

Title: Lichen planus pigmentosus post COVID-19-vaccination

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Lichen planus (LP) is a T cell-mediated chronic inflammatory disorder. Several clinical variants based on lesion morphology and localization are reported. LPP remains uncommon with an unknown etiology. Besides, some precipitating factors have been suggested in the literature including hepatitis C infection; restrictive underwear, localized friction, and sun exposure. ^(1,2) Herein, we present a case of new-onset of LPP following the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine. A literature review was also conducted to summarize the various cases of LP induced and/or triggered by Covid-19 vaccine.

Case report:

A 50-year-old man, phototype III, presented to our dermatology clinic for a persistent eruption of 2 weeks duration that developed 2 days after his second dose of the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine. He had no personal or family history of atopy, psoriasis, or other inflammatory skin conditions. He denied any recent topical treatment, past drug history or excessive sun exposure. The patient received the second vaccination dose in his left deltoid. Physical examination showed multiple, well-defined, oval-shaped, dark brown, smooth-surfaced macules with no elevated active borders symmetrically distributed on the forearms (Figure 1). There were no the nails, scalp, or mucosal involvement. Serologic tests hepatitis B and C virus infections were non-reactive. A skin biopsy was performed, showing epidermal atrophy, orthokeratosis, vacuolar degeneration of the basal cell, and a band-like lymphocytic infiltrate in the upper dermis with abundant colloid bodies and pigmentary incontinence in the papillary dermis (Figure 2). The patient was diagnosed with LPP and topical betamethasone 0.05% ointment was prescribed. A minor clinical improvement was observed after two months of follow-up.

Discussion:

All the vaccines induce some level of inflammation triggered by the stimulation of the innate immune response. The imbalance of these responses may give rise to inflammatory reactions, which can manifest in the skin. ⁽²⁻¹⁰⁾

The AstraZeneca vaccine consists of a replication-deficient chimpanzee adenoviral gene (ChAdOx1) that encode the SARS-CoV-2 spike protein. ⁽²⁾ Non-human adenovirus strains are not subject to preexisting host immunity (AZD1222), as the vector virus normally only affects chimpanzees. However, adjuvants deserve attention regarding vaccine-derived skin toxicity, as these agents bear the capacity to drive off-target inflammatory reactions. ⁽²⁾

The vaccination induces a Th1 cell response and leads to increased levels of IL-2, TNF- α , and IFN- γ . These cytokines are involved in the development and perpetuation of LP. ⁽⁴⁾ Different reports described the onset of LP after vaccination (hepatitis B, influenza, rabies and combined vaccines) and recently after COVID-19 vaccines. ^(5, 6)

Until August 2022, a total of 41 reports of LP associated with COVID-19 vaccines have been described. (table 1) The reports include various suspect vaccines: BioNTech/Pfizer, 21 reports; Moderna, 3 reports; AstraZeneca, 7 reports; Janssen, 4 reports and Sinopharm, 2 reports.

The average age was 55.4 years, with extremes from 28 to 86 years. The sex-ratio was (H/F) 0.7. In most reports, it was a new onset of the disease in a patient with no relevant history of LP, while in 8 reports a recurrence or an exacerbation of previously diagnosed LP was reported. The delay of the eruption varied from 1 to 60 days. The LP was diagnosed especially after the second dose (16 cases), the first dose (12 cases) and the third one in only one case.

Different forms were reported. We found cutaneous LP involvement in cases, oral LP and mixed form in cases. Coming to cutaneous LP, different forms were retained: LP (n=19), LPP (n=3), lichen planopilaris ⁸ (n=1) lichen striatus ³ (n=1), OLP (n=10), lichenoid drug eruption (n=7). The occurrence of new-onset LP with auto-immune disease was relevant in vitiligo ^{6, 28} (2 cases) and pemphigus vulgaris (PV) in one case ³⁰.

There is a growing body of evidence that LPP, like other variants of LP, represents a T-cell-mediated autoimmune process, as demonstrated by the inflammatory infiltrate of T-lymphocytes with varying populations of CD4+ and CD8+ cells, and the autoreactive cytotoxic T-lymphocytes, which cause degeneration and destruction of basal keratinocytes. ¹³ Its exact pathogenesis is yet to be uncovered.

Three cases of LPP were reported. ^{13, 30, 32} The causative vaccine was the Oxford-AstraZeneca COVID-19 vaccine in 2 reports. ^{13, 30} Our patient represents another reported instance of LPP following the same COVID-19 vaccination with a similar delay after a second dose. Nevertheless, reports of cutaneous reactions to COVID-19 vaccination are increasing. Thus, it remains an open question whether the time of vaccine delivery and the onset of symptoms was a simple coincidence. Obviously, it is essential to collect data regarding a large population to establish a causative link between LPP and COVID-19 vaccination in patients without prior history of auto-immune disorders.

