therapy were 289 days and 414 days, respectively. (Table 3)

Oral steroid use was significantly higher in patients who had dose impact of ICI due to their irCAE when compared to all patients who did not have dose impact ($p = 0.028$). Oral steroid use was also significantly higher in patients who had ICI dose impact due to their irCAE when compared to patients who had ICI dose impact for another reason ($p = 0.0123$).

Table 3
Overall survival and time to next treatment in melanoma patients.

	Overall survival, days, median (range)	Time to next treatment, days, median (range)
Nivolumab: Lichenoid dermatitis patients	673 (182–1171)	288 (63–745)
Nivolumab – all patients*	1107, 50,4[20,21]	289 (20–1523)
Combination therapy**: Lichenoid dermatitis patients	646 (290–987)	414 (70–686)
Combination therapy**: All patients*	>1800[20]	210 (21–1273)

* For overall survival, the "all patients" group includes published clinical trials data. For time to next treatment, the "all patients" group includes a consecutive cohort of melanoma patients treated at our institution over one year (2018) [unpublished data].
** Ipilimumab + nivolumab or pembrolizumab.

Discussion

Lichenoid dermatoses are a common and highly symptomatic irCAE with limited management options for high-grade presentations. To our knowledge, this is the first retrospective chart review on lichenoid eruptions following immune checkpoint inhibitor therapy.

One of the most significant symptoms present in lichenoid dermatitis is pruritus. Pruritus can negatively affect quality of life and is often the reason patients present to dermatology[18]. Similarly, lichenoid mucositis is often accompanied by pain, which can impose significant consequences including decreased oral intake and malnutrition[19]. These associated symptoms should not be underestimated as eruptions can persist well beyond cessation of the inciting agent with a median time to resolution of approximately six months.

While few patients required ICI dose reductions, patients with lichenoid mucositis were more likely to require ICI discontinuation. Roughly 53% of patients with lichenoid mucositis required ICI cessation

due to their rash compared to 28% of lichenoid dermatitis patients. Out of the 108 lichenoid dermatitis patients, 10 out of the 40 cases of ICI cessation were attributed to their lichenoid eruption. Other causes of ICI impact included disease progression, pneumonitis, transaminitis/hepatitis, gastroenteritis, colitis, adrenal insufficiency, and fatigue. Out of the 15 lichenoid mucositis patients, five out of the seven cases of ICI cessation were due to their lichenoid eruption. The remaining two were discontinued due to fatigue and gastroenteritis. It is apparent that symptom control is of utmost importance. In the very least, adequate symptom control could decrease the need to change ICI dose and prolong treatment of the more pressing malignancy. The challenge of lichenoid mucositis treatment should be studied further as it has a great degree of dose impact. Also, 40 cases of ICI discontinuation in patients with lichenoid dermatitis is quite significant in a category of medications that are relatively well-tolerated. Future study looking at the association of lichenoid dermatitis with all dose-limiting toxicities is warranted and would require a control group of patients.

Regarding treatment, cases of lichenoid dermatitis displayed a more favorable response than lichenoid mucositis eruptions. While only 6.5% of lichenoid dermatitis patients worsened or did not improve, 40% of lichenoid mucositis patients did not respond to treatment. Successful treatments for lichenoid dermatoses included topical steroids, oral antihistamines, oral steroids, and acitretin. Successful treatments of lichenoid mucositis included topical steroids, oral steroids, and acitretin. Again, both eruptions are in need of more adequate treatment regimens for high-grade presentations. Lichenoid mucositis in particular needs better treatment options as the ones that are currently used, including oral steroids, are not effective.

