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Annular elastolytic giant cell granuloma after COVID-19 vaccination

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Abstract

The pandemic of SARS-CoV-2 during the first years of the 2020s led to a great commitment to develop effective vaccines. Despite of the good safety and tolerability profile, vaccines may trigger a broad spectrum of cutaneous side effects. Granulomatous dermatitis has been rarely reported after SARS-CoV-2 mRNA vaccines, but no cases of annular elastolytic giant cell granuloma have been already described. Moreover, in our case, it was also associated with a central area of mid-dermal elastolysis, confirming the strong association between these two diseases already reported in literature. The observation of occasional eosinophils within the infiltrate and the presentation of the cutaneous eruption few days after the administration of the second dose of Pfizer/BioNTech (BNT162b2) vaccine are highly suggestive of a drug-related eruption. To our knowledge, this is the first report in literature of an annular elastolytic giant cell granuloma as an adverse effect of SARS-CoV-2 vaccination.

Introduction

The global spread of the COVID-19 during the first years of the 2020s led to a great commitment to vaccines development, in order to reach herd immunity and reduce morbidity and mortality.[1] Two mRNA vaccines, produced by Pfizer-BioNTech and Moderna, received emergency use authorization from the US FDA in December 2020, and subsequently from EMA, recommending them for individuals aged ≥12 and ≥18 years, respectively.[2,3] Although these vaccines display a good safety and tolerability profile, it has been widely reported in literature that they may trigger a broad spectrum of cutaneous side effects, rarely with severe prognosis.[4,5]

Case report

A 75-year-old woman came in January 2022 for the appearance of a broad asymptomatic V-shaped dermatosis, covering most of the trunk, with an erythematous raised centrifugal border, consisting of numerous confluent annular macules and papules, surrounding a pale atrophic center (Fig. 1a-c). The disease occurred few days after the second dose of Pfizer/BioNTech (BNT162b2) vaccine administration and worsened after the third. She was otherwise healthy; no personal or familiar history of dermatological or autoimmune diseases emerged. Laboratory tests and total body CT were unaffected.

Two skin biopsies were obtained from the edge and the atrophic center of the lesion, respectively. The first specimen revealed the presence, at various levels of the dermis, of a granulomatous inflammatory infiltrate with multinucleated giant cells exhibiting elastophagocytosis; in some areas, in the proximity to the granulomas, numbers of mononuclear cells and occasional eosinophilic

granulocytes were also noted (Fig. 2a-d). In the second biopsy, a scanty perivascular lymphohistiocytic infiltrate was observed in the upper dermis with few multinucleated giant cells showing elastophagocytosis in the mid-reticular dermis. Orcein staining better showed a well-demarcated band-like elastolysis in the mid and upper reticular dermis, with clear reduction or complete loss of the elastic fibers, and the preservation of the elastic component of the papillary dermis, as occurs in the so-called mid-dermal elastolysis (Fig. 3a-b).

Therefore, according to clinical-pathological findings and considering the temporal proximity with the vaccine administration, we diagnosed her with annular elastolytic giant cell granuloma (AEGCG), evolving into mid-dermal elastolysis, associated with Pfizer/BioNTech vaccine. The patient did not improve significantly after one month of topical steroids, then she was switched to 10 mg/week methotrexate therapy with folic acid supplementation for two months, with evident benefit (Fig. 1d).

Discussion

The skin is commonly involved by a broad spectrum of vaccine-derived adverse events, ranging from local site reactions to generalized rashes.[4] Nowadays, granulomatous dermatitis has been rarely reported after SARS-CoV-2 mRNA vaccines and, to our knowledge, no cases of AEGCG have been described.[6] AEGCG is a rare granulomatous disorder characterized by elastolysis and elastophagocytosis. Etiopathogenesis is still controversial: environment, neoplasm, infections, and autoimmune disorders may trigger the process by modifying the antigenicity of elastic fibers and precipitating cellular immunological reactions.[7,8]

