Checkpoint inhibitor–induced lichen planus differs from spontaneous lichen planus on the clinical, histological, and gene expression level

Barbara Meier-Schiesser, MD, PhD,[a] Christine Zecha, MD,[b] Sarah Zierold, MD,[b] Isabel Kolm, MD,[a] Magdalena Röckel, MD,[c] Waltraud Fröhlich,[c] Nora Mittag, MD,[b] Christina Schmitt, MD,[b] Joerg Kumbrink, PhD,[d,e] Jessica C. Hassel, MD,[f] Carola Berking, MD,[c] Dorothee Nashan, MD,[g] Lars Einar French, MD,[b,h] Julio Vera-González, PhD,[c] Reinhard Dummer, MD,[a] Katrin Kerl-French, MD,[b] and Lucie Heinzerling, MD, MPH[b,c]

Background: Although highly efficacious, immune checkpoint inhibitors induce a multitude of immune-related adverse events including lichenoid skin reactions (irLP) that are often therapy-resistant.

Objectives: To compare the clinical, histological, and transcriptional features of irLP with spontaneous lichen planus (LP).

Methods: Clinical and histological presentations of irLP and LP, as well as the gene expression profiles of irLP and LP lesional and healthy skin were assessed.

Results: irLP differed considerably from LP with regard to the distribution pattern of skin lesions with irLP appearing mostly in an exanthematous form, whereas lesions were more localized in the LP group. Histologically, dermal lymphocyte infiltration was significantly lower in irLP compared with LP, whereas lymphocyte exocytosis and apoptotic keratinocytes were significantly higher in irLP. Gene expression analysis revealed irLP to have a more inflammatory profile with elevated *IFNG* levels and a possible role of phagosome signaling compared with LP.

Limitations: The study is descriptive and necessitates further investigation with larger cohorts and broader analyses.

From the Department of Dermatology, University Hospital Zurich, Zurich, Switzerland[a]; Department of Dermatology and Allergy, University Hospital, Ludwig Maximilian University Munich, Munich, Germany[b]; Department of Dermatology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Deutsches Zentrum Immuntherapie (DZI), Erlangen, Germany[c]; Institute of Pathology, Faculty of Medicine, Ludwig Maximilian University Munich, Munich, Germany[d]; German Cancer Consortium (DKTK), German Cancer Research Centre (DKFZ), Heidelberg, Germany[e]; Department of Dermatology, University Hospital Heidelberg, Heidelberg, Germany[f]; Department of Dermatology, Hospital Dortmund, Dortmund, Germany[g]; and Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami, Miller School of Medicine, Miami, Florida.[h]

Drs Meier-Schiesser and Zecha contributed equally to this article.

Funding sources: Funded by (1) the German Federal Ministry of Education and Research (BMBF) as part of the project MelAutim (01ZX1905A), which aims a systems medicine investigation of melanoma and autoimmunity in the context of immune therapies and by (2) the Swiss Life Foundation. The funding sources had no influence on the design, conduct, analysis, and/or report of this research.

Patient consent: The authors obtained written consent from patients for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available. Patient consent forms were not provided to the journal but are retained by the authors.

IRB approval status: Reviewed and approved by the ethics committee of the University Hospital Erlangen (Nr. 2_20 B and Nr. 17_16Bc) and of the Ludwig Maximilians University, Munich (Project-nr. 20-1122, with amendment from February 9 to 21, 2022). All human samples were taken after informed written patient consent and according to the principles of Helsinki.

Accepted for publication November 22, 2023.

Correspondence to: Lucie Heinzerling, MD, MPH, Department of Dermatology and Allergy, University Hospital, Ludwig Maximilian University Munich, Frauenlobstraße 9-11, 80337 Munich, Germany. E-mail: lucie.heinzerling@med.uni-muenchen.de.

2666-3287

https://doi.org/10.1016/j.jdin.2023.11.013

Conclusion: irLP differs from spontaneous LP on the clinical, histopathological, and gene expression level. The inflammatory gene signature in irLP suggests that topical JAK inhibitors could be an effective treatment, targeting local skin inflammation without systemic immunosuppression. (JAAD Int 2024;15:157-64.)

Key words: cutaneous side effects; exanthematous; gene expression profiles; immune-related adverse events; inflammatory signatures.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are effective in many tumor entities by interfering with inhibitory signals between T cells and antigen-presenting cells or T cells and tumor cells.[1] However, they also induce a multitude of immune-related adverse events (irAEs) most frequently as cutaneous reactions in 46% to 62% of patients followed by colitis (22%-48%), hepatitis (7%-33%), and endocrinopathies (thyroiditis, hypophysitis, adrenalitis, and diabetes mellitus; 12%-34%).[2,3] Exanthema, pruritus, and psoriasiform dermatitis represent the most frequently reported dermatologic irAE[4,5] and can usually be managed by topical glucocorticosteroids.[1] However, some irAE-associated skin reactions are severe, including bullous pemphigoid and toxic epidermal necrolysis. Furthermore, a multitude of cases with lichen planus (LP)-like eruptions (immune-related lichen planus; irLP) have been documented[1,6,7] and these are often therapy resistant.[8,9] Clinically they range from mild cutaneous eruptions to severe mucocutaneous reactions[3,10,11] with verrucous plaques, bullae, or fissures.[12,13] Mostly, they are treated with topical or systemic glucocorticoids or with other immunosuppressant agents.[1] However, a considerable number of cases of irLP are particularly difficult to treat and associated with substantial discomfort.[12,13]