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Figure's legend:

Fig 1: multiple dark brown macules with no elevated active borders symmetrically distributed on the forearms.

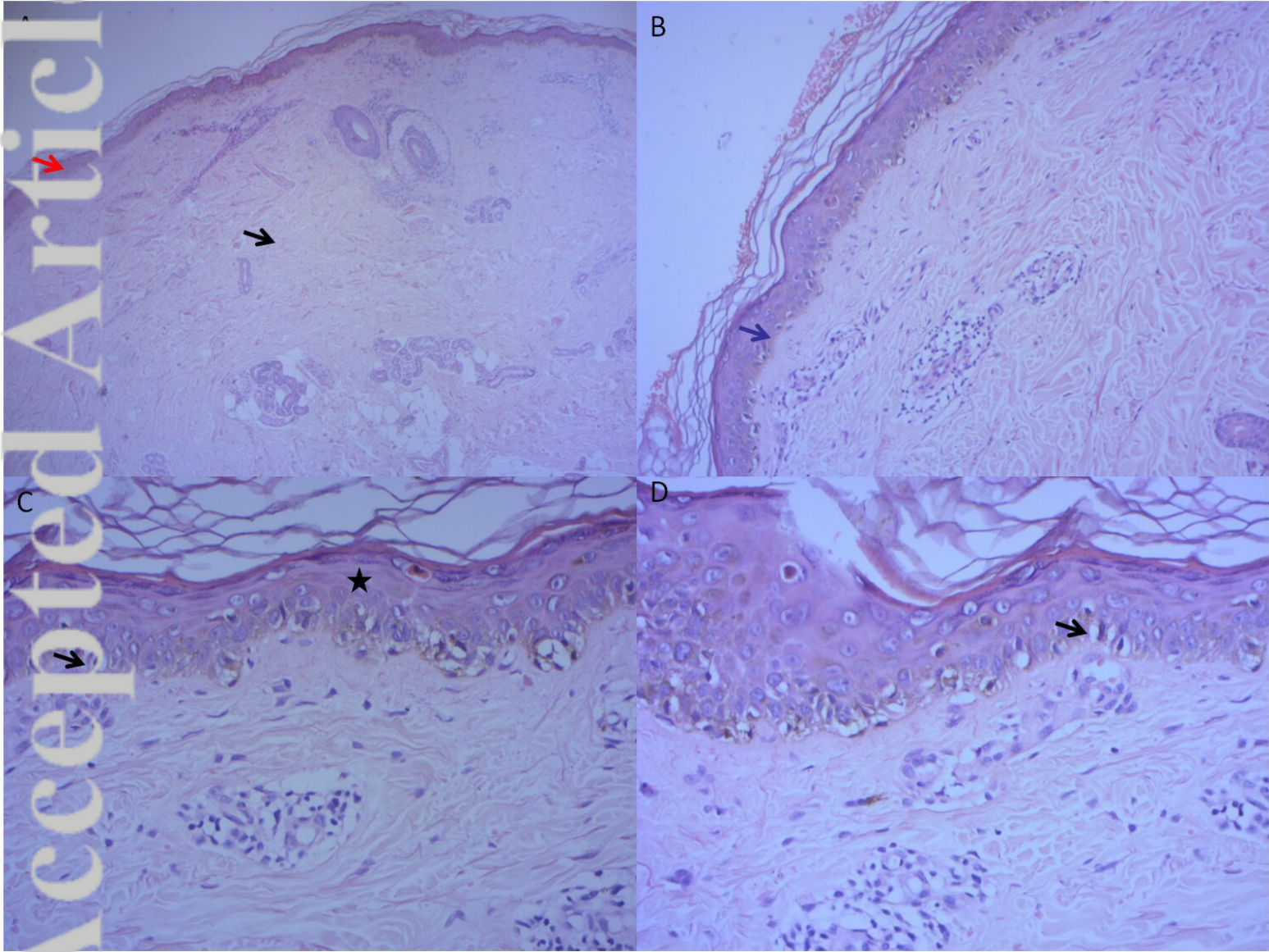
Fig 2: (A) Epidermal acanthosis, (red arrow) dermal fibrosis and lymphocytic infiltrate in the upper dermis (black arrow). (HE x 25)

