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Case report

Granuloma annulare after SARS-CoV-2 vaccination: A case report and a literature review

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ABSTRACT

Introduction: During the Cov-19 pandemic, many studies reported a broad spectrum of cutaneous reactions presenting as erythematous rashes or pernio-like, urticaria-like or vesicular/bullous patterns associated with Cov-19-infection and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination.
Methods: The authors documented the clinical and histopathological features of an unexpected case of granuloma annulare (GA) arising a few days after the SARS-CoV-2 vaccination and reviewed all GAs reported in the literature following the SARS-CoV-2 vaccination and Cov-19-infection.
Case report: A 69-year-old woman developed a single reddish lesion on the left deltoid region, where the SARS-CoV-2 vaccine seven days earlier was injected. The clinicians performed a punch skin biopsy, and histology revealed an interstitial GA.
Conclusions: Clinicians should be aware of the potential, though rare, GA occurrence as a possible adverse event after the SARS-CoV-2 vaccination. This additional case, like what happens after the administration of other vaccines, supports the idea that GA may result from the immune system activation following the vaccination. However, notwithstanding, they should encourage their patients to obtain immunization to assist the public health systems in overcoming the COVID-19 pandemic.

1. Introduction

Granuloma annulare (GA) is a benign, inflammatory skin disorder with an annualized incidence of 0.04% and a prevalence of 0.06%. It is most frequent during the fifth decade of life, with a predilection for Caucasian women (F: M ratio of about 3:1) [1]. Although uncertain etiology, it could represent a hypersensitivity reaction to triggers such as trauma, medications, malignancy, viral infections, and vaccinations [2]. Clinically, GA presents with localized, generalized, subcutaneous and perforating forms. It appears as one or more self-regressing erythematous papules that tend to form annular or arciform plaques, localized mainly on the dorsum of hands and feet or over the trunk.

Histologically, mainly GA presents a palisading pattern, characterized by a central zone of necrobiotic collagen surrounded by palisading histiocytes and varying numbers of lymphocytes, and an interstitial pattern, characterized by histiocytes and lymphocytes distributed between collagen bundles and around vessels with an increased amount of connective tissue mucin [3,4].

During the recent Cov-19 pandemic, four documented cases of GA, one after SARS-CoV-2 vaccination and three after SARS-CoV-2 infection, have been reported [2,5–8].

This report presented the second documented case of GA after the SARS-CoV-2 vaccination and, after briefly mentioning post-CoV-19 and SARS-CoV-2 vaccination reactive skin manifestations reported in the literature, reviewed all the GA correlated to the SARS-CoV-2 vaccine and infection.

2. Case presentation

In May 2022, a 69-year-old woman presented to the Dermatologic Unit of the University of Naples "Federico II with a 20-day before-onset asymptomatic reddish lesion on her left arm. The patient referred the

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lesion formed 7-days following the second dose of COVID-19 vaccination with mRNA BNT162b2 on the injection site, daily enlarged for up to 10 days and failed to respond to the topical corticosteroids. The lesion was about 1,5 cm in diameter and composed of multiple papules forming a plaque (Fig. 1A). Dermoscopy revealed linear arborizing vessels on a whitish-red background (Fig. 1B). Suspecting GA, the clinicians performed a 5-mm punch biopsy. Histology and subsequent immunohistochemical analysis revealed the presence, in the dermis, of an interstitial inflammatory infiltrate, mainly composed of histiocytes with some giant multinucleated cells and an accompanying perivascular lymphocytic population consisting primarily of T-cells (Fig. 2A-D). These findings led to the diagnosis of interstitial GA. At the 3-month follow-up, the lesion showed signs of resolution.

3. Discussion

During the Cov-19 pandemic, many studies reported a wide spectrum of cutaneous reactions after both SARS-CoV-2 infection and COVID-19 vaccination [9–18].

The most common skin manifestations are erythematous rashes, with mostly a maculopapular, pityriasis rosea-like and erythema multiforme-like pattern and vascular diseases, including the most peculiar chilblain-like lesions (also known as COVID-toes, pernio-like lesions, or pseudo-chilblain). Urticaria-like, vesicular/bullous and livedo-necrosis were also described.

Current evidence shows that most cutaneous reactions secondary to SARS-CoV-2 vaccination are like those associated with SARS-CoV-2 infection and share immunopathological mechanisms, including host immune activation against viral particles rather than direct viral damage [14,19].