Similar to spontaneous LP, irLP can affect the skin, mucosae, hair, and nails[14]; however, mucosal involvement appears to be less frequent than in spontaneous LP.[9,15-17] The suggested pathogenesis of LP is a cell-mediated immune response, leading to activation and migration of cytotoxic CD8+ T cells into the dermoepidermal junction zone with consecutive damage of basal keratinocytes. In comparison, irLP is thought to be an off-target effect of checkpoint inhibition, also leading to T cell-driven damage of keratinocytes.[10] However, the exact mechanism of action still has to be elucidated in both LP and irLP.

Since etiology and clinical presentation as well as response to therapy differ in LP and irLP, this study aims to identify potential differences between both diseases regarding clinical presentation, histology, and gene expression level. A better understanding of the pathomechanism could lead to better-suited therapy options for patients with irLP and therefore allow continuation of cancer therapy and improved management of the symptoms for these often distressed patients.

CAPSULE SUMMARY

- Immune-related lichen planus differs from spontaneous lichen planus on the clinical, histopathological, and gene expression level.
- Our results support the evaluation of topical JAK inhibitors as treatment option for therapy-resistant immune-related lichen planus in the context of controlled clinical trials.

METHODS

Study design and patient cohort

The cohorts of this multicenter study were recruited retrospectively in 5 skin cancer centers (Munich, Zurich, Dortmund, Heidelberg, and Erlangen) including all cases of irLP and a control group of 23 consecutive cases of LP. Of the 40 individuals examined, 14 had diagnosed irLP, 23 LP, and 3 were healthy individuals (nondisease controls; NDCs). LP and irLP were diagnosed via medical history, clinical evaluation, and histology. Adverse events were graded according to CTCAE version 5.0.

Biologic material collection and processing

Biopsies were taken from lesional skin of patients with LP and irLP, as well as from nondiseased skin of healthy individuals (NDCs). After paraffinization, 5 μm skin sections were stained with hematoxylin and eosin using a Bond RXm autostainer (Leica Biosystems). RNA was isolated from paraffin-embedded skin samples using the *Recover All Total Nucleic Acid Isolation Kit for FFPE* (40 prps) (Life Technologies/Ambion Art-Nr. AM1975).

Abbreviations used:

ICI: immune checkpoint inhibitor
IFN-γ: interferon gamma
irAE: immune-related adverse event
irLP: immune-related lichen planus
LP: lichen planus
NDC: nondisease control

Gene expression analyses

Gene expression analysis was performed on NanoString. Expression was determined using the nCounter PanCancer Immune Profiling Panel (human) (NanoString, XT-CSO-HIP1-12). Sample hybridization was performed according to the manufacturer's protocol. The nCounter Flex Digital analyzer was used for sample detection and analysis. The raw data processing, quality control, and normalization were run on the ROSALIND analysis software (Version 3.35.3.0; https://rosalind.onramp.bio/). Quality control and normalization was performed according to Perkins et al.[18] The Partitioning Around Medoids method from the fpc R library was used for heatmap gene clustering of differentially expressed genes.[19] Pathway analyses were performed on the ROSALIND platform.[20-26]

Statistics

For *P* value calculation of the clinical data, the Fisher's exact test, Fisher-Freeman-Halton test, Kruskal-Wallis test, and Student *t* test were used. Statistical analyses of histological evaluations were calculated using the Student *t* test. SPSS version 29.0 was used for Kaplan-Meier analysis to estimate the duration of overall survival and progression-free survival. The 95% 2-sided confidence interval (CI) for the objective response rate was calculated using the Clopper-Pearson method. NanoString data were analyzed using the fast method[27] for calculating fold changes and *P* values and the Benjamini-Hochberg method for *P* value adjustment. A fold change of 1.5 and a *P* value adjustment ≤.05 were defined as cut-offs.

RESULTS

Clinical features of irLP differ from LP with regard to clinical presentation and age

Within the irLP group (n = 14), 2 cases clinically resembled classical LP (14%), characterized by LP-like lesions at typical localizations ± mucosal lesions, 1 case showed mucosal manifestation only (7%). Eleven cases presented as exanthema that was defined as widespread LP-like rash (79%; Table I). Of these 14 cases, 4 patients showed irAEs of CTCAE grade ≥3. Other irAE were documented in 6 patients and included 1 case each of irAE colitis, irAE hepatitis, irAE pneumonitis, irAE nephritis, and irAE uveitis. Two patients presented with other cutaneous irAEs than irLP: one patient developed melanoma-associated hypopigmentation commonly termed vitiligo, the other patient suffered from a multitude of cutaneous adverse events including vitiligo, flush, xerosis cutis, pruritus, eczema, psoriasis, erysipelas-like inflammation, alopecia, and bullous pemphigoid (Supplementary Tables I and II, available via Mendeley at https://data.mendeley.com/datasets/ffzjcnfmcg/1). In the spontaneous LP cohort (n = 23), 15 patients presented with a classical LP (skin ± mucosa; 65%), 5 showed only mucosal manifestations (22%) and 3 patients with LP suffered from an exanthematous form (13%) (Table I). Exanthematous presentation was much more frequent in irLP than in LP with 11 of 14 (79%) (Fig 1, *A*) compared with 3 of 23 (13%) in LP where most of the lesions tended to be more localized (Fig 1, *B*, and Table I).

