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REVIEW

Lichen planus after COVID-19 infection and vaccination

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Abstract

Lichen planus (LP) is an inflammatory disorder believed to result from CD8 + cytotoxic *T*-cell (CTL)-mediated autoimmune reactions against basal keratinocytes. We present a review of LP following COVID-19 infection and vaccination. Literature searches were conducted on PubMed and Google Scholar from 2019 to 7/2022. 36 articles were selected based on subject relevance, and references within articles were also screened. 39 cases of post-vaccination LP and 6 cases of post-infection LP were found among case reports and case series. 152 cases of post-vaccination LP and 12 cases of post-infection LP were found in retrospective and prospective studies. LP is a rare complication of COVID-19 infection and vaccination that may be mediated by overstimulation of *T*-cell responses and proinflammatory cytokine production. However, it does not represent a limitation against COVID-19 vaccination, and the benefits of vaccination considerably outweigh the risks.

Keywords Lichen planus (LP) · Oral lichen planus (OLP) · CD8 + cytotoxic *T*-cell (CTL) · CD4 + helper *T*-cell (Th1) · Interleukin (IL) · Tumor necrosis factor (TNF) · Interferon (INF) · Oral lichenoid lesions (OLL)

Introduction

Lichen planus (LP) is a chronic inflammatory disorder of unknown origin that frequently involves the skin and mucosa. Skin lesions classically present as flat-topped, purple papules that can be pruritic [1]. Oral lichen planus (OLP) is a subset of LP that can present as white reticular or erythematous lesions, papules, plaques, or painful erosions [1, 2]. LP pathogenesis is believed to result from an autoimmune reaction involving CD8+ cytotoxic *T*-cell (CTL) attack against basal keratinocytes in the epidermis and other unknown antigens [1]. LP has been associated with hepatitis C viral infection and autoimmune disorders including alopecia areata and ulcerative colitis [1]. However, there has been limited inquiry into the potential association between LP and COVID-19 infection and vaccination. We present a review of LP following COVID-19 infection and vaccination and its implications for adverse event monitoring.

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Methods

Literature searches were conducted on PubMed and Google Scholar ranging from 2019 to 7/2022. Thirty-six articles were selected based on subject relevance; novel onset and flares of LP after COVID-19 infection and vaccination were included. References within selected articles were also screened. Selected articles included one review of LP, one prospective observational study, one retrospective registry-based study, one retrospective cohort study, one prospective cross-sectional study, one commentary, four case series, two letters responding to previously published studies, and twenty-four case reports.

Results

To date (7/2022), there have been 39 cases of LP after COVID-19 vaccination (M_{age} = 55.97 years, R_{age} = 28-86 years, Male:Female = 17:22) and 6 cases of LP after COVID-19 infection (M_{age} = 53.17 years, R_{age} = 41-63 years, Male:Female = 2:4) among published case reports and case series (Table 1, Appendix). Nine of the post-vaccination cases were flares. Tozinameran (Pfizer-BioNTech) was linked to 16 cases, Spikevax (Moderna) to four cases, Vaxzevria (Oxford-AstraZeneca) to eight cases, Sinopharm to eight cases, CoronaVac to two cases, and Jcovden

Table 1 Case reports and series of Lichen planus after COVID-19 infection and vaccination