Some authors hypothesized that the cutaneous damage might start with dysfunction of endothelial cells caused by SARS-CoV-2 infection or by immune system activation [20]. Pathophysiologically, skin lesions may be provoked by inflammatory mechanisms, including immune response to viral nucleotides, and vascular mechanisms, secondary to vasculitis or vasculopathy, and thrombosis [21]. The exaggerated inflammatory response is linked to the triggering of innate and adaptive immune responses and to the monocytic-macrophage system [22]. Some erythematous skin rashes may result from other viral infections that can occur in cases of drug reactions [23] or an adverse drug reaction used during SARS-CoV-2 infection [24]. In chilblains-like lesions, the most studied vascular disease, an exaggerated immune response with significant type 1 interferon signaling necessary for viral eradication would generate a generalized inflammatory response [25,26].

GA arising both after SARS-CoV-2 infection and vaccination are exceptional and unexpected events: three cases of GA after SARS-CoV-2 infection and one after SARS-CoV-2 vaccination have been reported in the literature (Table 1) [2,5–8].

In detail, the first patient was a 53 years-old woman with an annular lesion on the second finger on the left hand and a papule on the knuckle of the same finger, arising at the same time with the onset of SARS-CoV-2 typical symptoms (dysgeusia, anosmia and headache) and a positive real-time polymerase chain reaction (RT-PCR) test for SARS-CoV-2.

Histology showed an interstitial GA [5]. Later, the authors reported positive immunohistochemical staining for the viral spike protein in the cytoplasm of histiocytes of this lesion and the negativity of the RT-PCR on a fresh skin biopsy performed two months after the first one [6].

The second patient was a 31 years-old woman with an annular, irregular, pink-colored erythematous 3 × 2 in diameter papular lesion on the dorsum of the left foot, arising ten days after an RT-PCR SARS-CoV-2 positive test. Histology revealed an interstitial GA [7].

The third patient was a 63-year-old male with abrupt onset, multiple, asymptomatic, skin-colored to erythematous nodules involving abdomen, bilateral upper and lower limb, arising twenty days after a positive rapid antigen test for SARS-Cov-2. Histopathology was consistent with generalized and subcutaneous GA [8].

The first described patient with GA after the SARS-CoV-2 vaccination was a 58 years-old woman presented to the clinicians because of a 3-month-rash localized at the trunk and extremities, manifested two weeks after the second dose of the Pfizer SARS-CoV-2 vaccine. The treatment produced a clinical improvement after one month. Nevertheless, less than a week after the Pfizer SARS-CoV-2 booster dose, the patient showed new lesions, increased itching, and redness of her rash [2].

In our case, the patient developed a reddish lesion seven days after SARS-CoV-2 vaccination and in the same site with a histological finding of interstitial GA. The patient is under constant routine follow-up and is well and without lesions.

Furthermore, three inflammatory skin lesions resembling systemic GA cases have been described in three SARS-CoV-2 swab-negative adolescents [27]. The patients were two boys between 11 and 14 years old and an 11 years-old girl, and all of them showed acral nodular lesions with histological findings of chronic immune-mediated inflammation and immunohistochemical evidence of SARS-CoV-2 spike proteins in endothelial cells and eccrine sweat glands. Moreover, after a few months, serological tests were carried out and showed positivity for IgG, suggesting the possibility of a previous SARS-CoV-2 infection as a triggering event for the SGA.

The pathogenetic mechanism underlying these events has yet to be well established. The most plausible hypothesis proposed argues that the cause is to be found in the immune reaction triggered by vaccination and associated infections rather than by the direct role of the virus on the skin lesion. This hypothesis is reinforced by the description of GA in patients recently underwent other vaccinations, mainly Bacillus Calmette-Guérin (BCG) [2,28]. Furthermore, the key role of upregulation of the T-helper (Th) 1 and Th2 pathways in the onset of GA has recently been described. In addition, the key role Th17 and Th22 axes and the Janus kinase-signal transducer and activator of transcription (JAK--STAT) pathway were upregulated [29].

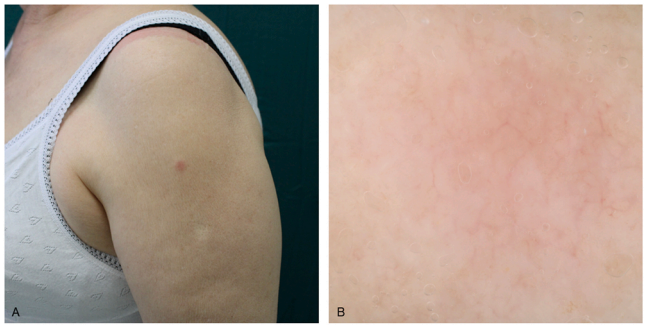

Fig. 1. A. A reddish lesion on left arm; B. At dermoscopy, linear arborizing vessels on a whitish-red background.