The mean age differed in the 2 groups with a higher age at diagnosis in the irLP group (69 years) compared with 55 years in LP. No significant differences were found with regard to sex distribution with 43% females in the LP group and 48% in the irLP group (Table I).

Table I. Clinical features of immune-related lichen planus compared with lichen planus

Characteristics of patients	irLP	LP	*P* values
Number of patients	14	23	
Age, y (mean)	69 (25-80)	55 (23-82)	.015*
Sex			1.00†
Female	6 (43%)	11 (48%)	
Male	8 (57%)	12 (52%)	
Type of LP			<.001‡
Classical (skin ± mucosa)	2 (14%)	15 (65%)	
Mucosa only	1 (7%)	5 (22%)	
Exanthematous	11(79%)	3 (13%)	
Distribution			<.001†
Localized	1 (7%)	17 (74%)	
Multiple localizations	13 (93%)	6 (26%)	
Mucosal manifestation			1.00†
Yes	6 (43%)	9 (39%)	
No	8 (57%)	14 (61%)	
Autoimmune diseases other than LP	1	1	
Hepatitis, HIV	0	3	

irLP, Immune-related lichen planus; *LP*, lichen planus.
*Student *t* test.
†Fisher's exact test.
‡Fisher-Freeman-Halton test.

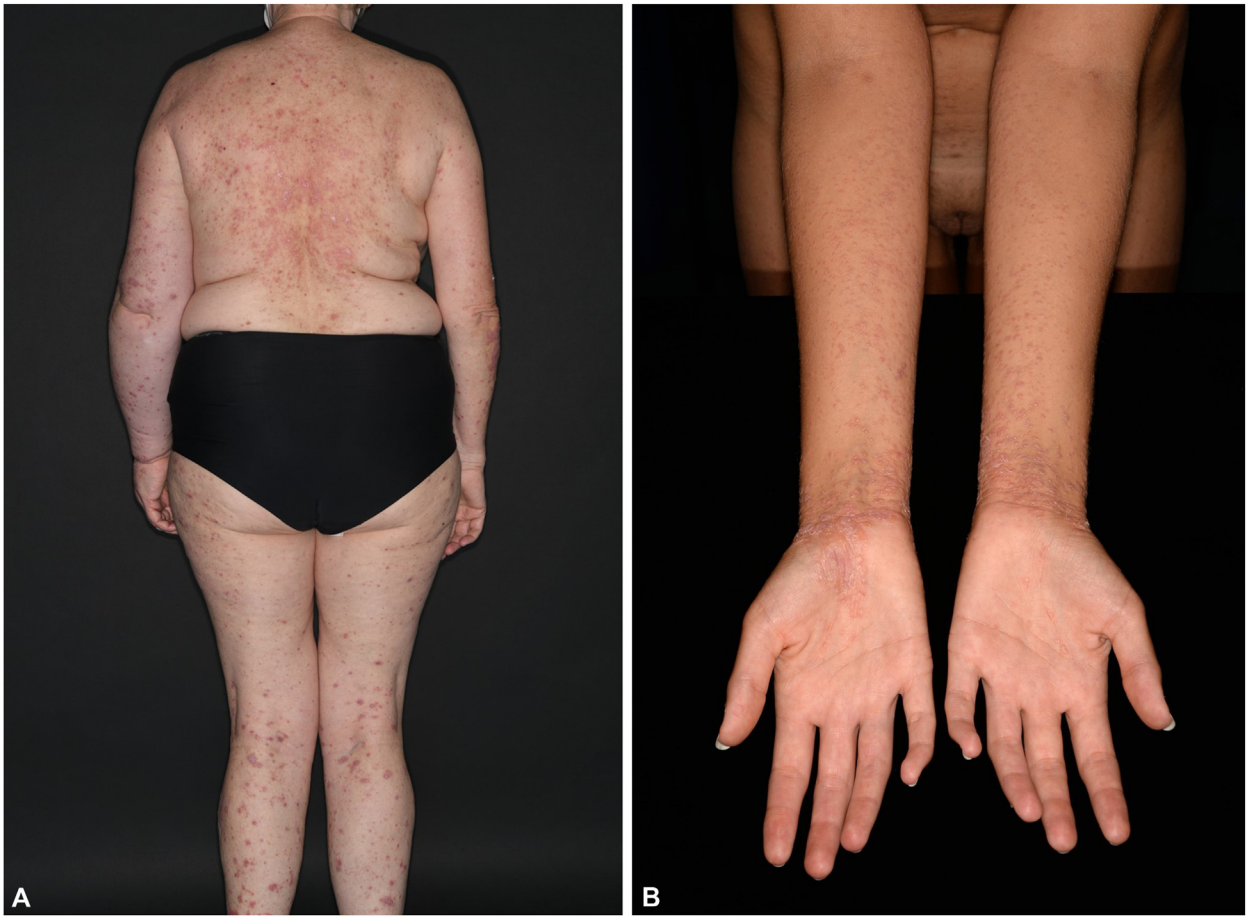

Fig 1. Cutaneous manifestations of immune-related lichen planus (irLP) and spontaneous lichen planus (LP). **A**, Disseminated erosive lesions on the trunk and extremities of a patient with irLP. **B**, Polygonal papules on the inside of the lower portion of the arm and wrist of a patient with LP.

The mean overall survival and progression-free survival in the irLP group was 46.8 months (95% CI, 24.4-69.1) and 37.9 months (95% CI, 23.5-52.4), respectively. The objective response rate under ICI was 57.1% (95% CI, 28.9-82.3) (Supplementary Table I).

Notable differences in lymphocyte infiltration, lymphocyte exocytosis, and apoptotic keratinocytes in irLP compared with LP

To study possible differences in the histopathologic features between irLP and LP, hematoxylin and eosin–stained lesional skin sections of irLP (n = 8) and LP (n = 19) were analyzed by a board-certified dermatopathologist. In detail, the presence of lymphocytes, eosinophilic granulocytes and histiocytes, the exocytosis of lymphocytes, apoptotic keratinocytes, and vacuolization of basal keratinocytes were scored as absent, sparse, moderate, and dense/strong. The dermatopathologic evaluation was conducted in a blinded manner to ensure objectivity.

Notably, a significantly higher dermal lymphocytic infiltrate was observed in LP compared with irLP. On the contrary, lymphocyte exocytosis was higher in irLP. The evaluation of eosinophil counts revealed higher eosinophil numbers in irLP; however, this was not statistically significant. Histiocytic cells were only marginally more frequent in irLP compared with LP in our patient cohort. A significantly higher number of apoptotic keratinocytes was detected in irLP compared with LP (Fig 2).

irLP shows a higher inflammatory signature than LP on the gene expression level

In addition to our clinical and histological comparison of irLP and LP, we performed a gene expression analysis of LP and irLP lesional as well as healthy skin (NDC) using NanoString, comparing the gene expression of 730 genes related to cancer and inflammation.

