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Case Report

Post COVID - 19 Infection Diffuse Patch Granuloma Annulare in a Female Patient with Rheumatoid Arthritis: A Case Report

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Abstract

Introduction: Granuloma Annulare (GA) is a benign, usually self-limited, inflammatory granulomatous skin disorder of unknown etiology and with a diversity of clinical variants. Genetic factors, associations with predisposing diseases along with several triggers such as certain infections and vaccines, have been described, SARS-CoV-2 virus being one of them.

Case Presentation: Localized, generalized and subcutaneous forms of GA have been reported following either SARS-CoV-2 infection or vaccination against the virus. Herein we present a case of diffuse patch GA in a middle-aged female patient with medical history of rheumatoid arthritis, one month after catching COVID -19 despite being fully vaccinated against the virus.

Discussion: Overall, taking into account the relevant literature, the occurrence of GA after infection with SARS-CoV-2 as well as after vaccination seems to be attributed to the activation of an immunologic reaction rather than to the direct effect of the virus on the skin lesions, with the latest also appearing in the form of diffuse patch rashes.

Conclusion: Dermatologists should be aware of such lesions appearing after COVID-19 infection or even vaccination especially in patients with autoimmune diseases.

Keywords: Granuloma Annulare; SARS-CoV-2; COVID-19 Virus; Immune Reaction

Introduction

Granuloma Annulare (GA) is a benign, often self-limited, inflammatory granulomatous skin disorder of unknown etiology. Localized and generalized GA are the most frequent forms observed, though rarest clinical variants have also been described (subcutaneous, perforating, patch, papular umbilicated, linear, acute painful acral) [1,2]. Despite its uncertain etiology, it has been associated with diabetes mellitus type I, dyslipidemia, trauma, thyroid gland disease, malignancy, viral infections, medications, vaccinations and the HLA-B35 haplotype [2]. Until now, only a few cases triggered by SARS-CoV-2 virus have been reported, in particular localized, generalized and subcutaneous forms [1-4,6-9]. Herein we present a case of diffuse patch GA in a female patient, occurring one month after infection with SARS-CoV-2.

Case Presentation

A 54-year-old female patient presented with a history of 8-month persistent, scaly, non-itchy, patchy lesions, mainly distributed on the trunk and proximal extremities with a tendency to expand the last three months (Fig. 1).

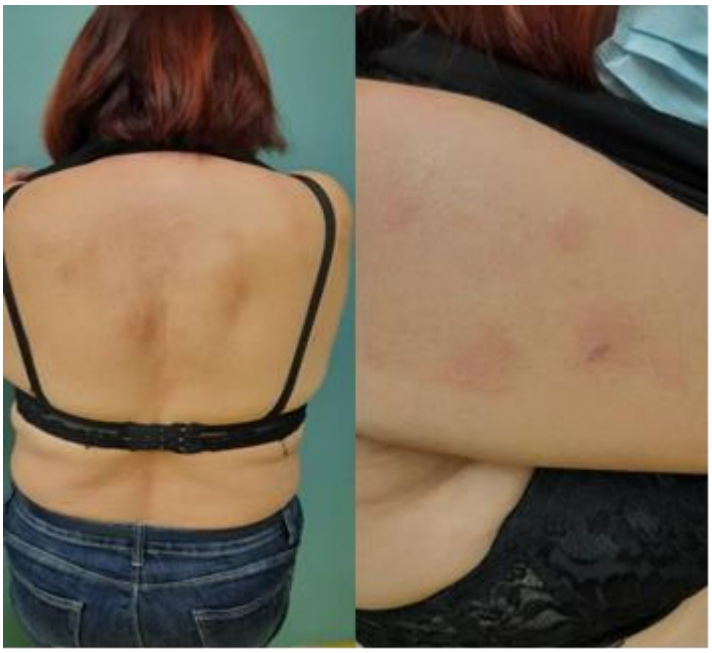

Figure 1: Patchy lesions on the trunk and the right forearm (on admission).

The patient was diagnosed with SARS-CoV-2 infection (verified by a positive SARS-CoV-2 PCR test) one month before the appearance of the lesions. It should be mentioned this was her second time catching the virus, while the first one being about one year ago. She had fulfilled her 3rd dose of mRNA COVID-19 vaccine three months before her recent infection, i.e. four months before the occurrence of the rashes.