Patient age and sex	Infection or vaccination?	COVID-19 Vaccine type	Latency (days)	Distribution	Treatment	Outcome
29-y.o. F [3] (Bularca et al.)	Vaccination	Tozinameran, 2nd dose (Pfizer-BioNTech)	7 days	Dorsum of the hands, wrists, eyelids, sub-mammary region, lower extremities, and oral mucosa	Methotrexate	Unspecified
63-y.o. F [4] (Paolino and Rongioletti)	Vaccination	Tozinameran, 2nd dose	3 days	Palms, wrists, and soles	Acitretin 25 mg/day, topical calcipotriene/betamethasone dipropionate foam	Total resolution of lesions in 1 month, but with residual palmar hyperpigmentation
49-y.o. M [5] (Troelzsch et al.)	Vaccination	Jcovden, single dose (Johnson & Johnson)	6 days	Oral mucosa	Topical clobetasol mouth irrigation solution 0.5 mg/mL	Significant improvement after 4 weeks
28-y.o. F [6] (Kaomongkolgit et aland Sawangarun)	Vaccination	Tozinameran, 2nd dose	7 days	Oral mucosa	Fluocinolone acetonide 0.1% in orabase paste	Significant improvement after 2 weeks
82-y.o. F [7] (Hlaca et al.)	Vaccination	Tozinameran, 2nd dose	14 days	Axillae, flexural wrists and forearms, ankles, buttocks, lower back, and abdomen	Prednisolone 20 mg/day	Gradual improvement after 6 week taper
68-y.o. F [7] (Hlaca et al.)	Vaccination	Spikevax, 2nd dose (Moderna)	14 days	Trunk, buttocks, extremities, ankles, forearms, flexural wrists, axillae, and palms	Prednisolone 30 mg/day	Resolution after 6 week taper
56-y.o. F [8] (Merhy et al.)	Vaccination	Tozinameran, 2nd dose	7 days	Trunk	Unspecified	Unspecified
54-y.o. M [9] (Zagaria et al.)	Vaccination	Tozinameran, 1st dose	10 days	Trunk, upper and lower limbs	Oral prednisolone 25 mg daily for 7 days, then tapered for up to 4 weeks	Rapid resolution without side effects or recurrence
72-y.o. M [10] (Alabdulaaly et al.)	Vaccination	Spikevax, 1st and 2nd doses	~30–60 days	Gingiva and upper lip	High potency topical steroids	Improved within 3 months
61-y.o. M [10] (Alabdulaaly et al.)	Vaccination	Spikevax, 2nd dose	~30–45 days (flare)	Gingiva and tongue	Continued topical pimecrolimus 1% cream	Recovered to baseline 12 weeks after 2nd dose
65-y.o. F [10] (Alabdulaaly et al.)	Vaccination	Tozinameran, 2nd dose	7 days (flare)	Buccal mucosa and tongue	Topical vitamin A 0.025% gel and clobetasol 0.05% gel four times daily	Resolution after 4 weeks
65-y.o. F [10] (Alabdulaaly et al.)	Vaccination	Tozinameran, 2nd dose	1 day (flare)	Gingiva and vestibular mucosa	Topical clobetasol and bethanechol	Significant reduction in erythema after 1 month
51-y.o. M [10] (Alabdulaaly et al	Vaccination	Tozinameran, 2nd dose	14 days (flare)	Posterior buccal mucosa	Topical pimecrolimus cream and turmeric supplementation	Returned to baseline after 2 months
40-y.o. M [11] (Caggiano et al.)	Vaccination	Tozinameran, 2nd dose	30–31 days	Buccal mucosa	Replacement of amalgam fillings	No clinical improvement after 6 months

Table 1 (continued)

Patient age and sex	Infection or vaccination?	COVID-19 Vaccine type	Latency (days)	Distribution	Treatment	Outcome
82-y.o. F [12] (Baba et al.)	Vaccination	Tozinameran, 2nd dose	7 days	Trunk, upper and lower limbs	Unspecified	Unspecified
49-y.o. M [13] (Zengarini et al.)	Vaccination	Vaxzevria (Oxford-AstraZeneca), 2nd dose	11 days	Trunk, upper and lower limbs	Topical steroids and systemic antihistamines	Near complete resolution with mild residual erythema after 1 month
59-y.o. F [14] (Herzum et al.)	Vaccination	Tozinameran, 2nd dose	14 days (flare)	Medial ankles and feet	Topical high-potency corticosteroids	Resolution after 3 weeks
46-y.o. M [15] (Alrawashdah et al.)	Vaccination	Vaxzevria, 1st dose	5 days	Forehead, abdomen, back, and legs	Topical clobetasol propionate 0.1% cream twice daily, hydroxyzine hydrochloride 25 mg three times daily. After 4 weeks, added hydroxychloroquine 200 mg twice daily	Mild improvement after 4 weeks of topical steroids/oral antihistamines. Significant reduction in pruritus after 2 months of adding hydroxychloroquine, but minimal improvement in skin lesions
56-y.o. F [16] (Hiltun et al.)	Vaccination	Tozinameran, 2nd dose	2 days (flare)	Ankles, flexural wrists and forearms, periumbilical area, breasts, and axillary folds	High-potency topical corticosteroids	Unspecified
86-y.o. M [17] (Gamonal et al.)	Vaccination	Vaxzevria, 1st and 2nd doses	7 days (1st dose), exacerbated after 2nd dose	Upper and lower limbs, trunk, buttocks	Halobetasol propionate 0.05% cream	Unspecified
60-y.o. F [18] (Diab et al.)	Vaccination	Vaxzevria, 2nd dose	14 days (flare)	Cheeks, forehead, and scalp	Intralesional corticosteroids and Tofacitinib	General improvement in follow-up visits
55-y.o. F [18] (Diab et al.)	Vaccination	Sinopharm, 1st dose	3 days	Lower limbs and buttocks	Metronidazole 500 mg twice daily	Improvement on follow-up
45-y.o. F [19] (Shakoei et al.)	Vaccination	Sinopharm, 1st dose	14 days	Arm, forearms, and ankle	Topical corticosteroid	Significant improvement
40-y.o. M [19] (Shakoei et al.)	Vaccination	Sinopharm, 1st and 2nd doses	10 days	Wrist and forearms	Topical corticosteroid	Significant improvement
38-y.o. M [19] (Shakoei et al.)	Vaccination	Sinopharm, 1st and 2nd doses	21 days (flare)	Arm and forearms	Topical corticosteroid, calcineurin inhibitor	Significant improvement
45-y.o. M [19] (Shakoei et al.)	Vaccination	Sinopharm, 1st and 2nd doses	7 days	Forearms and chest	Topical corticosteroid	Significant improvement
45-y.o. M [19] (Shakoei et al.)	Vaccination	Vaxzevria, 1st dose	7 days	Acral	Systemic prednisolone	Significant improvement
49-y.o. F [19] (Shakoei et al.)	Vaccination	Sinopharm, 1st dose	10 days	Acral	N/A	Significant improvement
32-y.o. M [19] (Shakoei et al.)	Vaccination	Sinopharm, 2nd dose	10 days	Extremities	Oral prednisolone	Significant improvement