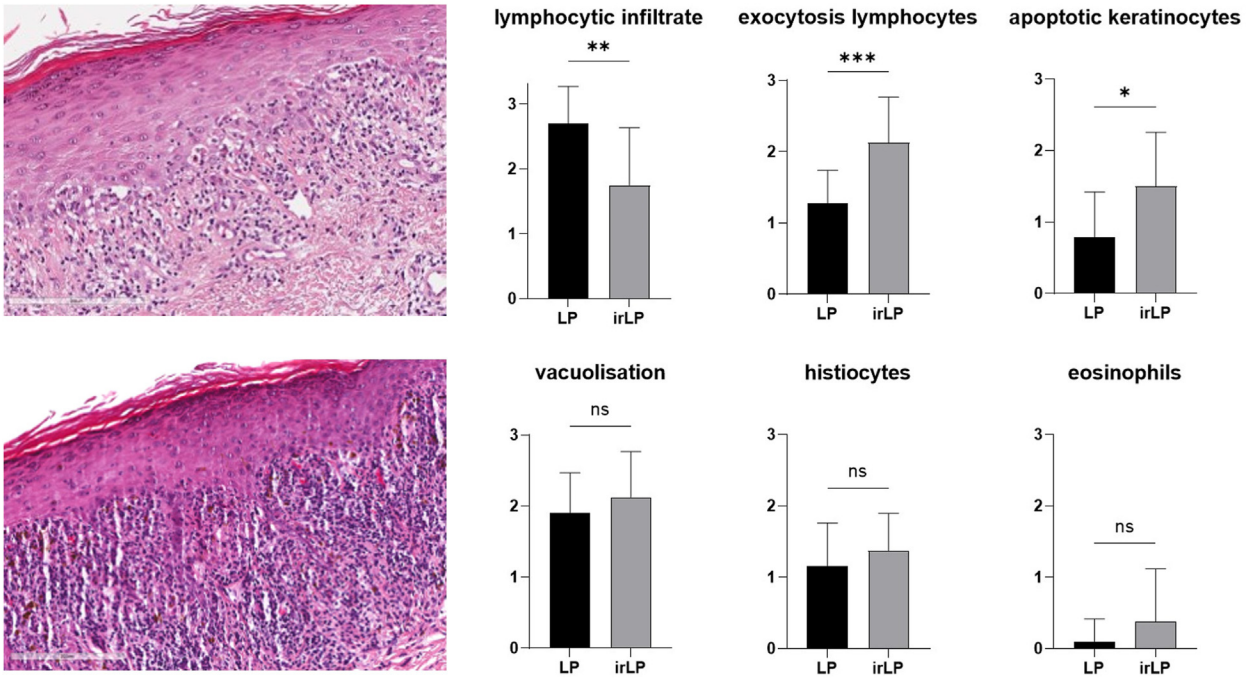

Fig 2. Histopathologic findings in immune-related lichen planus (LP) and spontaneous LP. Histology showing acanthosis, hypergranulosis, and vacuolar changes of the basal layer, several apoptotic keratinocytes in the basal and suprabasal layers of the epidermis and significant exocytosis of lymphocytes in the lower half of the epidermis in a representative case of immune-related lichen planus (irLP) (*top left*). Wedge-shaped hypergranulosis, "sawtooth"-like acanthosis, mild exocytosis of lymphocytes, few apoptotic keratinocytes, and a subepidermal dense band-like lymphocytic infiltrate with prominent pigment incontinence in a representative case of LP (*bottom left*). irLP (n = 8) and LP (n = 19) cases were evaluated regarding their lymphocytic infiltrate, lymphocyte exocytosis, apoptotic keratinocytes, vacuolization of basal keratinocytes, histiocytic, and eosinophil numbers. Grading 0 (absent) to 3 (strong presence) (*right*). (Hematoxylin-eosin stain [resolution: 96 dpi].)

A hierarchical cluster analysis revealed a clear distinction between lesional and NDC skin, but no clear clustering of irLP and LP was detected (Supplementary Fig 1, *A*, available via Mendeley at https://data.mendeley.com/datasets/ffzjcnfmcg/1). When comparing the gene expression of irLP lesional to NDC skin, we found 365 differentially expressed genes, of which 347 were upregulated and 18 were downregulated in irLP (Supplementary Fig 1, *B*, and Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/ffzjcnfmcg/1) ($P \leq .05$, log2 cut-off 1.5-fold). The most affected upregulated genes were related to cytotoxicity, T cell functions, NK cell functions, and macrophage functions (Supplementary Table IV, available via Mendeley at https://data.mendeley.com/datasets/ffzjcnfmcg/1). When comparing LP to NDC skin, 287 differentially expressed genes were detected, of which 268 were upregulated (Supplementary Table V, available via Mendeley at https://data.mendeley.com/datasets/ffzjcnfmcg/1) and 19 were downregulated in LP (Supplementary Fig 1, *C*).

Differences in the expression profiles of irLP and LP were analyzed in the same context. Notably, 101 genes were found to be differentially expressed in irLP compared with LP (Supplementary Fig 1, *D*), whereof the majority (88 genes) were upregulated (Supplementary Table VI, available via Mendeley at https://data.mendeley.com/datasets/ffzjcnfmcg/1) and 13 downregulated (Supplementary Table VII, available via Mendeley at https://data.mendeley.com/datasets/ffzjcnfmcg/1) ($P \leq .05$, log2 cut-off 1.5-fold) in irLP. The most affected genes were related to macrophage functions, followed by cell cycle, complement, transporter functions, antigen processing, and toll-like receptor (Supplementary Table VIII, available via Mendeley at https://data.mendeley.com/datasets/ffzjcnfmcg/1). There was a statistically significant increase in interferon gamma (IFN-γ; gene name: *IFNG*) in irLP compared with LP (fold change = 2.00507; P = .02555).