Her medical history was relevant for arterial hypertension, immune thrombocytopenia at the age of 17 treated twice with systemic corticosteroids - yet with no relapse the last 27 years, rheumatoid arthritis with a 10-year regimen with adalimumab followed by a 2-year treatment with abatacept ceased upon her 1st SARS-CoV-2 infection. The patient underwent left ovary removal at the age of 38 and thyroidectomy six years ago due to multinodular thyroid gland, thus receiving levothyroxine since then. The rash was initially treated as dermatitis with topical and systemic corticosteroids. Methotrexate was added (10 mg per week) due to inadequate response to treatment, nevertheless without significant improvement after a 2-month regimen. Upon admission to our dermatology department, a skin biopsy was performed revealing findings consistent with interstitial granuloma annulare (Fig. 2-4).

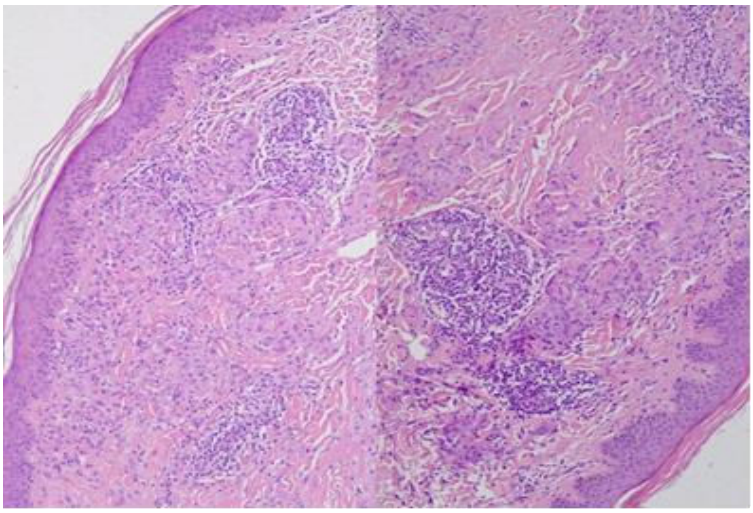

Figure 2: Findings compatible with GA in two separate histologic sections: In the dermis necrobiosis of collagen fibers centrally surrounded by granulomatus inflammatory infiltrate at the periphery consisting of histiocytes, giant cells and lymphocytes.

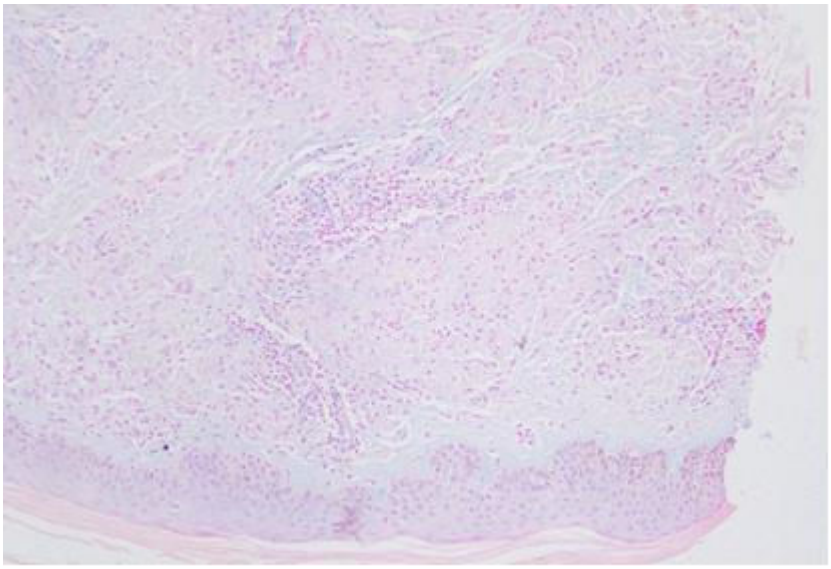

Figure 3: Detection of mucin stained with Alcian blue, indicative of GA.