Table 1 (continued)

Patient age and sex	Infection or vaccination?	COVID-19 Vaccine type	Latency (days)	Distribution	Treatment	Outcome
65-y.o. F [20] (Kulkarni and Sollecito)	Vaccination	Unspecified	"Immediately following the administration" (flare)	Left buccal mucosa	Unspecified	Regressed to baseline after 3 weeks
44-y.o. M [21] (Awada et al.)	Vaccination	Vaxzevria, 2nd dose	14 days	Axillae	Betamethasone cream once daily	Resolution after 4 weeks
65-y.o. F [22] (Masseran et al.)	Vaccination	Vaxzevria, 1st and 2nd doses	10 days (1st dose), 7 days (2nd dose)	Arms, legs, buttocks, and abdomen	Clobetasol propionate 0.05% cream	Near-complete remission in 4 weeks with residual pruritus and pigmentation
35-y.o. F [23] (Sharda et al.)	Vaccination	Unspecified	14 days	Buccal and gingival mucosa	Short term steroids course	Responded well
52-y.o. F [24] (Babazadeh et al.)	Vaccination	Sinopharm, 1st and 2nd doses	10 days (1st dose), 7 days (2nd dose)	Extremities, inguinal and axillary folds, lips, and buccal mucosa	Oral antihistamines, topical calcipotriol and triamcinolone	Favorable response to treatment
64-y.o. F [25] (Piccolo et al.)	Vaccination	Tozinameran, 1st dose	5 days	Lateral aspects of dorsal hands, in areas previously affected by vitiligo	Topical and systemic corticosteroids	Unspecified
64-y.o. F [26] (Sun et al.)	Vaccination	Vaxzevria, 1st dose	14 days	Inframammary folds, axillae, lower back, and groin	Topical betamethasone 0.05% ointment	Minor clinical improvement after 2 months
81-y.o. M [27] (Picone et al.)	Vaccination	Spikevax, 1st dose	7 days	Flexural wrists, lumbosacral region, posterior thighs, dorsal feet	Topical clobetasol propionate and cetirizine 10 mg daily × 10 days	Clinical remission after 15 days, no recurrence at 1-month follow-up
50-y.o. M [28] (Hertel et al.)	Vaccination	Tozinameran, 2nd dose	9 days	Buccal mucosa	Unspecified	Unspecified
57-y.o. F [28] (Hertel et al.)	Vaccination	Tozinameran, 2nd dose	14 days	Upper and lower vestibules	Unspecified	Unspecified
63-y.o. M [29] (Saleh et al.)	Infection	N/A	30–31 days	Oral mucosa	Topical corticosteroids 3 times daily for 10 days followed by a symptom-dependent taper	Marked improvement after 4 weeks (decreased pain and size of lesions)
41-y.o. M [10] (Alabdulaaly et al.)	Infection	N/A	14 days	Bilateral buccal mucosa and gingival margins	Fluocinonide 0.05% gel	Resolution in 1 month
56-y.o. F [10] (Alabdulaaly et al.)	Infection	N/A	30–31 days	Buccal mucosa	Fluocinonide 0.05% gel	Unspecified
51-y.o. F [30] (Gimeno Castillo et al.)	Infection	N/A	21 days	Lumbar area, feet, and hands	Tapered oral prednisone, then clobetasol cream	Responded to prednisone, but relapsed and only partially responded to clobetasol
56-y.o. F [31] (Burgos-Blasco et al.)	Infection	N/A	49 days	Buccal mucosa	Unspecified	Unspecified