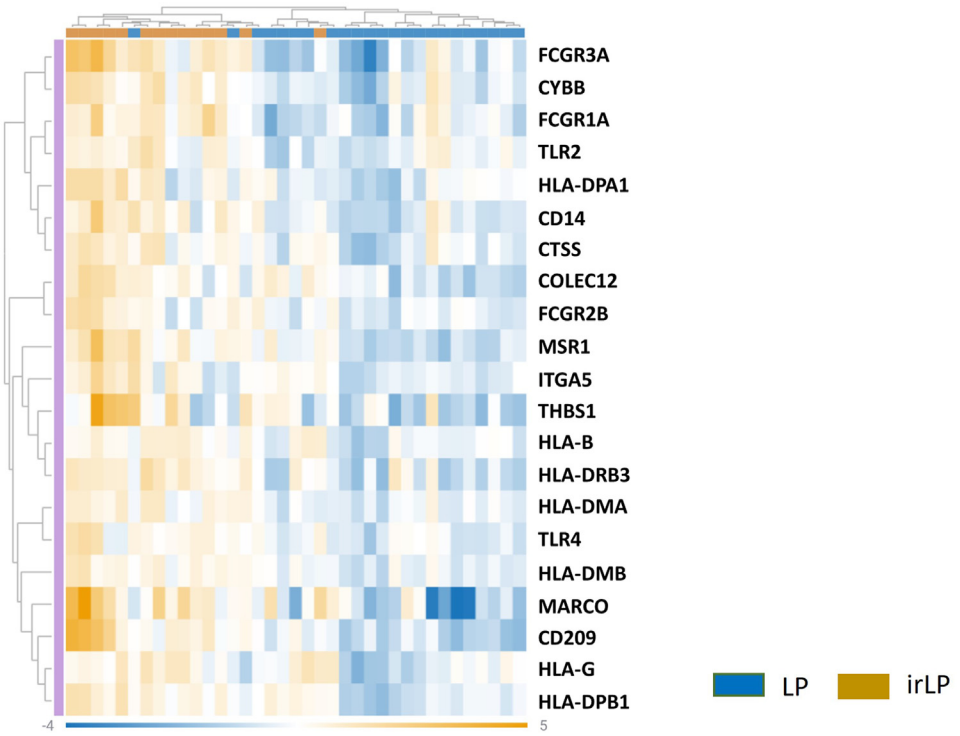

Fig 3. Gene expression analysis reveals significantly upregulated immune pathways in immune-related lichen planus (irLP) compared with spontaneous lichen planus (LP). RNA was isolated from lesional skin of patients with irLP and LP. Representative heatmap of genes involved in phagosome signaling, showing upregulation of involved genes in irLP compared with LP lesional skin.

No significant change in the cell type composition between irLP and LP

To study possible differences in the cell type composition between irLP and LP infiltrates, algorithms from meta-analysis *databases* (*PanglaoDB* and *Cell Atlas)* were applied and the cell type compositions were calculated according to the expression of defined genes per cell type. No significant differences in the cell type composition could be seen in irLP compared with LP. Macrophages showed a tendency to be higher expressed in irLP than in LP; however, this was not statistically significant (Supplementary Fig 2, available via Mendeley at https://data.mendeley.com/datasets/ffzjcnfmcg/1).

Possible role of IL-12 mediated signaling events and phagosome signaling in irLP

To identify possible key pathways in irLP, a pathway analysis was performed. Compared with healthy skin, irLP showed a significantly higher expression of genes involved in IL-12 mediated signaling events (based on the expression of *GZMB, CD8A, IFNG, CCL3, CCL4, IL12RB1, GZMA, TBX21, EOMES, CD8B, IL12RB, IL12B, IL2RA, LCK, IL18RAP, CD247, CD3D, SOCS1, IL12RB2*, and *STAT1*; $P = .0495$) (Supplementary Fig 3, available via Mendeley at https://data.mendeley.com/datasets/ffzjcnfmcg/1).

Likewise, pathway analysis revealed a significantly stronger involvement of the phagosome (based on the expression of *MARCO, CD209, FCGR3A, THBS1, FCGR1A, MSR1, HLA-DRB3, CYBB, HLA-DPA1, CD14, HLA-DPB1, CTSS, TLR4, COLEC12, HLA-DMB, HLA-B, HLA-DMA, FCGR2B, ITGA5, HLA-G*, and *TLR2*; $P = .00016$), in irLP when compared with LP (Fig 3).

DISCUSSION

ICI-induced lichenoid skin reactions are often therapy-resistant and associated with considerable discomfort. Although resembling spontaneous LP, this study shows considerable differences in clinical presentation, histology, and gene expression profiles. To our knowledge, this is the largest study to date characterizing the differences between irLP and spontaneous LP.

Clinically, irLP mostly manifested with an exanthematous distribution pattern (79%), whereas the majority of spontaneous LP lesions were localized. In line with this, cutaneous irAE with a lichenoid

histological pattern are mostly referred to as lichenoid rash, dermatitis, or eruption in the literature.[3,5,28]

Histologically, lymphocyte cell numbers were significantly lower in irLP than in LP, whereas lymphocyte exocytosis was significantly increased in irLP. As lymphocyte exocytosis is thought to be induced by cytokine release, this finding is suggestive of a stronger immune activation in irLP skin. Furthermore, even though not statistically significant, we found a trend toward higher eosinophil counts in irLP compared with LP in our study cohort. In accordance with these findings, Hashimoto et al[29] observed in their study that the presence of eosinophils is a distinguishing factor between irLP and LP. However, the patient cohort of this study was small. Another study previously reported an increase of histiocytic infiltrates and epidermal necrosis in irLP compared with LP,[13] which could not be confirmed in our patient cohort. At the gene expression level, a cell type distribution analysis showed only a trend toward higher macrophage counts in irLP. However, macrophage functions were found to be the most involved pathway indicating a strong activation of macrophages.

Notably, keratinocyte apoptosis was significantly increased in irLP lesional skin compared with LP at the gene expression level. Furthermore, there was a statistically significant increase of *IFNG* in irLP compared with LP. This is in accordance with the finding of Shao et al[30] who reported that IFN-γ enhances cell-mediated cytotoxicity against keratinocytes via JAK2/STAT1 in LP and might be one of the main factors for apoptotic cell death. Genes coding for other cytotoxic molecules such as *GNLY, GZMB*, or *FAS(L)* were not upregulated in irLP compared with LP.

irLP differed clearly from NDC with 365 of the 730 analyzed genes being significantly differently expressed. In line with the literature, cytotoxicity, T cell functions, and NK functions among others have been identified as most prominent biologic functions in irLP according to the gene signature.[30-32]

Furthermore, although no clear clustering of the irLP and the LP group was present, 101 genes were differentially expressed. Notably, 88 of these genes were upregulated in irLP compared with LP, identifying irLP as the more immunogenic condition. Interestingly, macrophage functions represented the most important biologic function in irLP compared with LP. This finding was in line with a trend in the cell composition analysis where macrophage-associated genes were higher expressed in irLP compared with LP; however, this was not statistically significant. A similar observation was made by Schaberg et al[13] who found that irLP contained more macrophages than LP. Our histological analysis could not reveal a significant increase of histiocytic cells though. This discrepancy is suggestive of a higher macrophage activation even though their cell number was not significantly increased.

