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Type 2 immunity links eczematous and lichenoid eruptions caused by immune checkpoint inhibitors

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Abstract

Background: Cutaneous immune-related adverse events (cirAEs) induced by immune checkpoint inhibitor (ICI) therapy share clinical features with spontaneous inflammatory dermatoses. However, the exact immunopathogenesis of cirAEs remains unclear.

Objective: To investigate the inflammation that mediates the most common cirAEs, lichenoid eruption (LE) and eczematous eruption (EE).

Methods: In a prospective cohort study, participants with cancer on ICI therapy with any clinically visible cirAEs were enrolled. T helper-1 (Th1) and Th2 cell responses in cirAEs were compared to spontaneous lichenoid dermatitis and eczematous dermatitis.

Results: Among 88 cirAE biopsies collected, LE (35.22%) and EE (31.81%) accounted for most cases. In contrast to lichenoid dermatitis, we found that the $CD4^+/CD8^+$ T-cells and Th2/Th1 ratios were increased in ICI-induced LE, similar to EE. Importantly, we identified several cirAEs displaying a combination of LE and EE on pathology.

Limitations: Only the most common types of cirAEs were evaluated, and Th17 cells were not analyzed.

Conclusion: Our findings indicate that LE and EE may represent a cirAE spectrum with a common underlying immunologic mechanism. Thus, understanding the immunopathogenesis of cirAEs can aid in their treatment and prevention.

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Keywords

cirAEs; eczematous dermatitis; eczematous eruption; ICI therapy; lichenoid dermatitis; lichenoid eruption; Th2 immunity

INTRODUCTION

Immune checkpoint inhibitors (ICIs), including anti-programmed cell death protein 1/ligand-1 (PD1/PDL1) and anti-cytotoxic T lymphocyte-associated antigen 4 antibodies, have been widely used in cancer treatment, revolutionizing the management and survival of cancer patients.[1,2] However, they are associated with immune-related adverse events (irAEs),[3,4] with cutaneous irAEs (cirAEs) being the most common and earliest, which clinically resemble spontaneous inflammatory dermatoses. irAEs can lead to treatment modification or discontinuation,[5–8] which impacts patient survival. Several mechanisms have been proposed in the pathogenesis of cirAEs, such as T-cell activation against shared tumor and normal tissue antigens and increased proinflammatory cytokine production by T-cells and B-cells.[4,9] Recent studies link cirAEs with improved cancer prognosis,[10,11] suggesting a common immune mechanism in cirAEs and tumor clearance.[12] However, the proposed mechanisms, including humoral immunity and cytotoxic T-cells, are limited to certain cancer types,[11–13] while the role of type 2 immunity, which is less characterized in the predominantly type 1 anticancer response, remains unexplored. Understanding the cirAEs immunopathogenesis will aid in developing novel therapeutic agents to effectively prevent and treat these conditions and improve outcomes.[14,15]

Lichenoid eruption (LE) and eczematous eruption (EE) are among the most prevalent cirAEs[7,16,17] and mimic their spontaneous counterparts both clinically and histologically.[18,19] Spontaneous lichenoid dermatitis (LD) shows band-like mononuclear immune cells, mostly activated T-cells, in the epidermal-dermal junction, with hyperkeratosis, hypergranulosis, and acanthosis.[20,21] Spontaneous eczematous dermatitis (ED) features spongiosis, intraepidermal vesicles, epidermal hyperplasia, and perivascular T-cell infiltration.[22,23] LD is predominantly infiltrated by cytotoxic $CD8^+$ T-cells,[20,24] whereas ED is mediated by $CD4^+$ T-cells.[25,26] Furthermore, LD is primarily associated with T helper 1 (Th1) cell immunity.[24,27] By contrast, ED is driven by Th2 responses.[25,27,28] Meanwhile, the composition of immune cells in LE and EE remains underexplored.[29,30]