(B) hyperpigmentation of the basal layer and pigmentary incontinence in the papillary dermis. (HE x40) (Blue arrow)

(C-D) hyperplasia of the granular layer (black asterix) with apoptotic bodies colloid of Civatte (HE x 200). (Black arrow)

Table's legend:

Table 1: a review of previous clinical cases and series of lichen planus and its variant following COVID-19 vaccination



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Author (reference)	Age/ Sex.	New onset, exacerbation, recurrence.	Delay/ dose of vaccine	COVID-vaccine name	Type of lichen	Treatment	Evolution
Hilmi I et al. (1)	56/F	Recurrence of LP	48 h (the second dose of the COVID-19 vaccine)	Pfizer	Lichen planus	high-potency TC	NA
Merhy R et al. (2)	56/F	New onset	One week (the first dose of the vaccine).	Pfizer-BioNTech COVID-19 vaccine	Lichen planus	NA	NA
Morgan E. Belina, et al. (3)	42/ F	New onset	3 days (the second dose)	Pfizer	Lichen striatus	0.1% topical tacrolimus and counseled on laser therapy.	Post-inflammatory hyperpigmentation.
Babazadeh et al. (4)	52/ F	New onset	A week (the second dose of vaccine).	Sinopharm COVID-19 vaccine	Lichen planus	Oral antihistamines and TC	Improvement
T. Teltzsch M et al. (4)	49/M	New onset	Six days.	COVID-19 vaccination (Ad26.COV2.S)	Oral lichen planus	NA	NA
Bassem Awada (5)	44/ M	New onset	2 weeks (the second dose)	Oxford-AstraZeneca	Inverse lichen planus	TC once daily.	Resolved 4 weeks afterward.
V. Piccolo et al. (6)	64/F	New onset	5 days (the first dose vaccine with a recurrence 24h after the second dose).	BNT162b2 mRNA COVID-19	Lichen planus	TC and SC.	NA

Astrid Mum et al. (7)	59/F	Exacerbation of previous LP	Two weeks (the second dose)	COVID-19 BNT162b2 vaccination	Cutaneous lichen planus	High-potency TC three weeks.	Resolution
Reem Diab et al. (8)	1 st case*60 / F Previous. 2 nd case 55/ F	History lichen planopilaris	1*14 days (second dose) 2*3 days (first dose of vaccine with extension after the 2 nd dose).	1-AstraZeneca vaccine 2-sinopharm	Lichen planopilaris and lichen planus (1case) Lichen planus (1case)	NA	NA
Mario Caggiano et al. (9)	40/ M	New onset	One month (second dose)	BNT162b2 (Comirnaty)	Oral lichen planus	NA	NA
Nikola Hlaca et al. (10)	1 st case 82/F 2 nd case68/F.	Exacerbation	1.14 days (the second dose) 2.14 days(the second dose)	1.Pfizer- BioNTech COVID-19 vaccine 2-Moderna COVID-19 (mRNA-1273) vaccine	Two cases of lichen planus.	1* SC 20 mg daily (3weeks). 2* 30 mg SC (6 weeks).	Gradual improvement of skin lesions.
Vincenzo Picone et al. (11)	81/ M	New onset	7 days (first dose)	Moderna vaccine	Associated cutaneous and oral lichen planus	High-potency TC and AH1 therapy for 10 days	Significant improvement at day 15 of follow-up.
Ruchadapor Kaomongko et al. (12)	28/ F	New onset	One week (second dose)	(BNT162b2, Pfizer/BioNTec h)	Oral lichen planus	TC, fluocinolone acetone 0.1% in orabase paste, for two weeks,	Improvement.

L. Sun et al. (13)	A 64/F	New onset	2 weeks (the 1 st dose of vaccine with worsening after the 2 nd dose).	Oxford–AstraZeneca COVID-19 vaccine	lichen planus pigmentosus–inversus	NA	NA
Giulio Zagaria et al. (14)	54 year-old male	New onset	10 days (first dose)	Pfizer mRNA BNT162b2	Lichen planus affecting trunk, nail and feet	SC (25 mg for 7 days) tapering the dose up to 4 weeks.	A rapid resolution of the disease.
Matthias Koeltzsch et al. (15)	49/M	New onset	6 days	Ad26.COV2.S/1	Oral lichen planus	Topical clobetasol mouth irrigation solution (0.5 mg/ml) for a four-week.	A significant improvement of the symptoms.
P. Merhy et al (16)	56/F	New onset	7 days (first dose)	mRNA BNT162b2/1 pfizer	Lichen planus	NA	NA
F. Bernarda, et al. (17)	35/F	New onset	14 days (first dose)	Not reported	Oral lichen planus	NA	NA
Luca Raccampo, et al. (18)	1 st case 54/F 2 nd case 56/f	New onset	10 days (second dose) Not reported.	BNT162b2 mRNA COVID-19 vaccination	Oral lichen planus (2cases)	TC	Partial remission
Harizeh M Airawashdeh et al (19)	46/M	New onset	5days (1st dose)	Oxford-AstraZeneca vaccine.	Lichenoid eruption	TC twice a day and oral AH1, three times a day. HC 200 mg twice daily.	Significant reduction in pruritus after the second month of using HC. Minimal improvement in skin eruption.