Pathway analyses revealed a significant upregulation of genes involved in IL-12 mediated signaling in irLP lesional skin compared with NDCs. Indeed, IL-12 has been implicated in the development of irAEs.[33] Moreover, the IL-12/23 inhibitor ustekinumab has been reported to be effective in immune-mediated colitis.[34] The treatment of irAEs with IL-12/IL-23 inhibition is controversial; however, it may decrease the differentiation of naive T cells toward Th1 type cells and thereby lead to a reduction of IFN-γ, which is a critical signal for effective tumor responses.[35]

Interestingly, genes involved in phagosome signaling were significantly upregulated irLP compared with LP. This might be due to increased macrophage activation and an important role of IFN-γ in enhancing phagocytosis.[36] The exact role of the phagosome in irLP, however, is still unclear. In line with our results Curry et al[37] found increased CD14+ and CD16+ monocytes in 3 cases of irLP compared with benign lichenoid keratosis.

The data generated here suggest the potential for targeting JAK/STAT signaling and IFN-γ in the treatment of therapy-resistant forms of irLP. The recent availability of an Food and Drug Administration (FDA)/European Medicines Agency (EMA) approved topical JAK inhibitor (ruxolitinib), opens the possibility for clinical investigation of efficacy in irLP in the context of controlled clinical trials. Topical JAK inhibitors would have the advantage of predominantly local antiinflammatory activity in the skin in the absence of systemic immunosuppression that is undesired in the context of tumor immunotherapy with checkpoint inhibitors.

Collectively, we could demonstrate differences between irLP and spontaneous LP at the clinical, histopathological, and gene expression level. Even though this study represents the largest study to date, the results are still limited due to the small patient cohort. Further studies with larger cohorts, broader transcriptomic and proteomic analyses, and functional experiments are needed.

Conflicts of interest

None disclosed.

REFERENCES

1. Heinzerling L, de Toni EN, Schett G, Hundorfean G, Zimmer L. Checkpoint inhibitors. *Dtsch Ärztebl Int*. 2019;116(8):119-126.
2. Bastacky ML, Wang H, Fortman D, et al. Immune-related adverse events in PD-1 treated melanoma and impact upon