To determine the immunopathogenesis of LE and EE, we examined the histological features and immune cells in the skin biopsies from cancer patients on ICI therapy, compared with biopsies from patients with LD and ED. We observed that $CD4^+$ T-cells predominantly infiltrate both LE and EE. Interestingly, Th2 cells were found to equally dominate the immune environment of ICI-induced LE and EE. The $CD4^+$ /$CD8^+$ T-cells and Th2/Th1 ratios were similarly increased in these cirAEs. In addition there was no significant correlation between these cirAEs and the type of ICI therapy, cancer diagnosis, and patient age. Notably, we identified a subset of cirAE samples exhibiting both lichenoid and eczematous features on pathology, characterized by spongiosis and perivascular and interface T-cell infiltrates. Our findings indicate that LE and EE may represent a cirAE

spectrum with a shared underlying immunologic mechanism and certain distinctions from the spontaneous conditions with similar dermatologic appearances. The observed efficacy of type 2 cytokine blockade in treating ICI-induced LE and EE supports this concept.[31] Thus, understanding the immunopathogenesis of cirAEs will improve the treatment and prevention of these conditions.

METHODS

Study approval

This study was approved by the Massachusetts General Hospital (MGH) Institutional Review Board (IRB protocol #2020P001944). Cancer patients on ICI therapy were enrolled in the study. All participants provided informed consent to participate in the study, granting access to their protected health information and tissue samples, and signed a written consent form. Deidentified spontaneous LD and ED tissue samples were obtained retrospectively from the Department of Pathology at MGH, Boston. All patient data were deidentified.

Case selection

In a prospective cohort study, skin biopsy specimens of cirAEs were collected from all participants with cancer on ICI therapy who developed dermatitis on therapy from January 2020 to December 2024 in dermatology clinics at MGH. Skin biopsies were performed regardless of the clinical presentation to enable pathological assessment across all cirAEs subtypes. All types of cirAEs were classified based on both their clinical features and pathological results at MGH. Among the collected LE and EE samples, we selected 15 biopsies that had the most histological similarity with their spontaneous counterparts based on hematoxylin and eosin-stained tissue sections. The collected LE and EE were biopsied at the first appearance, and as a result, they represent the acute or subacute phase of the eruption. Demographic data, including participant sex, age, cancer diagnoses, and the type of ICI therapy at the time of biopsy, were collected. Twelve spontaneous acute or subacute LD, excluding lichenoid keratoses, and 10 spontaneous acute or subacute ED specimens were collected retrospectively from January 2020 to January 2024 from the Department of Pathology at MGH. Demographic data, including patient sex and age at the time of biopsy, were collected. Test and control samples were matched based on clinical and histological features.

Histology and immunofluorescence

The cirAEs samples were fixed in 4% paraformaldehyde (Sigma-Aldrich) and maintained at 4 °C overnight. Tissues were washed with Phosphate-Buffered Saline and dehydrated in ethanol. The samples were processed and embedded in paraffin. Paraffin-embedded tissues of 5 μm sections were cut and stained for hematoxylin and eosin. For immunofluorescence staining, cirAEs slides were rehydrated and permeabilized in 0.2% Triton X (for transcription factors) for 5 minutes. The slides were then heated in antigen unmasking solution (Vector Laboratories, catalog no. H-3300) at high pressure in a Cuisinart pressure cooker for 12 minutes. Slides were then washed with 0.1% Tween 20 (Sigma-Aldrich) 3 times for 5 minutes each in 1x Dulbecco's Phosphate-Buffered Saline. Then, the sections were blocked in a blocking buffer containing 5% goat serum (Millipore Sigma) for 1 hour

and stained with antihuman primary antibodies, including anti-CD3 (CD3-12, Origene, SM1754P), anti-CD4 (SP35, Abcam, ab213215), anti-CD8 (C8/144B, Cell Signaling, 70306), anti-GATA3 (L50-823, BioCare Medical, CM405A), and anti-Tbet (MRQ-46, Cell Marque, 368R-74) monoclonal antibodies, overnight at 4 °C followed by fluorochrome-conjugated secondary antibodies and 4', 6-diamidino-2-phenylindole dihydrochloride nuclear stain (Thermo Fisher Scientific). Slides were then mounted using 2-3 drops of mounting media (ProLong Gold Antifade reagent, Invitrogen). The Axio Scanner (Axio Scan.Z1, Zeiss) was used to scan the slides, and high-resolution images were obtained by a Zeiss Axio Observer Z1 (Zeiss) and analyzed using the Zeiss ZEN Image Processing software. The cell population was quantified within 20X magnified high-power fields in both the epidermis and dermis digitally by the HALO Image Analysis Platform (Indica Labs).

