Comment on '*De novo* generalized pustular psoriasis following Oxford-AstraZeneca COVID-19 vaccine': possible role for Type I interferons

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Dear Editor,

We read with interest the article by Elamin *et al*. published recently in *Clinical and Experimental Dermatology*.[1] The authors described a 66-year-old woman who developed new-onset generalized pustular psoriasis (GPP) 3 weeks after receiving her first dose of the Oxford-AstraZeneca COVID-19 vaccine.[1] The authors then contemplated the possible underlying immunopathological mechanisms. We would like to highlight the Type I interferons (IFN-I) and their chief cellular source, the plasmacytoid dendritic cell (pDC), as possible connections that may explain the development of GPP after COVID-19 vaccine.

In psoriasis, the role of the innate immune system, especially IFN-I and pDCs, in driving the autoimmune T-cell cascade is well known.[2,3] Characterized by their unique surface phenotype and plasma cell-like morphology, pDCs are distinctive DCs that are key effectors in innate antiviral immunity because of their potent ability to secrete large IFN-Is.[2] This is achieved by their ability to sense nucleic acids via their endosomally located Toll-like receptor (TLRs), TLR-9 and TLR-7, which upon activation, lead to massive production of IFN-I, which are crucial cytokines functioning in controlling viral replication by inducing gene expression.[2] In addition, pDCs link the innate and adaptive immunity by their ability to regulate the function of other immune cells. In normal conditions, pDCs are usually present in the blood and lymphoid organs; however, active pDC recruitment occurs from the blood into peripheral sites of infection or inflammation. In psoriasis, pDCs infiltrate lesional skin, where they contribute to the early disease processes mainly through pDC-derived IFN-I production.[2] In particular, GPP, which is a clinical psoriasis variant characterized by recessive mutations of the interleukin (IL)-36 receptor antagonist gene (*IL36RN*), has recently been shown to demonstrate a prominent systemic IFN-I signature that correlates with the known abnormal upregulated IL-36 activity.[3] The underlying immune mechanism leading to this effect in GPP, which also applies to psoriasis vulgaris, has been shown to be mediated by the direct action of IL-36 on pDCs, potentiating TLR-9 activation and production of IFN-α.[3] These findings thus reveal the IL-36/IFN-I axis as a major contributor to inflammation in psoriasis.[3] Additional evidence of a significant role of IFN-I and pDCs in psoriasis/GPP originates from clinical observations such as reports describing psoriasis/GPP induction in patients treated with recombinant IFN-α, and the frequently reported association of psoriasis/GPP with inflammatory diseases such as lupus and alopecia areata, in which evidence suggests an important pathogenic role for IFN-I and pDCs.[3]

In turn, IFN-I and pDCs play a critical role against coronaviruses.[4] Coronaviruses, including COVID-19, have been shown to be effective stimulators of pDCs, leading to strong induction of IFN-Is.[4] In addition, COVID-19 vaccines, including adenovirus vector systems (such as the Oxford–AstraZeneca vaccine) and mRNA vaccines (such as the Moderna and Pfizer–BioNTech vaccines), provoke immunity to COVID-19 by making high spike-protein levels.[5] While mRNA vaccines interact with several endosomal (especially TLR-7) and cytosolic innate sensors, adenovirus vaccines interact with numerous pattern-recognition receptors (mainly TLR-9).[5] Despite this difference, both types of vaccines meet on IFN-I production, which at least partly occurs through the pDC-mediated immune response.[5]

In conclusion, COVID-19 vaccination (or infection) can activate an IFN-I-mediated immune response that may serve as a trigger to an IFN-driven inflammatory disorder such as GPP in genetically susceptible individuals.

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