anti-tumor efficacy: a real world analysis. *Front Oncol*. 2021;11:749064.
3. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378(2):158-168.
4. Belum VR, Benhuri B, Postow MA, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. *Eur J Cancer*. 2016;60:12-25.
5. Nikolaou VA, Apalla Z, Carrera C, et al. Clinical associations and classification of immune checkpoint inhibitor-induced cutaneous toxicities: a multicentre study from the European Academy of Dermatology and Venereology Task Force of Dermatology for Cancer Patients. *Br J Dermatol*. 2022;187(6):962-969.
6. Logan IT, Zaman S, Hussein L, Perrett CM. Combination therapy of ipilimumab and nivolumab-associated toxic epidermal necrolysis (TEN) in a patient with metastatic melanoma: a case report and literature review. *J Immunother*. 2020;43(3):89-92.
7. Gopee NH, Gourley AM, Oliphant TJ, Hampton PJ. Toxic epidermal necrolysis occurring with immune checkpoint inhibitors. *Dermatol Online J*. 2020;26(8):13030-qt8fc428f6.
8. Apalla Z, Nikolaou V, Fattore D, et al. European recommendations for management of immune checkpoint inhibitors-derived dermatologic adverse events. The EADV task force 'Dermatology for cancer patients' position statement. *J Eur Acad Dermatol Venereol*. 2022;36(3):332-350.
9. Sibaud V. Dermatologic reactions to immune checkpoint inhibitors: skin toxicities and immunotherapy. *Am J Clin Dermatol*. 2018;19(3):345-361.
10. Goldinger SM, Stieger P, Meier B, et al. Cytotoxic cutaneous adverse drug reactions during anti-PD-1 therapy. *Clin Cancer Res*. 2016;22(16):4023-4029.
11. Si X, He C, Zhang L, et al. Management of immune checkpoint inhibitor-related dermatologic adverse events. *Thorac Cancer*. 2020;11(2):488-492.
12. Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer*. 2016;60:190-209.
13. Schaberg KB, Novoa RA, Wakelee HA, et al. Immunohistochemical analysis of lichenoid reactions in patients treated with anti-PD-L1 and anti-PD-1 therapy. *J Cutan Pathol*. 2016;43(4):339-346.
14. Böer-Auer A, Lütgerath C. Lichen planus: fundamentals, clinical variants, histological features, and differential diagnosis. *Hautarzt*. 2020;71(12):1007-1021.
15. Chan L, Hwang SJE, Byth K, et al. Survival and prognosis of individuals receiving programmed cell death 1 inhibitor with and without immunologic cutaneous adverse events. *J Am Acad Dermatol*. 2020;82(2):311-316.
16. Geisler AN, Phillips GS, Barrios DM, et al. Immune checkpoint inhibitor-related dermatologic adverse events. *J Am Acad Dermatol*. 2020;83(5):1255-1268.
17. Shi VJ, Rodic N, Gettinger S, et al. Clinical and histologic features of lichenoid mucocutaneous eruptions due to anti-programmed cell death 1 and anti-programmed cell death ligand 1 immunotherapy. *JAMA Dermatol*. 2016;152(10):1128-1136.
18. Perkins JR, Dawes JM, McMahon SB, Bennett DL, Orengo C, Kohl M. ReadqPCR and NormqPCR: R packages for the reading, quality checking and normalisation of RT-qPCR quantification cycle (Cq) data. *BMC Genomics*. 2012;13:296.
19. Hennig C. Cran-package fpc. 2023. Accessed March 20, 2022. https://cran.r-project.org/web/packages/fpc/index.html
20. Alexa A, Rahnenfuhrer R. topGO: Enrichment Analysis for Gene Ontology. 2019. Accessed April 26, 2023. https://www.bioconductor.org/packages/release/bioc/manuals/topGO/man/topGO.pdf