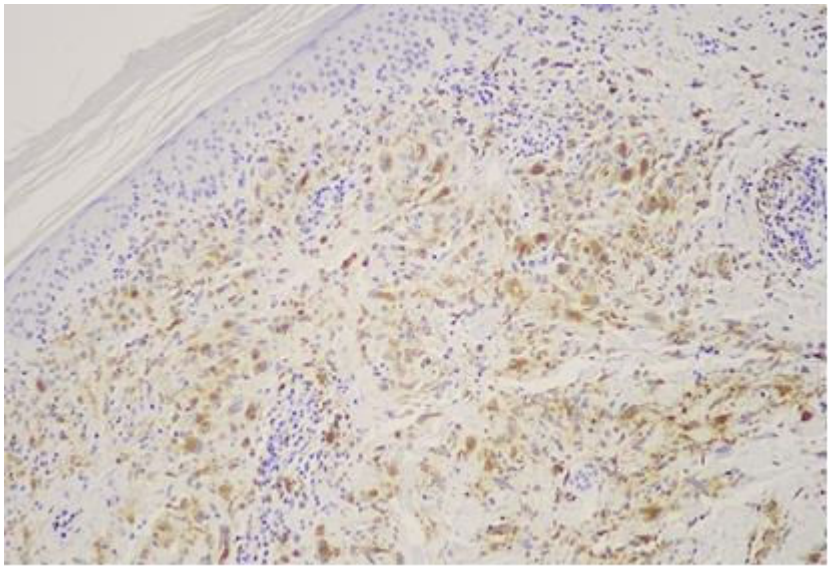

Figure 4: Positive staining CD68 for histiocytes in patient's lesions.

Regarding the patient's blood tests performed, values were within normal ranges. Interestingly measurement of specific to SARS-CoV-2 antibodies had revealed a very high titer (56.433 U/ml) one week before the appearance of the eruption.

Given the disseminated form of the rash, hydroxychloroquine 200 mg per day was administered along with topical corticosteroids at a tapering dosage. Methotrexate was kept being prescribed by her rheumatologist for the treatment of rheumatoid arthritis. After one month of treatment the patient showed signs of improvement and on 3-month follow-up visit she appeared with almost total resolution of the lesions (Fig. 5), without any clinical or laboratory side effects so she was advised to continue the same regimen till the next follow-up visit in six months.

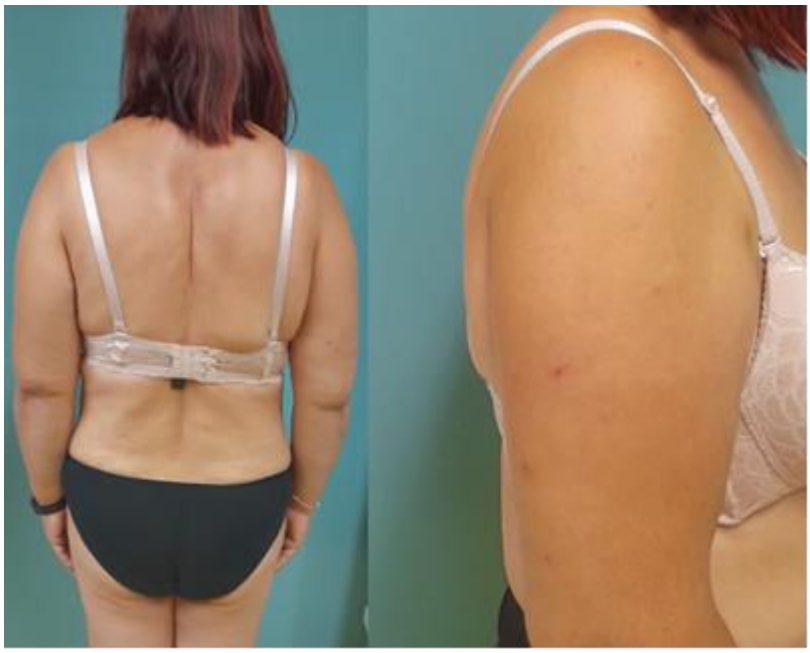

Figure 5: 3 months after initiation of hydroxychloroquine.

Discussion

There have also been only a few reports of GA attributed to recent SARS-CoV-2 infection, mainly localized and subcutaneous forms [1,3,4,6-9]. There have also been reports of localized and generalized forms of GA having occurred after COVID -19 vaccine [10,11].

Almost all of the cases (except for one) have been observed in female patients their age ranging from 31 to 69 years old. Latency period for the occurrence of GA lesions varied from 0 to 20 days whereas biopsy findings were indicative of interstitial GA. Clinical and histological features of the aforementioned cases along with those of our patient are summarized in Table 1 (Supplement).

Attempts to detect the RNA of the virus with specific RT-PCR techniques in biopsy specimens of GA lesions of patients with recent SARS-CoV-2 infection have been unsuccessful [9].

In all the above cases testing of skin biopsy specimens revealed a similar pattern of immunohistochemistry-based cytoplasmic staining in the GA histiocytes with the viral spike protein of SARS-CoV-2 though similar results were also seen in negative control specimens of patients diagnosed with GA in 2019 -before the pandemic- which could be explained by lack of specificity against SARS-CoV spike and SARS-CoV-2 spike proteins with the stains used [3,9-11]. Given the unavailability of specific immunohistochemical stains along with the fruitless efforts to detect the genome of the virus in skin lesions, the association of GA either to SARS-CoV-2 infection or to the vaccination in the aforementioned reports has been suggested taking into account the time correlation with the relevant event, along with the titer of antibodies against SARS-CoV-2 having been measured in some of the cases [8,11].