Table 1 (continued)

Patient age and sex	Infection or vaccination?	COVID-19 Vaccine type	Latency (days)	Distribution	Treatment	Outcome
52-y.o. F [32] (Diaz-Guimaraens et al.)	Infection	N/A	5 days	Right shin, buccal mucosa	Clobetasol propionate 0.05% cream twice daily	Resolution of pruritus after 10 days with a residual brown patch on shin

(Johnson and Johnson) to one case; the administered vaccine was unspecified in two post-vaccination LP cases. Retrospective and prospective studies yielded 152 cases of LP after COVID-19 vaccination and 12 cases of LP after COVID-19 infection (Table 2, Appendix).

Discussion

Multiple authors have hypothesized that exposure to the COVID-19 spike protein antigen via infection or vaccination may trigger immune dysregulation including altered *T*-cell activity and elevated cytokines that mediate LP pathogenesis [2, 5, 7–10]. SARS-CoV-2 antigens in COVID-19 vaccines induce *B*-cell activation and a strong CD8+ cytotoxic *T*-cell (CTL) response that can escalate into an autoimmune reaction against basal keratinocytes in the epidermis, triggering keratinocyte apoptosis and subsequent LP development [2, 5]. Furthermore, the vaccines also activate CD4+ helper *T*-cells (Th1), which release proinflammatory cytokines including interleukin-2 (IL-2), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) that maintain the CTL response, further upregulate Th1 activity, and induce tissue damage [2, 7–10]. TNF-α, and IFN-γ result in basal keratinocyte apoptosis, the hallmark of LP. Their upregulation may thus help explain LP pathogenesis after COVID-19 infection and vaccination [4]. COVID-19 infection has also been associated with dysregulation of the mammalian target of rapamycin (mTOR) signaling pathway, which has been implicated in dysfunctional *T*-cell proliferation and OLP pathogenesis [2]. Moreover, it has been hypothesized that SARS-CoV-2 triggers the overexpression of TRIM21 (tripartite motif containing-21), which stimulates antiviral CTLs, increases cytokine production, and has been identified in OLP lesions using immunohistochemistry [2].

Another hypothesis is that molecular mimicry is responsible for triggering the autoimmune CTL and Th1 responses that mediate LP in both infection and vaccination [2, 4, 22, 32]. The SARS-CoV-2 antigen has demonstrated cross-reactivity with multiple endogenous human antigens, including those found on the basal keratinocytes of the epidermis [2, 4, 22, 32]. Some attribute this antigen cross-reactivity to genetic similarities or shared epitopes [4, 22]. Specifically, SARS-CoV-2 proteins demonstrated similarities to human mitochondrial M2 proteins, F-actin, and TPO proteins on selective epitope mapping [2]. However, others suggest that the propensity for SARS-CoV-2 to target the ACE2 receptor for host cell entry may be implicated, as ACE2 receptors are found in abundance among cells in the skin and oral mucosa [2, 13, 33]. Binding of the SARS-CoV-2 spike protein to ACE2 receptors on epidermal cells may trigger Th1 recruitment and the subsequent autoimmune cascade responsible for LP pathogenesis [13, 33].