Furthermore, our results support the notion that current management guidelines for lichenoid eruptions are lacking for high-grade events. While most cases were readily managed with topical steroids, severe or steroid-resistant cases were left without options. There is a growing body of clinical evidence supporting the use of several non-steroidal treatment options for lichenoid dermatoses. These previously successful treatment options have included cyclosporine and other immunomodulators[13]. This review opens the door for future prospective studies to find additional efficacious treatments for lichenoid eruptions. A literature review on potential alternative treatments as well as a prospective study using treatments such as doxycycline, niacinamide, rituximab, and omalizumab for lichenoid eruptions would further add to the growing body of clinical evidence. These alternatives could decrease the side effects associated with long-term steroid use and increase cancer therapy adherence. In fact, the use of oral steroids was associated with increased ICI cessation, further supporting the need for more effective non-steroidal systemic therapies. Although there did not appear to be an association between diffuse rash distributions and ICI dose impact, there was a trend associating diffuse presentation in patients who have an ICI dose impact ($p = 0.0747$). The sample size of patients with ICI dose impact due to their irCAE was low, which may account for our inability to obtain a significant p value. If this trend is true, it supports the use of more aggressive treatments in patients with diffuse presentations to avoid ICI dose impact.Previous research has demonstrated a positive association between irCAE development and tumor response in melanoma patients[14, 15, 16]. The median overall survival data for cancer patients with ICI-induced lichenoid dermatitis and lichenoid mucositis was 661 days and 924 days, respectively. The overall survival in patients with both types of lichenoid eruptions was relatively high, although no conclusions can be drawn from this heterogeneous group in terms of utilizing lichenoid eruptions as a prognostic indicator. The median time to next treatment was 364 days for the lichenoid dermatitis group and 581 days for the lichenoid mucositis patients, indicating both efficacy and tolerability for the ICIs used.

Clinical trials in melanoma patients found that median overall survival for nivolumab and combination therapy were 504–1107 days[20, 21] and over 1800 days[20], respectively. In the melanoma patients with lichenoid dermatitis from our study, the overall survival for nivolumab and combination therapy were 673 days and 646 days, respectively, which falls in the range of values found in previous studies. Prior data from our institution looking at consecutively treated melanoma patients over one[22,23] found that time to next treatment for nivolumab and combination therapy were 289 days and 210 days, respectively. In the melanoma patients from our study, the time to next treatment for nivolumab and combination therapy were 289 days and 414 days, respectively. Our patients include standard of care and trials patients; and, although direct comparison to clinical trial data is difficult, our data suggests that overall survival and time to next treatment are not negatively impacted by the presence of lichenoid eruptions. Additionally, our patients were not followed as long as the trials patients, which could explain their longer overall survival values. There is also the possibility that because of the symptomatic nature of lichenoid dermatoses and the high percentage that have alteration of cancer therapy, patients have a worse prognosis compared to other irCAEs. No definitive conclusions can be made from this study, but it does cast doubt as to whether lichenoid dermatitis is a positive prognostic indicator in melanoma patients as vitiligo has been shown to be.

As the use of ICI therapies increases, the knowledge base for adverse events continues to grow, but more research is needed to optimize the treatment of lichenoid eruptions and other cutaneous adverse events. Currently, the CTCAE outlines treatment guidelines for various adverse events; however, it is not comprehensive and lacks specific guidelines for lichenoid eruptions. Additionally, the entire cutaneous adverse events section emphasizes the use of topical and systemic steroids with little mention of alternative systemic therapies.

In the next five years, we anticipate a better understanding of ICI induced lichenoid eruptions and other cutaneous adverse events and the development of more advanced treatment guidelines including the expansion of non-steroidal systemic therapies and biologics. Limitations to this study include its origins from a single institution which limits our patient population and makes the data less reproducible. Including multiple institutions across the country would improve the results of this study. Another limitation to this study is the heterogeneous cancer population. The variety of cancers presented in this paper lead to difficult-to-interpret overall survival and time to next treatment results. Additionally, the role cancer type plays in the development and progression of adverse events is unknown. Lastly, there is inherent error withretrospective chart reviews because of the potential incomplete and/or inaccurate documentation within each patients' chart.

Conclusion

While the majority of ICI-induced lichenoid dermatoses appear clinically mild, their associated symptoms can have a significant and lasting impact on quality of life. The lack of treatment options for severe or recalcitrant lichenoid irCAEs necessitates prospective studies on non-steroidal systemic treatment alternatives in an effort to reduce long-term oral corticosteroid use and improve ICI adherence. Clinicians should carefully observe patients on ICIs for lichenoid eruptions as early recognition and treatment initiation could reduce disease severity and keep patients on their life-saving cancer therapy.

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CRediT authorship contribution statement

Wylie M. Masterson: Data curation, Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Alexandria M. Brown:** Data curation, Investigation, Writing – original draft, Writing – review & editing. **May A. Al Ameri:** Data curation, Investigation. **Anisha B. Patel:** Conceptualization, Formal analysis,

Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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