L. Camela et al. (20)	59/M		2 weeks (1st dose)	Pfizer-BioNTech COVID-19 vaccine	Lichen planus	NA	NA
C. Masseran et al. (21)	65/F		10 days (1st dose), worsening 7 days after the 2nd dose ,	AstraZeneca adenovirus-based vaccine (ChAdOx1 nCoV-19).	Extensive lichenoid cutaneous eruption	TC cream.	complete remission in four week
Corrado Zengari et al. (22)	49/M	New onset	11 days (2nd dose)	Adenoviral vector Vaxevria (Astrazeneca) vaccine	Eruptive lichen planus	TC and AH.	Significant improvement after 1 month.
D. Mintoff (23)	53/M	New onset	3 days (3 rd dose)	Pfizer-BioNTech	lichenoid dermatitis	SC (0.5 mg/kg/day).	Complete resolution 2 weeks after.
C. Correia et al. (24)	66/M		5 days (1st dose)	Oxford–AstraZeneca COVID-19 vaccine	Lichenoid drug eruption	TC	Complete clinical resolution after 4 months.
Stavanni Paolino et al. (25)	63/F	New onset	3 days (2nd dose)	Pfizer-BioNTech COVID-19 vaccine	Palmoplantar lichenoid drug eruption	25 mg/d of acitretin and topical calcipotriene/betamethasone dipropionate foam.	Complete resolution 5 months after.

Mathieu Zinido et al. (26)	66/F		3 weeks (1st dose)	Vaxzevria (AstraZeneca, Cambridge, UK)	Drug-induced lichenoid exanthema	Degressive SC	Improvement
Atsunori Baba et al. (27)	82/F		7days (2nd dose)	mRNA vaccine (Comirnaty; BioNTech- Pfizer)	Lichenoid drug eruption	NA	NA
Shirley Braga Lima Limonal et al. (28)	86/M	New onset	7 days (1st dose)	(ChAdOx1 nCoV-19, AZ-FIOCRUZ, Rio de Janeiro, Brazil),	Generalized cutaneous lichen planus and vitiligid macules	TC	NA

Lana Abdulaaly et al. (29)	2* 56/F	New onset	2* NR	2*Pfizer- BioNTech vaccines	Oral lichenoid reaction (six cases)	2* Fluocinonide 0.05% gel	NA
	3* 72/M	New onset	3* 4 weeks	3* Moderna vaccines		3* high potency TC	NA
	4*61/M	Exacerbation and new location	4*4weeks	4* Pfizer- BioNTech vaccine		5* topical vitamin A 0.025% gel and TC daily with excellent response	Resolution in 4 weeks
	5*44/F	Exacerbation	5* 1week	5* Pfizer- BioNTech vaccine		6* topical clobetasol and bethanechol for dry mouth.	Improvement at 1month of follow-up
	6* 62/F	Exacerbation	6* 24 hours	6*Pfizer- BioNTech vaccine		7*topical pimecrolimus cream with turmeric supplementation	At the 2-month follow-up, clinical signs and symptoms returned to baseline
	7*51/M	Exacerbation	7*2 weeks	7*Pfizer- BioNTech vaccine			

Zeinab Arvinian et al. (30)	43/M	New onset	2 days (second dose)	Oxford-AstraZeneca COVID-19 vaccine	lichen planus pigmentosus with pemphigus vulgaris (PV)	TC for the LP lesions + azathioprine, rituximab (PV)	Considerable clinical response.
Junji kato et al. (31)	47/F	New onset	2 weeks (2 nd dose)	Pfizer-BioNTech COVID-19	Linear lichen planus	TC	Mild pigmentation.
Yusuf Canbek et al. (32)	NA	NA	NA	NA	Lichen planus pigmentosus inversus with nail involvement	NA	NA

F: female

M: male

NA: not available

TC: topical corticosteroids

SC: systemic corticotherapy

AH: antihistaminic