In this context, different hypotheses may explain the elastic tissues damage. The immune response induced by SARS-CoV-2 mRNA vaccines, based on neutralizing antibodies development by the expression of SARS-CoV-2 spike protein, determines pleiotropic effects on the host cells. Vaccine-induced T-cell activation and release of TNF-α and IFN-γ cause an exaggerated immune response that, in certain vulnerable settings, could initiate hyper-inflammatory changes and increase cytokine release, with following macrophage activation.[4] The macrophage-mediated inflammatory events imply the release of destructive enzymes and cytokines against various components of the extracellular matrix, i.e. towards the elastic fibers in the case here reported. Damaged elastic fibers and intense macrophage activation could explain the development of the granulomatous inflammatory process.[9]

Further supposed pathogenic mechanisms, could be represented by molecular mimicry and crossed immune reactivity, between antibodies against SARS-CoV-2 spike glycoprotein and host peptide protein, such as elastic tissue.[9]

Cota et al. supported the autoimmune hypothesis of mid-dermal elastolysis recognizing the role of increasing susceptibility to develop local and/or systemic autoimmune conditions to inflammatory environment and to the loss of immune self-tolerance to tissue-associated antigens.[10]

The presence of eosinophils in the inflammatory infiltrate accompanying a cutaneous eruption has long been considered a histopathological clue for differentiating drug eruptions from other diseases presenting with lichenoid and/or perivascular lymphocytic infiltrates in the superficial dermis, such as viral exanthema. At least isolated eosinophils are reported in the 2/3 of cases of confirmed drug eruptions and, when present, are scattered within the lymphocytic infiltrate.[11] In our case, the observation of occasional eosinophils in association with the temporal criterion of the presentation of the cutaneous eruption few days after the administration of the second dose of Pfizer/BioNTech (BNT162b2) vaccine, is highly suggestive of a drug-related eruption.

Granulomatous features are classically present, both clinically and histopathologically, in the course of type IV cutaneous hypersensitivity reactions. An interesting paper by Magro et al. concerning the COVID-19 vaccine-induced cutaneous changes, reported granulomatous features in 5/22 patients examined, with interstitial pattern in the majority of the cases, but also granulomatous vasculitis and folliculitis have been observed.[12] Some of these reactions resembled classic cutaneous manifestations of mild COVID-19, leading to consider that a potential responsible for this vaccine-related reactions could be the novel protein manufactured. These considerations may be extended also to AEGCG, which is definitely a granulomatous disorder that may be triggered by factors modifying the antigenicity of elastic fibers, thus precipitating cellular immunological reactions.

Conclusions

To our knowledge, AEGCG has not yet been reported in literature as a side effect of SARS-CoV-2 vaccination. Its appearance after the second dose, and its worsening after the third, could be explained by the need of reaching a sufficient antigenic title to stimulate an autoimmune response, or of getting an immunological memory. Therefore, AEGCG may represent a possible vaccine-derived adverse reaction.