4. Conclusion

We find this case of GA instructive because of the remarkable exceptionality: in fact, it represents the second case of GA arising after SARS-CoV-2 vaccination; even though it cannot be ruled out a coincidental association, the time relationship between the vaccination and the onset of GA supports a causative association. Together with the other cases we reviewed here, it may help us to confirm that GAs, some of which recently described in patients underwent other vaccinations, may occur due to a severe immune system activation caused by vaccination.

In dermatopathological practice, it should be aware of the potential, though rare, of GA as a possible adverse event after vaccination, including the SARS-CoV-2 vaccination.

Anyway, colleagues should encourage patients to obtain the vaccination in order to assist the public health systems to overcome the COVID-19 pandemic.

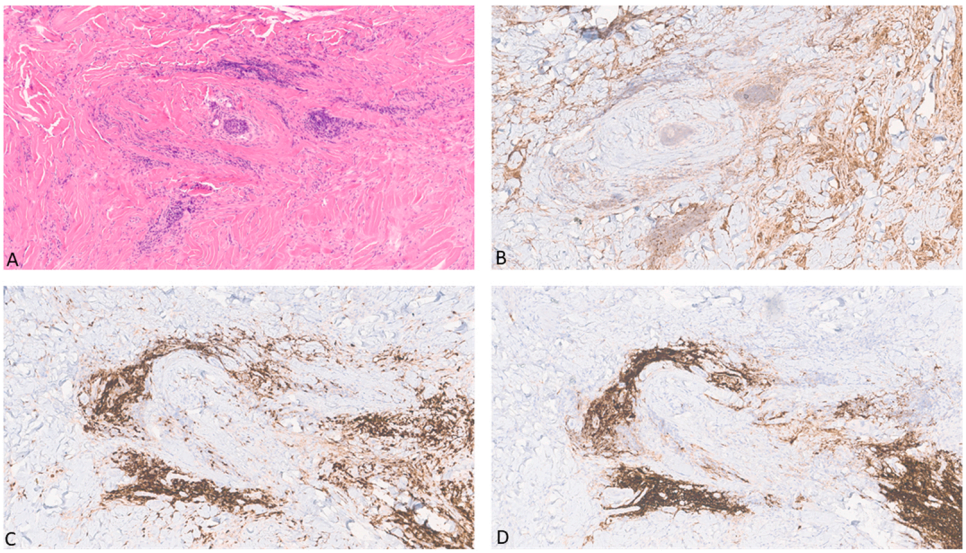

Fig. 2. A. The inflammatory cell infiltrate interspersed between the collagen fibers (haematoxylin and eosin, original magnification, x10); B. Histiocytes stained for CD68 (CD68, original magnification, x10); C. T lymphocytes stained for CD3 (CD3, original magnification, x10); D. B lymphocytes stained for CD20 (CD20, original magnification, x10).

Table 1
Clinical and histological features of post-Cov-19-infection and post-SARS-Cov-2 vaccination GA patients.

Author	Sex and Age	Post-infection or post-vaccination	Latency time	Site of the lesion	Type of the lesion	Histological diagnosis
Garcìa-Gil MF (2020)	F, 53	Post-infection	0 days	Knuckle of on the second finger on the left hand	An annular lesion and a papule	Interstitial GA
Emre S (2022)	F, 31	Post-infection	10 days	Dorsum of the left foot	An annular, irregular, sharply demarcated, pink-colored erythematous papular lesion,	Interstitial GA
Kaur L (2022)	M, 63	Post-infection	20 days	Abdomen, bilateral upper and lower limbs	Multiple, asymptomatic, skin-colored to erythematous nodules	Generalized and subcutaneous GA
Nguyen TH (2022)	F, 58	Post-vaccination	14 days, with recurrence after the Pfizer SARS-CoV-2 booster dose.	Back, flank, inguinal folds, and extremities.	Multiple papules coalescing into plaques with central clearing	GA
Russo D (2022)	F, 69	Post-vaccination	7-days	Left arm	Multiple papules forming a plaque	Interstitial GA

F: female; GA: granuloma annulare.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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