Statistical analysis

A two-tailed unpaired *t*-test was used to compare 2 variables (continuous). A Fisher's exact test was used to compare 2 variables (categorical). A Pearson correlation coefficient was used for age comparison in each group. One-way analysis of variance with Dunn's multiple comparisons test was used for more than 2 comparisons. A *P* value of less than 0.05 was considered significant. All error bars represent SD. All the graphs and statistical analyses were performed using GraphPad Prism 9.

RESULTS

Lichenoid and eczematous eruptions are the 2 most common cirAEs

Among 88 cirAE biopsies collected from cancer patients who developed dermatitis on ICI therapy at MGH from January 2020 to December 2024, LE (31 samples, 35.22%) and EE (28 samples, 31.81%) were the most common. Nine samples showed a mixed combination of LE and EE (ME, 10.22%). Six samples showed bullous pemphigoid (6.81%), 5 samples (5.68%) showed psoriasiform eruptions, 2 samples (2.27%) showed morbilliform eruptions, 2 samples were granulomatous eruptions, and 2 samples were consistent with Stevens-Johnson syndrome. In addition, cutaneous lupus erythematosus, sclerodermoid eruption, and leukocytoclastic vasculitis each accounted for 1 sample (1.13%) (Fig 1). There was no significant association between cirAEs and the type of ICI therapy, the cancer diagnosis, and the patient's sex and age. Although the *P* value is less than 0.05 for ME, it is nonsignificant after controlling for multiple hypothesis testing (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/8k7v9gfrnh/1).

Next, we evaluated the clinical and histological features of LE, EE, and ME. LE presented as violet-colored polygonal papules or plaques, often with a flat top and symmetrical distribution similar to LD (Supplementary Fig 1, A, available via Mendeley at https://data.mendeley.com/datasets/8k7v9gfrnh/1). EE lesions were characterized by erythematous papules, sometimes accompanied by scaling and excoriation, similar to the features of ED (Supplementary Fig 1, A, available via Mendeley at https://data.mendeley.com/datasets/8k7v9gfrnh/1). Histologically, parakeratosis and a band-like lymphocytic infiltrate at the epidermal-dermal junction (band-like lymphocytic infiltration) were observed for ICI-induced LE (Supplementary Fig 1, B, available via Mendeley at

https://data.mendeley.com/datasets/8k7v9gfrnh/1). By contrast, spongiosis, hyperkeratosis, and perivascular lymphocytic infiltration marked EE (Supplementary Fig 1, B, available via Mendeley at https://data.mendeley.com/datasets/8k7v9gfrnh/1). ME demonstrated a combination of superficial to mid-dermal lymphocytic infiltration and spongiosis (Supplementary Fig 1, B, available via Mendeley at https://data.mendeley.com/datasets/8k7v9gfrnh/1).

$CD4^+$ T-cells predominantly infiltrate ICI-induced lichenoid and eczematous eruptions

To examine the immunopathogenesis of LE and EE, we evaluated $CD3^+$, $CD4^+$, and $CD8^+$ T-cells in the immune microenvironment of these lesions in comparison with their spontaneous counterparts (Supplementary Fig 2, A and B, available via Mendeley at https://data.mendeley.com/datasets/8k7v9gfrnh/1). $CD3^+$, $CD4^+$, and $CD8^+$ T-cells were significantly increased in ICI-induced LE compared with EE and ME ($P < .0001$, Fig 2, A, and Supplementary Fig 2, C–E, available via Mendeley at https://data.mendeley.com/datasets/8k7v9gfrnh/1). No significant differences were observed between EE and ME in their $CD3^+$, $CD4^+$, and $CD8^+$ T-cell counts ($P = .8917$, $P = .7202$, and $P = .3436$, respectively, Supplementary Fig 2, C–E, available via Mendeley at https://data.mendeley.com/datasets/8k7v9gfrnh/1). Surprisingly, the $CD4^+$ to $CD8^+$ T-cell ratio was not significantly different between LE, EE, and ME (Fig 2, B and Supplementary Fig 2, F, available via Mendeley at https://data.mendeley.com/datasets/8k7v9gfrnh/1). However, ICI-induced LE showed a significantly higher $CD4^+$ to $CD8^+$ T-cell ratio compared with spontaneous LD (Fig 2, B). $CD4^+$ to $CD8^+$ T-cell ratio was similar in ICI-induced EE and spontaneous ED (Fig 2, B). These findings demonstrate that $CD4^+$ T^-cells are the dominant T-cells in the immune microenvironment of ICI-induced LE, EE, and ME and help distinguish ICI-induced LE from spontaneous LD.