Table 2 Retrospective and prospective studies of Lichen planus after COVID-19 infection and vaccination

Authors		Fidan et al. [33]	Hertel et al. [28]	McMahon et al. [34]	Cebeci Kahrman et al. [36]
Infection or vaccination?		Infection	Vaccination	Vaccination	Vaccination
Study type		Prospective observational	Retrospective cohort	Retrospective registry-based	Prospective cross-sectional study
All patients in sample	Number of patients	74	435,726 (Cohort I of 217,863 vaccinated matched to Cohort II of 217,863 unvaccinated)	58 (patients with post-vaccination cutaneous reactions who had available biopsy samples)	2290
	Percentage of males	66.2%	Cohort I: 43.88% Cohort II: 44.20%	Unspecified	43.6%
	Percentage of females	33.8%	Cohort I: 56.12% Cohort II: 55.80%	62%	56.4%
	Mean age ± SD (years)	45.6 ± 12.8	Cohort I: 53.10 ± 21.81 Cohort II: 53.00 ± 22.54	Mean age unspecified Median age = 61	50.4 ± 17.9
	Age range (years)	19–78	Cohort I: 12–90 Cohort II: 12–90	Range unspecified Interquartile range = 44–77	20–96
Lichen planus patients in sample	Number of patients	12	Cohort I: 146 Cohort II: 59	4	2
	Percentage of total sample	16.2%	Cohort I: 0.067% Cohort II: 0.027%	6.90%	0.1%
	Age range (years)	Unspecified	Unspecified	31–72	"60 s"
	Location of lesions	Tongue ($n = 3$), buccal mucosa ($n = 4$), gingiva ($n = 4$), palate ($n = 1$)	Unspecified	Trunk and extremities	Bilateral forearms
	Vaccines	N/A	Cohort I only: 88 received mRNA-based, 58 received adenovirus vector-based	Tozinameran ($n = 3$), Spikevax ($n = 1$)	CoronaVac ($n = 2$)

Some also suggest that COVID-19 infection and vaccination can induce a hyperinflammatory reaction mediated by the reticuloendothelial system, leading to the development of LP or LP-like lesions [18, 30]. Meanwhile, specific ingredients in the formulations of COVID-19 vaccines might trigger type IV hypersensitivity reactions that can manifest as oral lichenoid lesions (OLL) [28]. Finally, there are concerns that immunocompromising comorbidities including hypertension, diabetes, vitamin D deficiency, and vitiligo are risk factors that may increase susceptibility to LP after COVID-19 infection or vaccination [2, 25]. Diabetes and hypertension have been identified as risk factors for OLP development and COVID-19 mortality, and vitamin D has been found to modulate Th1 cells and regulate *T*-cell-mediated immune activity [2].

The association between COVID-19 infection and LP remains under debate. A prospective observational study of 74 COVID-19 positive patients found that 16.2% of them had oral lesions attributed to LP [33]. However, the authors did not specify whether the diagnosis was confirmed by histopathological analysis or only based on clinical findings [35].

The potential relationship between COVID-19 vaccination and OLP was investigated through a retrospective cohort study that matched 217,863 vaccinated patients to 217,863 unvaccinated patients using the TriNetX database [28]. Incidence of OLP/OLL was significantly higher among vaccinated patients relative to unvaccinated patients (risk difference = 0.04%; $p < 0.001$; 95% confidence interval = 0.00027; 0.00053) [28]. The authors acknowledged that they were unable to clinically differentiate between OLL and OLP or entirely eliminate distribution differences in the frequency of NSAID use between the two cohorts [28]. Such adverse reactions are rare, often experience spontaneous remission, and should not be considered a contraindication to COVID-19 vaccination at a population level [28]. Both the retrospective cohort study ($N = 435,726$) and another retrospective registry-based study (N=58) found that mRNA-based vaccines were most commonly implicated

in post-vaccination LP onset [28, 34]. Similarly, mRNA-based vaccines (Tozinameran and Spikevax) accounted for 20/39 cases of post-vaccination LP identified by this review. We hypothesize that the stronger immune responses induced by mRNA-based vaccines relative to other vaccines correlate with a higher risk of autoimmune *T*-cell-mediated reactions that can manifest as LP.

Conclusions

LP is a rare complication following COVID-19 infection and vaccination, and patients with immunocompromising comorbidities may be particularly vulnerable. OLP and OLL are considered premalignant, and healthcare providers should carefully monitor for LP-like adverse effects among vaccinated and unvaccinated patients as well as those with a history of COVID-19. Nonetheless, there is no definitive causal link between COVID-19 vaccination and LP. Moreover, there is scientific consensus that LP-related adverse effects do not constitute a contraindication against vaccination and that the benefits of COVID-19 vaccination continue to outweigh the risks significantly.

Appendix

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Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

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