21. Fabregat A, Jupe S, Matthews L, et al. The reactome pathway KnowledgeBase. *Nucleic Acids Res*. 2018;46(D1):D649-D655.
22. Geer LY, Marchler-Bauer A, Geer RC, et al. The NCBI BioSystems database. *Nucleic Acids Res*. 2010;38(Database issue):D492-D496.
23. Liberzon A, Subramanian A, Pinchback R, Thorvaldsdóttir H, Tamayo P, Mesirov JP. Molecular signatures database (MSigDB) 3.0. *Bioinformatics*. 2011;27(12):1739-1740.
24. Mitchell AL, Attwood TK, Babbitt PC, et al. InterPro in 2019: improving coverage, classification and access to protein sequence annotations. *Nucleic Acids Res*. 2019;47(D1):D351-D360.
25. Slenter DN, Kutmon M, Hanspers K, et al. WikiPathways: a multifaceted pathway database bridging metabolomics to other omics research. *Nucleic Acids Res*. 2018;46(D1):D661-D667.
26. Subramanian A, Tamayo P, Mootha VK, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci U S A*. 2005;102(43):15545-15550.
27. nCounter® Advanced Analysis 2.0 User Manual. Accessed March 23, 2022. https://nanostring.com/wp-content/uploads/MAN-10030-03_nCounter_Advanced_Analysis_2.0_User_Manual.pdf
28. Quach HT, Johnson DB, LeBoeuf NR, Zwerner JP, Dewan AK. Cutaneous adverse events caused by immune checkpoint inhibitors. *J Am Acad Dermatol*. 2021;85(4):956-966.
29. Hashimoto H, Ito T, Yamada Y, Oda Y, Furue M. Eosinophilic infiltration discriminates lichen-planus-like eruption caused by an immune checkpoint inhibitor from ordinary lichen planus. *J Dermatol*. 2021;48(2):e102-e103.
30. Shao S, Tsoi LC, Sarkar MK, et al. IFN-γ enhances cell-mediated cytotoxicity against keratinocytes via JAK2/STAT1 in lichen planus. *Sci Transl Med*. 2019;11(511):eaav7561.
31. Wenzel J, Peters B, Zahn S, et al. Gene expression profiling of lichen planus reflects CXCL9+-mediated inflammation and distinguishes this disease from atopic dermatitis and psoriasis. *J Invest Dermatol*. 2008;128(1):67-78.
32. Wenzel J, Scheler M, Proelss J, Bieber T, Tüting T. Type I interferon-associated cytotoxic inflammation in lichen planus. *J Cutan Pathol*. 2006;33(10):672-678.
33. Lim SY, Lee JH, Gide TN, et al. Circulating cytokines predict immune-related toxicity in melanoma patients receiving anti-PD-1-Based immunotherapy. *Clin Cancer Res*. 2019;25(5):1557-1563.
34. Thomas AS, Ma W, Wang Y. Ustekinumab for refractory colitis associated with immune checkpoint inhibitors. *N Engl J Med*. 2021;384(6):581-583.
35. Berg MHH, Del Rincon SV, Miller WH. Potential therapies for immune-related adverse events associated with immune checkpoint inhibition: from monoclonal antibodies to kinase inhibition. *J Immunother Cancer*. 2022;10(1):e003551.
36. Hawley KL, Cruz AR, Benjamin SJ, et al. IFNγ enhances CD64-potentiated phagocytosis of *Treponema pallidum* opsonized with human syphilitic serum by human macrophages. *Front Immunol*. 2017;8:1227.
37. Curry JL, Reuben A, Szczepaniak-Sloane R, et al. Gene expression profiling of lichenoid dermatitis immune-related adverse event from immune checkpoint inhibitors reveals increased $CD14^+$ and $CD16^+$ monocytes driving an innate immune response. *J Cutan Pathol*. 2019;46(9):627-636.