

## LETTER TO THE EDITOR

## Real-world data on primary cutaneous lymphoproliferative disorders following SARS-CoV-2 vaccination: A multicentre experience from tertiary referral hospitals

Dear Editor,

From the beginning of mass COVID-19 vaccination campaign, several people sought dermatological attention due to cutaneous adverse manifestations following the three-dose immunization regimen, as recently described.<sup>1,2</sup> SARS-CoV-2 vaccine-related cutaneous adverse reactions encompass a protean spectrum of clinical courses, with primary cutaneous lymphoproliferative disorders (PCLDs) following SARS-CoV-2 vaccination only being partially explored.<sup>3</sup>

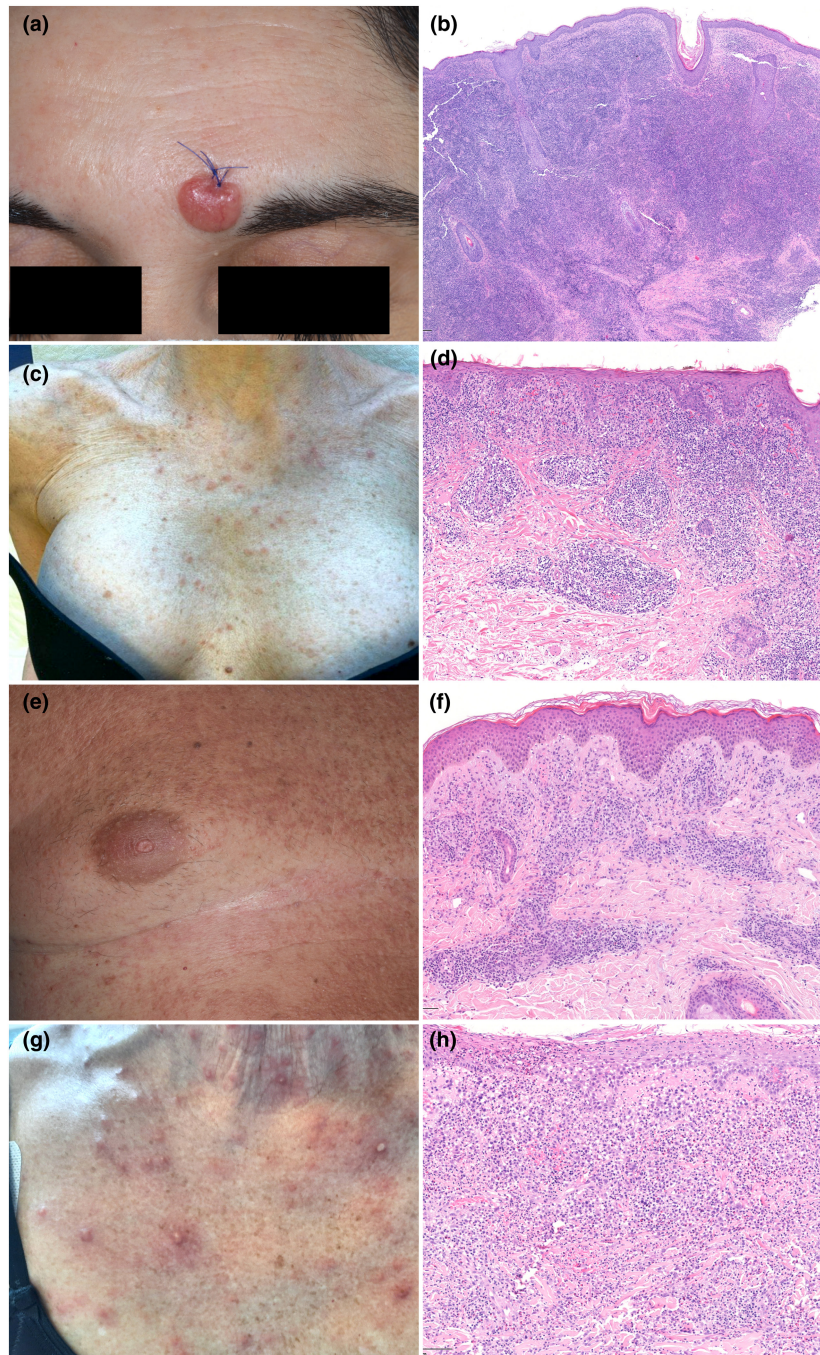
In this regard, we report a retrospective review of patients attending seven Italian tertiary referral centres between January 2021 and July 2022. Information was collected through hospital operating systems. Inclusion criteria were (1) the presence of complete charts, (2) a biopsy-proven PCLDs (3) onset, relapse or regression within 30 days after COVID-19 vaccine administration. A total of 14 PCLDs were gathered: 6 classified as PCLDs relapse [2 Sézary syndrome (SS), 1 cutaneous lymphoid hyperplasia (CLH), 1 erythrodermic mycosis fungoides, 1 lymphomatoid papulosis (LyP), 1 primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (PCSMPLD)] and 8 diagnosed as new-onset PCLDs [2 LyP, 2 CD4+ PCSMLPD, 1 atypical pityriasis lichenoides *et* varioliformis acuta (PLEVA), 2 CLH and 1 SS] (Figure 1a–h). Demographics, vaccine type, clinical features and onset time of cutaneous reactions are summarized in Table 1. More than half (64.2%) were males, and their median age was 61 years [interquartile range (IQR): 58–61]. The median onset time was 15 days (IQR: 9–15). No recrudescence either following the booster dose or thereafter was identified (mean follow-up time: 13 months, IQR: 3–15).

