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BRIEF COMMUNICATIONS

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Interface dermatitis: Delineating the diagnosis with adaptive immune markers

Interface dermatitis is non-specific histopathological terminology that encompasses a range of inflammatory skin conditions characterized by a T-cell infiltrate attacking the basilar epidermis with resultant vacuolization of the epidermal basal layer. When the inflammation is more intense and accompanied by a band-like inflammatory T-cell infiltrate, it is preferentially referred to as lichenoid dermatosis and there can be overlap between lichenoid dermatitis and other interface processes.

The timing of the biopsy relative to the inflammatory event can also affect microscopic findings. For example, dermatopathologists may use the terminology "late-stage interface" or "late-stage lichenoid" when microscopic examination shows only minimal interface change and sequelae of inflammation at the dermal–epidermal junction such as loss of rete ridge pattern, colloid bodies, Civatte bodies, and papillary dermal melanophages.

Therefore, the diagnosis of interface dermatitis generates a wide differential including connective tissue diseases such as subacute cutaneous lupus erythematosus (SCLE) and dermatomyositis (DM), viral eruptions, and specific conditions such as lichen planus pigmentosus (LPP) among other entities. Drug eruptions may also present with lichenoid and interface dermatitides. Recently, SCLE and DM-like eruptions have been reported to occur in patients undergoing treatment with immune checkpoint inhibitor therapy with anti-PD-1/PD-L1.[1]

It is important to distinguish among these conditions as management can be vastly different. Clinicopathologic correlation can be critical but is not always a reliable method of distinguishing among these entities, posing a challenge to both the clinician and the pathologist. Reliable diagnostic histopathological methods would better inform treatment options and maximize patient outcomes. In this study, we investigate the possibility of identifying discernable immunohistochemical (IHC) staining patterns among processes that are most often "top-lined" as interface dermatitis, including SCLE, DM, LPP, and drug eruptions.

After gaining IRB approval, we searched our pathology database for cases between 2016 and 2018 that were "top-lined" as interface dermatitis and contained a differential diagnosis of SCLE or cutaneous lupus erythematosus (CLE), DM, and LPP. We were able to confirm a clinical diagnosis of SCLE/CLE, DM, or LPP in the electronic medical record in 28 cases. We included five biopsy specimens from patients with interface dermatitis secondary to PD-L1 checkpoint inhibitor therapy from a previous study at our institution.[2] For IHC staining we used a panel of T-cell markers (CD3, CD4, and CD8), the plasmacytoid dendritic cell marker CD123, and the costimulatory immune cell markers PD-1 and PD-L1.

Control specimens were isolated from uninvolved tips of excision biopsies from age and sex-matched patients, resulting in 33 total biopsy samples (Table 1). Age and sex were recorded for all samples. All formalin-fixed, paraffin-embedded tissue biopsy specimens were stained with routine H&E and CD3 (2GV6; 1:150), CD4 (SP35; 1:200), and CD8 (SP57; 1:150) (Roche Tissue Diagnostics), CD123 (NCL-L-CD123; 1:300; Leica Biosystems), PD-1 (NAT105; 1:100), and PD-L1 (SP142; 1:100; Abcam) IHC markers. Using HALO Image Analysis Software (Indica Labs), scanned slides were annotated to select desired areas of analysis, which included the entire epidermis and dermis with the exclusion of areas of folding and fixation/embedding artifact. Positive cells for each immunomarker were quantified using HALO analytic software (Figure 1B,C). Statistical analysis was done with GraphPad Prism version 8.4.3 using one-way analysis of variance non-parametric testing (Kruskal–Wallis test) with Dunn's multiple comparisons post hoc test.

We did not observe a statistically significant difference in the expression of CD3, CD4, CD8, or CD123 between the interface dermatitides. Qualitatively there was increased CD3, CD4, and CD8 expression in SCLE, DM, LPP, and PD-1/PD-L1 inhibitor-induced dermatitis compared to the controls, but statistical significance was only observed in CD3 and CD8 expression between LPP and controls ($p = 0.02$ and $p = 0.002$, respectively).

Previous studies of CD123+ quantification in DM and CLE have shown that, although there is a spatial difference in CD123+ cells between the dermis and the epidermis, the overall quantity of CD123+ cells in both conditions is similar.[3] Our findings are in keeping with these prior studies as we found no significant difference in CD123 expression between SCLE and DM.