A significant increase in inflammatory genes related to Tumor Necrosis Factor (TNF)-a, Interleukin (IL)-1b and IL-12/23p40 has recently been described in GA [4]. Besides, SARS-CoV-2 induces a cytokine storm, producing inflammatory mediators including IL-1β, IL-6, TNF-α, IL-12/23 which might precipitate GA as a reactive phenomenon [4,6]. Vascular damage associated with viruses causing immune-complex deposition may also explain chronic granulomatous changes seen in GA [6]. Additionally, pathogenetic and histological similarities with vasculitis induced by SARS-CoV-2 have been described in lesions of GA in paediatric patients with history of recent SARS-CoV-2 infection [8]. Furthermore in cases of GA associated with SARS-CoV-2 infection an interstitial pattern was also observed in the histopathology. It has been suggested recently that interstitial granuloma

annulare be classified as "reactive granulomatous dermatitis". It is thought that this type of dermatitis may be triggered by an inflammatory mechanism that occurs after a trigger such as an infection and is self-resolving. A SARS-CoV-2 infection, like other viral and bacterial infections associated with the activation of the immune system and immune response, may be responsible for the emergence of GA [3].

Taken together, it seems that the occurrence of GA lesions reported after SARS-CoV-2 infection as well as after vaccination against SARS-CoV-2 might be associated with an immune reaction triggered by such stimuli rather than with the direct role of the virus on the skin. This hypothesis is also reinforced by the description of GA in patients having undergone other vaccinations, mainly Bacillus Calmette-Guerin (BCG) [11]. Moreover, GA skin profile shows activation of T-helper cell type 1, T-helper cell type 2 and Janus kinase pathways favoring the notion that immune mechanisms drive the pathophysiological background of the disease [11].

In our case the patient had an established medical history positive for autoimmune disorders and was infected with SARS-CoV-2 one month before the appearance of the lesions, having already been received the 3rd dose of m-RNA vaccine against the virus three months before the infection. As aforementioned three weeks after being diagnosed with the infection - i.e. one week before the appearance of the rash - measurement of specific antibodies against SARS-CoV-2 had revealed a very high titer (56.433 U/ml) favoring our suspicion that the recent infection might have played the major role in the immunologic cataract mediating the occurrence of GA lesions without excluding a possible enhancement of this immunoreaction by the previous past infection and vaccination with the 3rd dose four months before the eruption.

It is also well known that GA has been associated with autoimmune disorders including rheumatoid arthritis [2]. Rheumatoid arthritis is an autoimmune disease characterized by granulomatous inflammation whereas granulomatous dermatoses can present as a reaction to underlying systemic inflammation [5].

A case of resistant disseminated patch GA treated successfully with upatacitinib has also been described in a patient with rheumatoid arthritis. Skin lesions had developed within 3 years and no triggering factor was mentioned. The patient had a medical history of diabetes mellitus, obesity and coronary heart disease whereas seropositive Rheumatoid Arthritis (RA) had been diagnosed over one year before the appearance of the lesions [12].

Another example is that of a 70-year-old woman who was diagnosed with rheumatoid arthritis due to symmetric polyarthritis and skin lesions histologically confirmed as rheumatoid nodules, erythema nodosum and granuloma annulare, the latest in the form of extensive pink scaly annular plaques on her upper back, arms and legs. The rash had gradually progressed within 20 years without any kind of precipitating factor being reported in this case either [5].

In our patient the eruption occurred in a few days after SARS-CoV-2 infection, even though she had been suffering from rheumatoid arthritis for more than 12 years. She had a noteworthy high titer of specific to the virus antibodies indicative of the recent infection. Overall, we assume that the infection of the patient with SARS-CoV-2 might have acted as a trigger contributing to the stimulation of immunologic mechanisms resulting in the occurrence of diffuse patch lesions of GA non responsive to initial treatment thus requiring systemic administration of hydroxychloroquine in order to resolve.

Conclusion

Dermatologists should be aware of such GA lesions especially in patients with background of autoimmune disorders when infected by SARS-CoV-2 or even vaccinated against the virus, considering this kind of rashes as immunologic reactions rather than a direct effect of the virus on the skin. In addition, analysis of further cases might elucidate whether such patients are more susceptible to resistant forms of GA and therefore in need of being more cautious against this kind of trigger in order to receive the most suitable treatment.

Conflict of Interest

The authors have no conflict of interest to declare.

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