The outlined manifestations appear quite heterogeneous, generally of short duration, with a tendency to self-resolve and easily treatable with standard therapies, when needed. One of the patients with LyP exceptionally reported the same skin manifestations immediately after HBV vaccine administration several decades before. This latter and a second patient with new-onset LyP type A showed a non-diagnostic diffuse cutaneous eruption with marked

cellular atypia and numerous GATA3+ blasts. Similarly, a case of new-onset PLEVA had atypical histological findings with marked nuclear pleomorphisms and blasts, falling within the PCLD spectrum.<sup>4</sup> To our knowledge, this is the first multicentre study displaying the largest number of patients and unreported vaccine-related clinical presentations to date (e.g. SS following the third BNT162b2 dose).

The relationship between PCLDs and SARS-CoV-2 vaccination appears multifaceted and the exact pathogenic mechanisms, if any, are not fully understood. Recurrent primary cutaneous anaplastic large-cell lymphoma, as well as primary cutaneous follicle centre cell lymphoma, spontaneously regressed after the first dose COVID-19 vaccination, has been reported.<sup>5,6</sup> These findings might reflect, in a genetically predisposed individual, an immune system overstimulation secondary to SARS-CoV-2 vaccination, potentially enhancing anti-tumor response. Interestingly, regression has not been detected in our series and its role should be further elucidated. Conversely, in a recent case series, low-grade cutaneous lymphoid reactions after COVID-19 vaccination have been observed.<sup>7</sup> Recurrence of pre-existing complete remission PCLDs has also been described following COVID-19 vaccine, with several case reported so far.<sup>3,8,9</sup> The overproduction and exhaustion of CD4+ and CD8+ lymphocytes, expressing CD30 after being triggered by the vaccine, might be held responsible for the disease recurrence. Although recurrences have been observed even in the current multicentre experience, these entities are known for displaying a waxing and waning course of the disease, which could account for the aforementioned observation.

Owing to the retrospective nature of the present study and to the small sample, definite conclusions regarding the causal link between COVID-19 vaccine and the observed event cannot be drawn. However, the temporal relation of our findings points at the potential effects of COVID-19 vaccine on PCLDs and calls for further studies. Compelling COVID-19 vaccines safety profiles, not only perceived from the dermatology perspectives, remain ascertained and reassuring in the ongoing second booster era.



**FIGURE 1** (a) A single erythematous nodule on the forehead. (b) A diffuse dense infiltrate in the dermis, sparing the epidermis and composed of small- to medium-sized hyperchromatic lymphocytes. Atypical lymphocytes, arranged in clusters, are CD4+, PD1+ and exceptionally GATA3+ (data not shown) consistent with primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder [haematoxylin and eosin (H&E), 10 $\times$ ]. (c) an erythematous maculopapular eruption on the chest. (d) Histopathological findings diagnostic for atypic pityriasis lichenoides and varioliformis acuta: A dense lichenoid and perivascular infiltrate in the upper dermis composed of small-medium sized, hyperchromatic lymphocytes mixed with some blasts, few plasma cells, mast cells and red blood cells. Lymphocytes are positive for CD3, CD4, CD7 (H&E 20 $\times$ ), Ki-67 20% (data not shown). (e) A diffuse and confluent erythematous papular eruption on the trunk. (f) Histology revealing lymphomatoid papulosis type A: Perivascular infiltrate in the superficial dermis of medium/large-sized pleomorphic lymphocytes mixed with eosinophils and blast cells (around 30% of the infiltrate). Atypical lymphocytes were CD3+, CD4+, CD7+, CD30+ (blasts included) and GATA3+ (data not shown) (H&E 20 $\times$ ). (g) A diffuse vesicular and papulo-pustular eruption on the chest. (h) A dense perivascular and interstitial infiltrate in the superficial dermis of small-sized and large, blast-like, pleomorphic lymphocytes mixed with numerous neutrophils, eosinophils and histiocytes. Large cells were CD3+, CD4+, CD7+, CD30+, GATA3+ (data not shown) consistent with lymphomatoid papulosis type A (H&E 20 $\times$ ).

