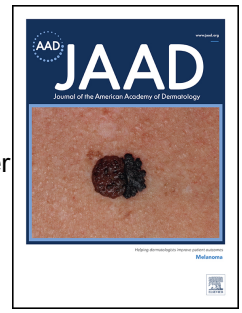

Response to McMahon et al.'s "Cutaneous reactions reported after Modrna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases"

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Title: Response to McMahon et al.'s "Cutaneous reactions reported after Modrna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases"

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Body of manuscript

McMahon et al.[1] reported cutaneous reactions that occurred after the administration of mRNA COVID-19 vaccines. The authors recorded 414 unique patients and observed a broad spectrum of reactions after vaccination, from local injection site reactions and delayed large local reactions, to urticaria and morbilliform eruptions. Several unusual reactions (erythromelalgia, pernio/chilblains, filler reactions and pityriasis-rosea-like eruptions) were also observed. All these lesions are characterized as local (near the injection site), according to the authors. Similar lesions, which were characterized as injection-site reactions, were also reported by Blumenthal et al.[2] and Baden et al[3] after the administration of the mRNA1273 vaccine.

A close examination of the data presented by McMahon et al.[1] in Figures 1 and 2 shows that the reactions were not limited to the injection site but were also distant. These findings should be considered as distant skin reactions, seemingly having the same origin/pathophysiology as the local reactions observed at the injection site. Additionally, many patients exhibited other systemic symptoms concurrently with the skin reactions. Fatigue was reported by 62% of vaccine recipients after the second dose of the mRNA1273 vaccine, while 25% experienced myalgia after the second dose of the BNT162b2. Other symptoms and clinical signs were also reported, such as gastrointestinal symptoms (3.9% after mRNA1273 second dose), syncope episodes, metallic taste and hematuria. All these findings were not discussed in depth and, in our opinion, deserve further consideration.

The case series by McMahon et al.[1] presented three types of adverse effects: local skin reactions at the injection site, distant skin reactions and/or more generalized adverse reactions. The authors did not consider the possibility that these phenomena may be closely linked. They did, however,

mention that these exanthemas mimic dermatologic manifestations of COVID-19 and suggested that an unexplained immune response may be responsible for the findings. Since similar skin reactions and generalized adverse events have been reported after the administration of all SARS-CoV-2 vaccines available so far (mRNA or viral-vectored), we formulate the hypothesis that the spike glycoprotein, which is produced as a result of the vaccination with all currently-available vaccines, is responsible for these phenomena.

In silico modelling studies suggest that an epitope of the SARS-CoV-2 Spike protein, adjacent to the receptor-binding domain, may interact with the alpha7 nicotinic acetylcholine receptors (nAChRs).[4] These receptors are widely present in different cells, including T-lymphocytes and macrophages, and have a pivotal role as part of the cholinergic anti-inflammatory pathway. The potential interaction of the spike with alpha7 nAChRs in macrophages was recently described[5]. Dysregulation of this system could explain many of the clinical manifestations of COVID-19, could be linked to both systemic effects and skin lesions and may play a role in the pathophysiology of severe COVID-19, in which immune dysfunction and hyper-inflammatory response appear to be implicated. Since this hypothesis is based on the interaction between the spike and alpha7 nAChRs, it could be applicable to adverse effects related to the vaccination (which results in spike production), and this needs to be further explored. Considering that, in many cases, skin lesions is not an isolated clinical manifestation, it is important that dermatologists record systemic symptoms and signs, and be alert for the possibility that similar skin and systemic reactions may appear after the second vaccine dose.

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