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Comment on 'Vitiligo in a COVID-19-vaccinated patient with ulcerative colitis: coincidence?': Type I interferons as possible link between COVID-19 vaccine and vitiligo

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Dear Editor

We read with interest the article by Aktas and Ertuğrul[1] published recently in *Clinical and Experimental Dermatology*.[1] The authors describe a 58-year-old man with ulcerative colitis who developed symmetrically distributed vitiligo facial patches about 1 week after receiving the first dose of mRNA vaccine.[1] The authors then pondered on the possible underlying immunological mechanism. We would like to highlight the possible link of Type I interferons (IFN-I) and their main cellular source, the plasmacytoid dendritic cell (pDC), which may explain vitiligo development after COVID-19 vaccine.

The significant role that IFN-I and pDCs play against coronaviruses including COVID-19 has recently been established.[2] Having plasma cell morphology, pDCs are a unique subset of DCs that play an important role in innate immunity through their ability to sense nucleic acids via their Toll-like receptors, (TLR)9 and TLR7, located in endosomal compartments.[3] Upon activation of TLR7/9, pDCs produce massive amounts of IFN-I, which chiefly function in antiviral immunity. Essentially, pDCs are the most potent producers of IFN-I, which are crucial cytokines functioning in the control of viral replication by inducing gene expression.[2,3] pDCs also contribute to the adaptive immunity by regulating other immune cells through IFN-I and proinflammatory cytokines. Coronaviruses, including COVID-19, have been shown to be strong inducers of IFN-I by being effective pDC stimulators.[2] Additionally, COVID-19 vaccines, including adenovirus (DNA delivered within nonreplicating recombinant adenovirus vector systems) and mRNA vaccines, incite immunity to COVID-19 by producing high levels of viral spike proteins.[4] Whereas adenovirus vaccines interact with multiple pattern-recognition receptors (especially TLR9), mRNA vaccines interact with various endosomal (particularly TLR7) and cytosolic innate sensors (inflammasome components).[4] Notwithstanding these variations, both kinds of vaccines converge on IFN-I production, which possibly occurs through pDC-mediated immune response.[4] However, non-pDC-mediated innate immune responses may also be at play.

Concerning vitiligo pathogenesis, multiple complex pathogenic factors contribute to the pathogenic hallmark of epidermal melanocyte loss, among which the leading hypothesis is vitiligo being an immune-mediated inflammatory disorder involving adaptive and innate immunity.[5] Both IFN-I and pDCs were first shown to be important mechanistic players in vitiligo when the presence of pDCs was demonstrated to be part of the inflammatory infiltrate in progressive vitiligo with local production of human myxovirus resistance protein 1 (MxA), the tissue expression of which is considered as a surrogate marker of local tissue MxA production.[5] The intense MxA expression demonstrated in perilesional areas close to the remaining melanocytes that were surrounded by noticeable T-cell inflammatory infiltrate suggested that IFN-I production and pDC recruitment is an early event in vitiligo progression.[5] Further evidence of an important role of IFN-I and pDCs in vitiligo comes from clinical observations.[5] Vitiligo or vitiligo-like hypopigmentation can be induced by treatment of patients with recombinant IFN-α or at the site of application of imiquimod, a TLR-7 agonist known to enhance IFN-α production by being a potent pDC activator.[5] Finally, vitiligo is often associated with inflammatory diseases such as lupus, alopecia areata and psoriasis, for which evidence suggests an important role for IFN-Is and pDCs in their underlying pathogenesis.[3,5] Given this, the ability of COVID-19 vaccine to induce IFN-I leading to induction of vitiligo would not then be surprising.

In summary, COVID-19 infection or vaccination is capable of activating an IFN-I-mediated immune response that may serve as a trigger to IFN-driven inflammatory disorders such as vitiligo in genetically predisposed persons.

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Abrupt onset of Sweet syndrome, pityriasis rubra pilaris, pityriasis lichenoides et varioliformis acuta and erythema multiforme: unravelling a possible common trigger, the COVID-19 vaccine

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Dear Editor,

The development and manufacturing of effective vaccines against COVID-19 has been an epic achievement in record time, and we believe that the vaccine will help stop the pandemic. As with other medical interventions, vaccines may carry a small risk of adverse reactions (ARs), especially when used on large populations outside the highly controlled setting of Phase 3 clinical trials. We report five cases of different rare and severe cutaneous conditions arising in close connection with COVID-19 vaccination (Table 1).

By April 2021, about 15% of the 849 000 inhabitants of the province of Vicenza (in the Veneto region of north-east Italy) had been vaccinated, with a male : female ratio of 3 : 2. The priority was accorded to older people (> 80 years), healthcare workers and school staff. Overall, 187 adverse events were recorded. Besides the more common reactions reflecting aspecific activation of the immune system such as urticaria and cutaneous rash, we observed four rare acute conditions in five recently vaccinated patients [pityriasis rubra pilaris (PRP) in two patients, and Sweet syndrome (SS), pityriasis lichenoides et varioliformis acuta (PLEVA) and erythema multiforme (EM) in one patient each] (Fig. 1). All these conditions were confirmed histologically (Fig. 2) and appeared within the first 2 weeks following the first dose of the COVID-19 vaccine.

Table 1 Brief summary of the demographic and clinical features of the patients.

Patient	Diagnosis	Sex	Age, years	Type of COVID-19 vaccine	Time lag, days	Comorbidities	Clinical course
1	PRP	F	62	Moderna, first dose (second dose not administered)	5	Metabolic syndrome, T2DM, hypertensive heart disease, hypothyroidism, CKD	Progressive remission with systemic prednisone (1 mg/kg/day for 2 weeks, then tapered) and topical steroids at 1-month follow-up. Hospitalization for COVID-19 infection 4 months after PRP onset
2	PRP	F	82	Pfizer–BioNTech, first dose (second dose not administered)	7	Plaque and nail psoriasis, CLL, T2DM, hypertension, COPD	Clinical improvement achieved with subcutaneous MTX 15 mg/weekly. Residual PP hyperkeratosis and scaly plaques on head and neck at the 4-month follow-up
3	SS	F	69	Oxford–AstraZeneca, first dose (second dose not administered)	12	Overweight, hypertension, dyslipidaemia, iron-deficiency anaemia	Treated with steroid administration (prednisone 1 mg/kg/day for 4 weeks, then slow tapering). At 3-month follow-up, complete healing of the ulcerated plaques with residual hyperpigmentation
4	PLEVA	M	70	Pfizer–BioNTech, second dose	5	Acute lymphocytic leukaemia in complete remission	Treated with topical combination of fusidic acid 2% plus betamethasone cream 0.1%. Complete remission within 10 weeks
5	EM	F	76	Pfizer–BioNTech, first dose (second dose administered)	4	Lung adenocarcinoma (Stage IV), arterial hypertension, T2DM, COPD	Topical prescription of methylprednisolone 0.1% cream twice daily for 10 days. Complete clearance achieved in 10 days. No recurrence with the second vaccine dose

CKD, chronic kidney disease; CLL, chronic lymphocytic leukaemia; COPD, chronic obstructive pulmonary disease; EM, erythema multiforme; PLEVA, pityriasis lichenoides et varioliformis acuta; PP, palmoplantar; PRP, pityriasis rubra pilaris; T2DM, Type 2 diabetes mellitus; MTX, methotrexate; SS; Sweet syndrome.