ICI-induced LE, unlike its spontaneous counterpart, is marked by T helper 2 cell immunity

To determine which $CD4^+$ T-cell subtype mediates the immunopathogenesis of ICI-induced LE and EE, we examined T-box expressed in T-cells (T-bet) and GATA-binding protein 3 (GATA3) expression in $CD4^+$ T-cells, which are transcription factors defining Th1 and Th2 cells, respectively (Supplementary Fig 3, A and B, available via Mendeley at https://data.mendeley.com/datasets/8k7v9gfrnh/1). $GATA3^+$ $CD4^+$ $CD3^+$ T (Th2) cells and $Tbet^+$ $CD4^+$ $CD3^+$ T (Th1) cells were significantly higher in ICI-induced LE versus EE and ME ($P = .0021$ and $P < .0001$ for LE versus EE and $P = .0093$ and $P = .0095$ for LE versus ME, respectively; Fig 3, A and Supplementary 3, C and D, available via Mendeley at https://data.mendeley.com/datasets/8k7v9gfrnh/1). However, Th2 cells equally dominated the $CD4^+$ T-cell infiltrates in LE, EE, and ME as measured by Th2 to Th1 cell ratio (Fig 3, B and Supplementary Fig 3, E, available via Mendeley at https://data.mendeley.com/datasets/8k7v9gfrnh/1). In addition, Th2 to Th1 cell ratio was significantly higher in ICI-induced LE compared with spontaneous LD, as well as ICI-induced EE versus spontaneous ED ($P < .0001$ and $P = .0362$, respectively, Fig 3, B). Importantly, spontaneous LD was the only dermatosis in which the mean Th2/Th1 cell ratio was less than 1 (0.66) (Fig 3, B). A comparison of spontaneous LD versus ED showed a significantly higher Th2 to Th1 cell ratio in ED (Supplementary Fig 3, F, available via Mendeley at https://data.mendeley.com/datasets/8k7v9gfrnh/1). Thus, Th2 cells dominate the T-cell infiltrates in ICI-induced LE,

EE, and ME, which indicates the distinct immunopathogenesis of ICI-induced LE compared with its spontaneous counterpart.

DISCUSSION

cirAEs are the most common and earliest manifestation of immunotherapy-related toxicities.[32] LE and EE are the 2 most common cirAEs caused by anti- PD1/PDL1, anti-cytotoxic T lymphocyte-associated antigen 4, or combination immunotherapy.[7,16,17] Our findings demonstrate the highest frequency of these 2 types of cirAEs among patients presented to MGH dermatology clinics due to immunotoxicity from 2020 through 2024. cirAEs are associated with significant morbidities and mortalities and can lead to ICI discontinuation.[33,34] In addition, recent studies show a significant association between cirAE and the development of other irAEs, as well as a positive survival outcome in cancer patients, highlighting the importance of understanding the exact mechanisms behind this immunotoxicity.[8,35] Furthermore, there is no significant association between various cirAE subtypes and types of cancers and ICIs,[36,37] which may suggest a common immunopathogenesis among various cirAEs.