Most notably we observed increased PD-L1 expression in DM and SCLE as compared to LPP (DM vs. LPP $p = 0.0001$, SCLE vs. LPP $p = 0.0083$) (Figure 1A). This raises the possibility of using PD-L1 staining to differentiate these interface dermatitides. This finding may

TABLE 1 Patient demographics and specimen diagnoses

Diagnosis	Total specimens	Total patients	Total female patients	Total male patients	Age range (years)
Controls	5	5	4	1	31–56
LPP	8	8	5	3	28–61
SCLE	6	6	6	0	21–71
DM	9	7	6	1	49–79
PD-1/PD-L1 interface dermatitis	5	5	2	3	48–65
Overall totals	33	31	23	8	21–79

Note: A total of 33 specimens were evaluated from 31 patients. Specimens consist of 28 inflammatory dermatitis samples and five control samples isolated from uninvolved tips of non-inflammatory dermatitis excisions. The patients' ages ranged from 21 to 79 years old (mean = 52 years old). 75% of patients were female and 25% were male.
Abbreviations: DM, dermatomyositis; LPP, lichen planus pigmentosus; SCLE, subacute cutaneous lupus erythematosus.

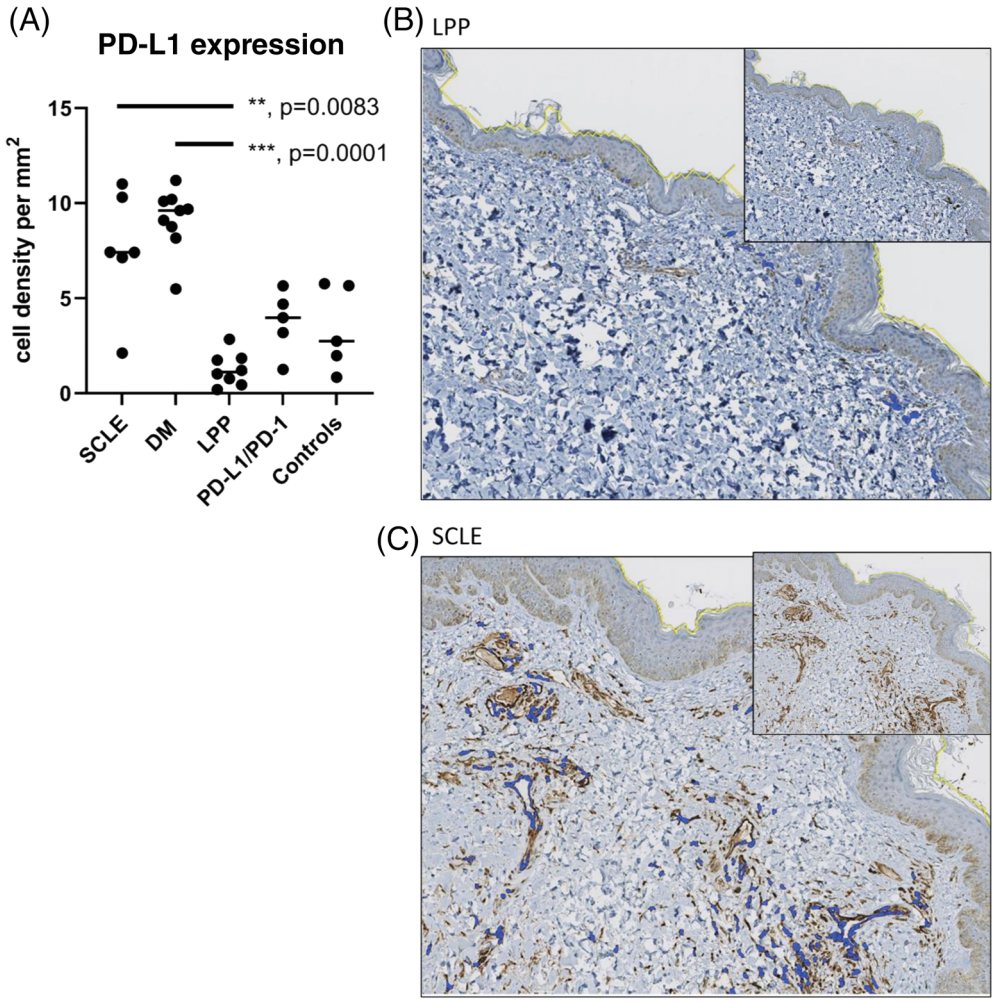

FIGURE 1 (A) There is increased PD-L1 expression in SCLE and DM when compared to LPP measured in cell density per μm^2. The top bold bar connecting SCLE and LPP represents the statistically significant increase in PD-L1 expression in SCLE compared to LPP (**$p = 0.0083$). The bottom bold bar connecting DM and LPP represents a statistically significant increase in PD-L1 expression in DM compared to LPP (***$p = 0.0001$). (B) PD-L1 staining in a representative LPP biopsy. Positive cells quantified by HALO imaging analysis are highlighted in blue (insert: PD-L1 staining before HALO imaging analysis). (C) PD-L1 staining in a representative SCLE biopsy. Positive cells quantified by HALO imaging analysis are highlighted in blue (insert: PD-L1 staining before HALO imaging analysis). ANOVA, analysis of variance; DM, dermatomyositis; LPP, lichen planus pigmentosus; SCLE, subacute cutaneous lupus erythematosus

be because of an ongoing immune response in DM and SCLE resulting in low PD-L1 expression, compared to downregulation of the immune response in LPP resulting in high PD-L1 expression. Using the overall density of CD3+ cells as a marker for the intensity of T-cell inflammation, we noted no significant difference in CD3+ cell density between any of the skin conditions. While the driving mechanism behind variable PD-L1 expression in LPP is unknown, it may reflect a tendency to biopsy inactive LPP lesions when PD-L1 is downregulated compared to active LPP lesions.