**TABLE 1** Demographics, vaccine type, clinicopathologic features and onset time of cutaneous adverse reactions in the study population

Age (years) and sex (M/F)	History of previous PCLDs	Vaccine type (1st and 2nd dose)	Vaccine type (3rd and 4th dose)	Onset (days)	Clinical features	TCR	Diagnosis	Therapy	Outcome	Follow-up time (months)
47F	CLH diagnosed in 2012. CR following TCS and ICS. Relapsed twice. In complete remission from 2 years	BNT162b2	mRNA-1273 <sup>a</sup>	10	Erythematous plaques on right deltoid and temporal region following the 2nd BNT162b2 dose	NP	CLH relapse	TCS, ICS	CR	17
67M	Lyp diagnosed in 2019, relapsed in 2020	BNT162b2	mRNA-1273 <sup>a</sup>	15	Violaceous necrotic papules on upper and lower limbs following the 2nd BNT162b2 dose	$\gamma$ +	Lyp type A relapse	MTX	CR	16
49M	CD4+ PCSM-LPD diagnosed 2 years before in complete remission	BNT162b2	BNT162b2 <sup>a</sup>	15	Erythematous plaque on the neck, no other symptoms were observed following the 2nd BNT162b2 dose	-	CD4+ PCSM-LPD	None	SR	14
58M	Complete remission SS under tislelizumab	BNT162b2	BNT162b2	4	Erythroderma, itch and fever following the 2nd BNT162b2 dose	$\gamma$ +	SS relapse	TCS, OCS, MOGA	CR	2
61M	Early-stage mycosis fungoides diagnosed in 2018, well-managed with the only use of TCS	BNT162b2	BNT162b2 <sup>a</sup>	14	Erythroderma and itch following the 3rd BNT162b2 dose	$\gamma$ +	Erythrodermic MF	OCS, PUVA	CR	5
61M	Well-managed SS under mogamulizumab	BNT162b2	BNT162b2 <sup>a</sup>	15	Sub-erythroderma following the 3rd BNT162b2 dose	$\gamma$ +	SS relapse	ECP	PR	9
55M	New onset	BNT162b2	BNT162b2 <sup>a</sup>	30	Erythematous plaque on the back following the 3rd BNT162b2 dose	-	CLH	SE	CR	2
55M	New onset	BNT162b2	NP	7	Erythematous plaque on right deltoid region following the 1st BNT162b2 dose	NP	CLH	TCS	CR	19
80F	New onset	BNT162b2	BNT162b2	15	Erythroderma, itch and blood skin compatible with mSWAT 100 following the 3rd BNT162b2 dose	$\gamma$ +	SS	TCS, OCS	CR	1
60M	New onset	BNT162b2	NP	30	Erythematous papular lesions diffuse at trunk and arms following the 2nd BNT162b2 dose	$\gamma$ +	Lyp type A	CS iv + Trime-ton iv	CR	14
52F	New onset	BNT162b2	NP	3	Erythematous nodule (diameter: 15 mm) on the forehead following the 1st BNT162b2 dose	-	CD4+ PCSM-LPD	RT	CR	15
62F	New onset	ChAdOx1 nCoV-19, BNT162b2	NP	7	Erythematous maculo-papular and vesicular lesions on the trunk and upper limbs following the 1st ChAdOx1 nCoV-19 dose	-	Atypical PLEVA	OCS	CR	16

(Continues)

TABLE 1 (Continued)

Age (years) and sex (M/F)	History of previous PCLDs	Vaccine type (1st and 2nd dose)	Vaccine type (3rd and 4th dose)	Onset (days)	Clinical features	TCR	Diagnosis	Therapy	Outcome	Follow-up time (months)
61F	New onset	BNT162b2	BNT162b2	10	Erythematous-vesicular pustular lesions on the chest following the 1st BNT162b2 dose. Occurrence of similar elements at trunk, face and limbs	$\gamma$ +	Lyp type A	none	SR	13
45M	New onset	BNT162b2	BNT162b2 <sup>a</sup>	20	Single nodule on the left cheek (diameter: 8 mm) following the 3rd BNT162b2 dose	$\gamma$ +	CD4+ PCSM-LPD	SE	CR	3

Abbreviations: CD4+ PCSM-LPD, primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder; CLLH, cutaneous lymphoid hyperplasia; CR, complete response; ECP, extracorporeal photopheresis; F, female; ICS, intranasal corticosteroids; Lyp, lymphomatoid papulosis; M, male; MOGA, mogamulizumab; mSWAT, Modified Severity-Weighted Assessment Tool; MTX, methotrexate; NBUVB, narrowband ultraviolet B; NP, not performed; OCS, oral corticosteroids; PLEVA, pityriasis lichenoides et varioliformis acuta; PUVA, psoralen plus ultraviolet-A radiation; RT, radiotherapy; SE, surgical excision; SR, spontaneous resolution; SS, Sézary syndrome; TCR, T-cell receptor ( $\gamma/\beta$ ) gene rearrangement assay; TCS, topical corticosteroids.  
<sup>a</sup>4th dose not performed.

## FUNDING INFORMATION

None.

## CONFLICT OF INTEREST











The authors have no conflict of interest to declare.

## DATA AVAILABILITY STATEMENT

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

## ETHICS STATEMENT

The patients in this manuscript have given written informed consent to the publication of their case details.

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