The immunopathogenesis of cirAEs is mostly attributed to the loss of T-cell tolerance and autoimmune-like reactions.[4,7] The proposed mechanisms include T-cell cross-reactivity between the skin basal layer and targeting proteins in tumor cells in bullous pemphigoid,[38] immune responses against the shared antigen by the normal and malignant melanocytes in vitiligo,[39] and infiltration of proinflammatory cytokines by activated T-cells and B-cells, including interleukin (IL)-2, interferon-gamma, IL-17, and IL-22 in oral lichen planus and psoriasis.[40,41] These mechanisms are specific to certain types of cirAEs associated with specific malignancies and do not fully explain the immunopathogenesis of all cirAEs. While $CD8^+$ T-cells and Th1 cells are the dominant immune cells in spontaneous LD,[20,24,27] the immune microenvironment of ICI-induced LE is mostly infiltrated with $CD4^+$ T-cells over the $CD8^+$ T-cells.[16,18,42–44] However, several studies show the role of cytotoxic $CD8^+$ T-cells in driving ICI-induced LEs.[29,45] PD1 blockers activate antigen-specific $CD8^+$ T-cells to eliminate antigen-expressing epidermal cells, leading to LE.[29] However, this break in immune tolerance may not explain the immunopathogenesis of other ICIs in inducing LE.[46,47] Our findings reveal a significantly higher $CD4^+$ /$CD8^+$ T-cell ratio in LE versus LD. Although the role of innate immunity and Th1 cells in the pathogenesis of LE has been explored previously,[48] we show that Th2 cells dominate the immune environment of LE and Th2/Th1 cell ratio is significantly increased in LE compared with spontaneous LD. By contrast, the immunopathogenesis of EE is similar to spontaneous ED and is primarily driven by $CD4^+$ Th2 cells.[25–28,30] Nonetheless, Th2/Th1 cell ratio is significantly higher in ICI-induced EE versus spontaneous ED, indicating an even stronger role for type 2 immunity in EE. Thus, our findings support the critical role of type 2 immunity in the immunopathogenesis of both LE and EE.

In our study, we have observed several cirAEs with both lichenoid and eczematous histopathological features (ie, ME), including band-like T-cell infiltration and epidermal spongiosis, perhaps highlighting the mechanistic connection between ICI-induced LE and EE.[4,19] Emerging evidence on the management of cirAEs highlights the efficacy

of type 2 cytokine blockers, including dupilumab, for the treatment of LE and EE.[49,50] Th2-mediated cytokines, including IL-4 and IL-13, play a significant role in ICI-induced EE similar to its spontaneous counterpart.[51] The observed dupilumab efficacy for LE treatment supports the role of Th2 cells in LE, which is distinct from spontaneous LD. Interestingly, other cirAE subtypes also demonstrate an increase in Th2-mediated cytokines and dupilumab responsiveness, suggesting that type 2 immunity may be a broader driver of cirAEs.[52] Further studies are required to evaluate the role of type 2 immunity in the immunopathogenesis of other cirAE subtypes and to address the major gaps in cirAE treatment.

CONCLUSIONS

Our findings indicate that ICI-induced LE and EE may represent a cirAE spectrum with a common underlying immunologic mechanism driven by type 2 immunity. The observed efficacy of type 2 cytokine blockade in treating ICI-induced LE and EE supports this concept. Future studies are warranted to further define the immunopathogenesis of other cirAE subtypes, which will aid in improved management of these rising dermatological conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest

Dr Fisher discloses ownership and consulting relationships with Soltego, Tasca, Swiss Rockets, Coherent Medicines, and Biocoz, and a consulting relationship with Pierre Fabre. These interests were reviewed and are managed by Massachusetts General Hospital and MGB HealthCare in accordance with their conflict-of-interest policies. Dr Fisher acknowledges support from NIH grants P01 CA163222, R01 AR072304, and R01 AR043369 and the Melanoma Research Alliance and the Lancer Professorship in Dermatology (Harvard Medical School). The other authors have no conflicts of interest to declare.

Data availability:

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Abbreviations used:

cirAEs	cutaneous immune-related adverse events
ED	eczematous dermatitis
EE	eczematous eruption

ICI	immune checkpoint inhibitor
IL	interleukin
LD	lichenoid dermatitis
LE	lichenoid eruption
MGH	Massachusetts General Hospital

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CAPSULE SUMMARY

- Cutaneous immune-related adverse events resemble their spontaneous inflammatory dermatoses.
- We find that lichenoid eruption and eczematous eruption represent a common spectrum of cutaneous immune-related adverse events driven by type 2 immunity, highlighting the potential for novel therapeutic strategies to improve their management and prevention.