To investigate drug-induced interface processes, we evaluated cases of dermatologic adverse events in patients receiving PD-L1 checkpoint inhibitor therapy. Lichenoid dermatoses represent a significant portion of the cutaneous toxicity seen in these patients[4,5] and the culprit drug is clear, making the diagnosis of a drug-induced interface process reliable. We found no significant difference in PD-L1 expression between these drug-induced interface processes and SCLE, DM, or LPP. This is in concordance with prior studies which failed to show a significant difference in PD-L1 expression between PD-1/PD-L1 checkpoint inhibitor-induced lichenoid dermatitis and the de novo lichenoid processes lichen planus and lichenoid keratosis.[6]

In summary, we found that LPP may be distinguished from other similar mild interface dermatitides using PD-L1 IHC staining. Our findings are limited by the small number of samples studied and the lack of exact disease time course information among the patients in our cohort. In follow-up studies, it would be interesting to biopsy LPP at the earliest clinical presentation to better explore a chronological relationship between PD-L1 expression and lesion development. It may also be useful to utilize PD-L1 expression as a marker of ongoing activity to help clinicians gauge the need for treatment with anti-inflammatory agents or whether the inflammatory insult has resolved.

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DATA AVAILABILITY STATEMENT

Data Availability Statement: No datasets were generated or analyzed during the current study.

Eugene N. Brooks[1]
Michelle D. Colbert[1]
Inbal B. Sander[1,2]

[1]*Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA*
[2]*Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA*

Correspondence
Inbal B. Sander, Department of Pathology, Johns Hopkins University School of Medicine, 600 N Wolfe Street, Blalock 920D, Baltimore, MD 21287, USA.
Email: ibrauns2@jhmi.edu

ORCID

Eugene N. Brooks https://orcid.org/0000-0002-4058-3402
Michelle D. Colbert https://orcid.org/0000-0003-2798-476X
Inbal B. Sander https://orcid.org/0000-0001-6045-3165

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Combining three-dimensional histopathology with bread loafing and orientation without artificial coloring

1 | INTRODUCTION

Basal cell carcinoma (BCC), one of the subtypes of non-melanoma skin cancer (NMSC), is the most common cancer of the skin, and its incidence is increasing worldwide.[1] BCCs rarely metastasize but can cause significant morbidity because of local invasion and tissue destruction. In up to 80% of patients, BCCs develop in the head and neck region, and surgical removal is generally considered the treatment of choice.[2] Given the proximity of many sensitive anatomic landmarks, there is a need for resection margin control. Especially in small