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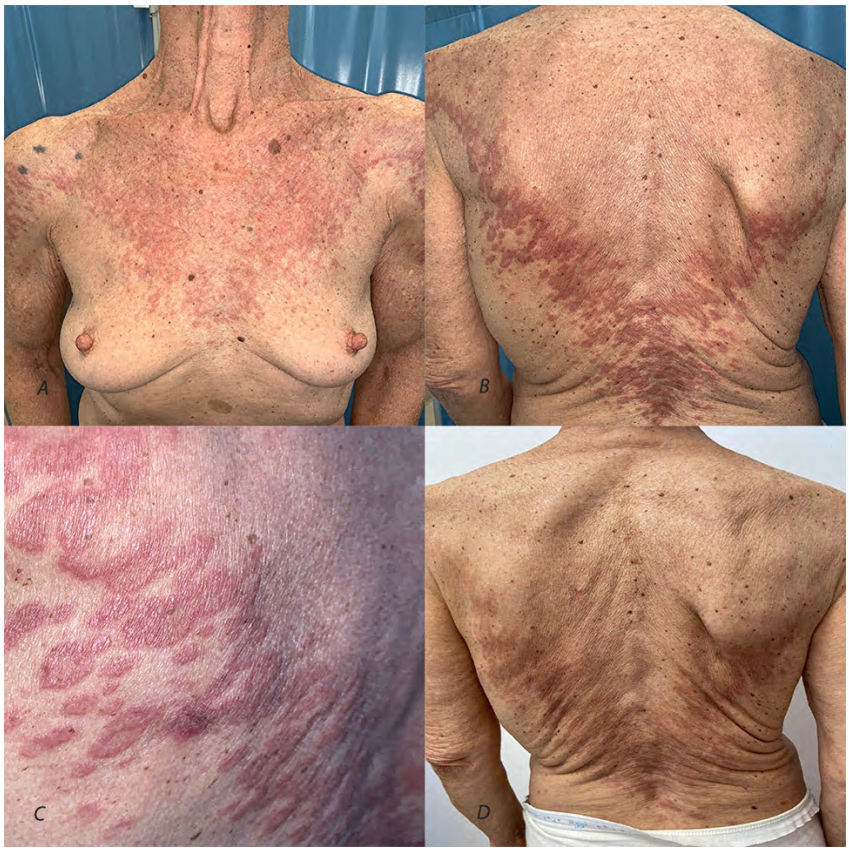

Figure 1. Clinical images of elastolytic granulomatous dermatitis associated with Pfizer/BioNTech (BNT162b2) vaccine. (a, b) A broad V-shaped dermatosis of the chest and the back. (c) A detail of the slightly raising erythematous border consisting of annular macules and papules with a tendency to coalesce, surrounding a pale atrophic center. (d) After two months of methotrexate therapy, the rash appears reduced in size, less infiltrated and less erythematous.

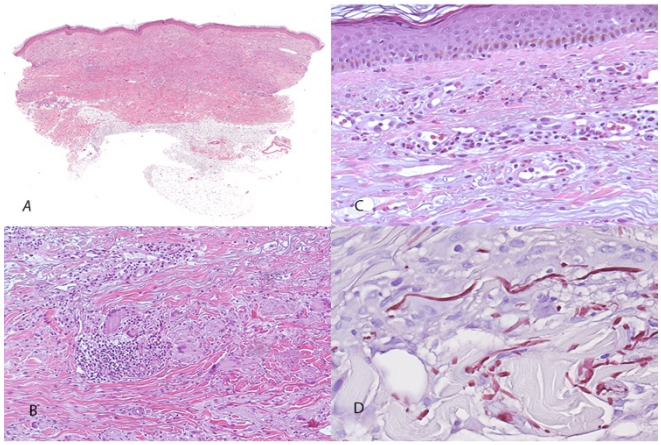

Figure 2. Histopathological images of the punch biopsy from the erythematous infiltrated border of the lesion, showing (a) a granulomatous reaction pattern (original magnification 25x).

(b) The dermal inflammatory infiltrate is composed mostly by multinucleated giant cells, associated with small aggregates of lymphocytes (original magnification 100x). (c) At higher magnification, occasional eosinophils are present within the infiltrate (original magnification 200x). (d) Orcein stain reveals fragmented elastic fibers and elastophagocytosis (original magnification 200x).

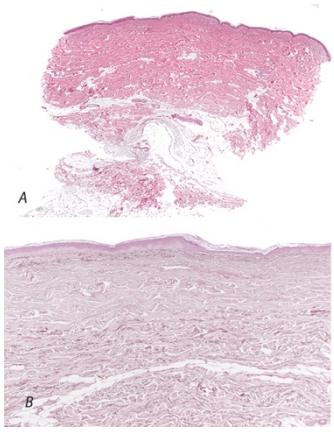

Figure 3. Histopathological images of the punch biopsy from the atrophic center of the lesion, showing (a) a mild superficial perivascular inflammatory infiltrate (original magnification 25x). (b) Orcein stain demonstrates the absence of elastic fibers in the mid dermis, with their preservation in the papillary dermis and in the lower reticular dermis (original magnification 40x).