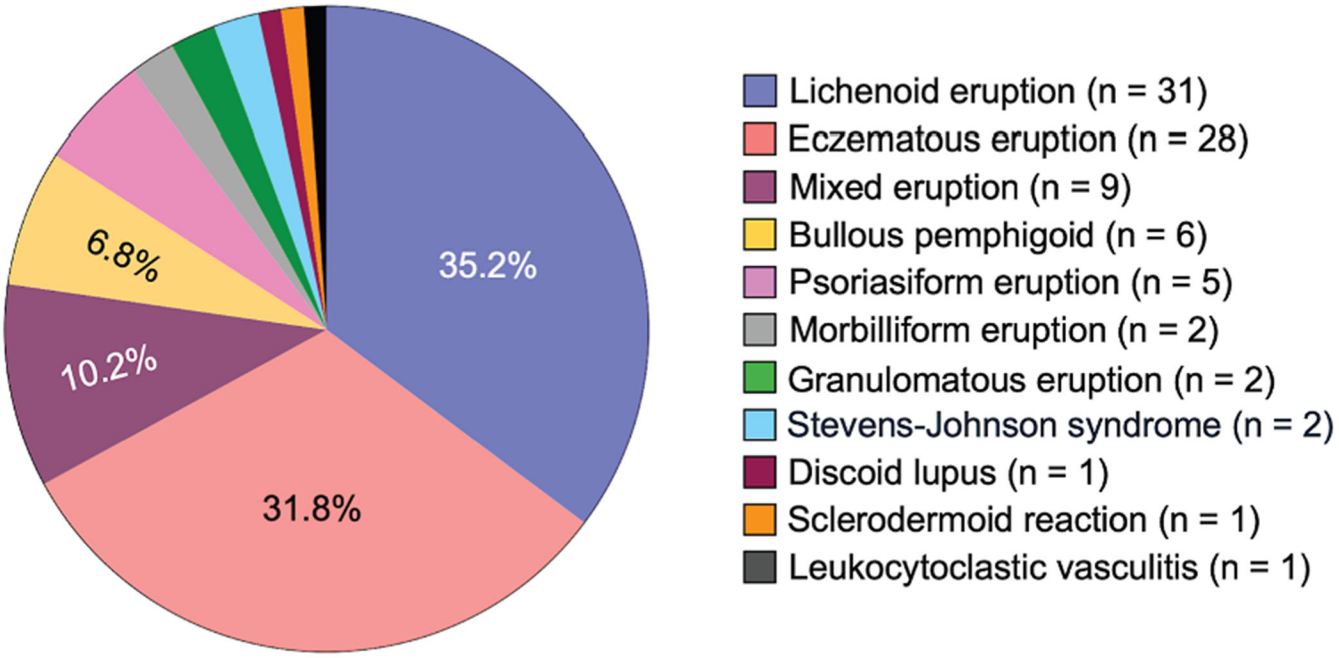

Fig 1.

The distribution of cirAEs at MGH dermatology clinics between January 2020 and December 2024. LE and EE constitute 67% of cirAEs at MGH. *cirAEs*, Cutaneous immune-related adverse events; *EE*, eczematous eruption; *LE*, lichenoid eruption; *MGH*, massachusetts General Hospital.

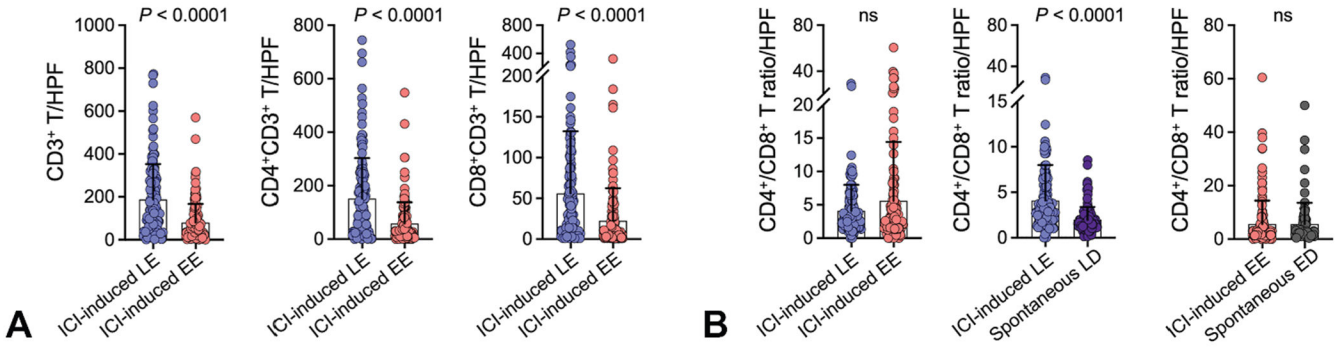

Fig 2.

CD4$^+$ to CD8$^+$ T-cell ratio is significantly higher in ICI-induced LE compared with spontaneous LD. **A,** Quantification of CD3$^+$ T, CD4$^+$ T, and CD8$^+$ T-cells in ICI-induced LE (n = 15) versus EE (n = 15). **B,** Quantification of CD4$^+$ /CD8$^+$ T-cell ratio in ICI-induced LE (n = 15) versus EE (n = 15), ICI-induced LE (n = 15) versus spontaneous LD (n = 12), and ICI-induced EE (n = 15) versus spontaneous ED (n = 10). Unpaired *t*-test, ns: not significant. *ED*, Eczematous dermatitis; *EE*, eczematous eruption; *HPF*, high-power field; *ICI*, immune checkpoint inhibitor; *LD*, lichenoid dermatitis; *LE*, lichenoid eruption.

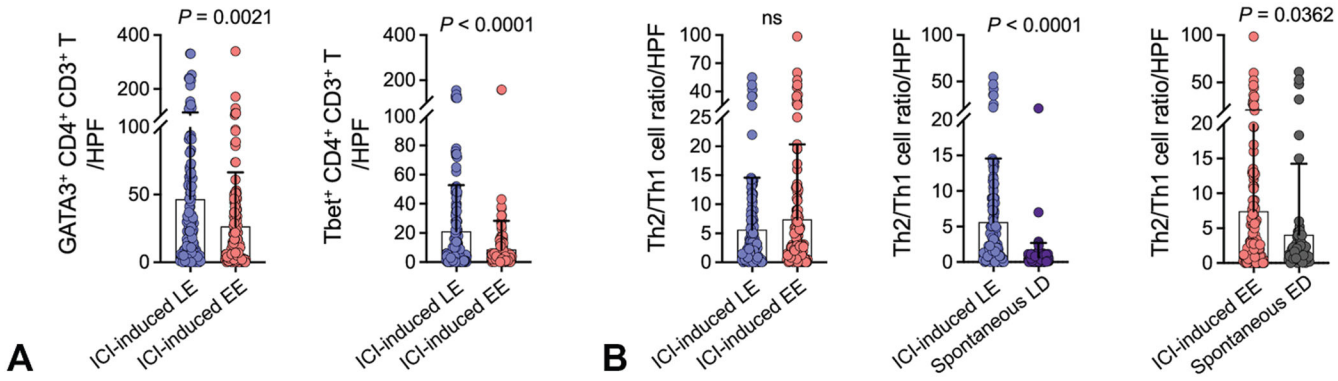

Fig 3.

The Th2 to Th1 cell ratio is significantly higher in ICI-induced LE than in spontaneous LD. **A,** Quantification of $GATA3^+$ $CD4^+$ $CD3^+$ (Th2) and $Tbet^+$ $CD4^+$ $CD3^+$ (Th1) cells in ICI-induced LE (n = 15) and EE (n = 15). **B,** Quantification of $Th2^+$ /$Th1^+$ cell ratio in ICI-induced LE (n = 15) versus EE (n = 15), ICI-induced (n = 15) LE versus spontaneous LD (n = 12), and ICI-induced EE (n = 15) versus spontaneous ED (n = 10). Unpaired *t*-test, ns: not significant. *ED*, Eczematous dermatitis; *EE*, eczematous eruption; *HPF*, high-power field; *ICI*, immune checkpoint inhibitor; *LD*, lichenoid dermatitis; *LE*, lichenoid eruption.