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DERMATOLOGIC THERAPY WILEY

LETTER

The case of granuloma annulare associated with SARS-CoV-2 infection

Dear Editor,

Granuloma annulare (GA) is a non-infectious, granulomatous skin reaction characterized by the annular pattern of skin-colored erythematous papules, often localized on the dorsum of the hands and/or feet. Although it is pathogenesis is not fully understood, GA has been reported to be triggered by viral and bacterial infections.[1] Only one severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related case is described in available medical literature to date. But two different articles have been published about the same case.[2,3] Here, a case of localized GA that appeared on the dorsum of the foot on the tenth day of a COVID-19 infection is presented.

An asymptomatic skin lesion appeared on the left foot of a 31-year-old female patient for 1 week. From the patient's history, it was learned that she had been infected with COVID-19 for 10 days before the lesion appeared, verified by a positive SARS-CoV-2 PCR test. A dermatological examination revealed an annular, irregular, sharply demarcated, centrally inactive, pink-colored erythematous papular lesion, measuring 3 × 2 cm in diameter, on the dorsum of the left foot (Figure 1). The patient had no dermatological condition prior to the diagnosis with COVID-19 infection. In histopathological examination of the skin biopsy taken from the lesion, histiocytic inflammation is noted between mononuclear cells and collagen bundles around the vessels, in the upper dermis. Increased dermal mucin with Alcian blue is observed in the dermis (Figure 2). Histopathological examination was found to be compatible with interstitial GA. The patient had no other systemic disease or history of drug use that could be related to the GA. Blood tests indicated that total blood count, blood biochemistry, erythrocyte sedimentation rate, c-reactive protein and thyroid function tests were within normal limits. HIV, hepatitis B, and C tests were negative. SARS-CoV-2 PCR positivity was considered as a possible trigger since it occurred 10 days before the onset of the skin lesions. Based on the clinical appearance of the lesions, histopathological findings and the temporal relationship between the SARS-CoV-2 infection, a diagnosis of GA triggered by SARS-CoV-2 infection was made. We did not consider any treatment to our patient before the definitive diagnosis. However, the lesion disappeared spontaneously in 10 days, probably with effect of inverse Koebner phenomenon of the skin biopsy. No new lesion developed in the patient's 2-month follow-up.

A complete etiology of GA is mostly unknown. A relationship with diabetes mellitus seems to have been defined in recent years and an association with several systemic diseases including malignancy, thyroid disease, and dyslipidemia has also been suggested but not proven.[1] Bacterial and viral triggers have been reported in published research, however, large-scale studies describing the role of infectious agents in triggering GA are scarce. GA has been reported to occur in the presence of viral infections such as the Epstein–Barr virus, human immunodeficiency virus and varicella-zoster virüs.[1]

To date, only one case associated with the SARS-Cov-2 virus has been reported.[2] In order to expand the knowledge about the etiopathogenic role of the virus, the authors published a second report about the same patient. With this second report, the SARS-CoV-2 specific RT-PCR result performed on the fresh skin biopsy sample of the case was negative.[3] In addition, they determined that the viral spike protein showed positive staining in a granular pattern in the cytoplasm of histiocytes in the lesion using immunohistochemical methods. However, they reported the same positive staining pattern was also observed in two SARS-CoV-2 negative patients who were examined as control cases. The authors interpreted these results as poor specificity of histochemical stains against the SARS-CoV and

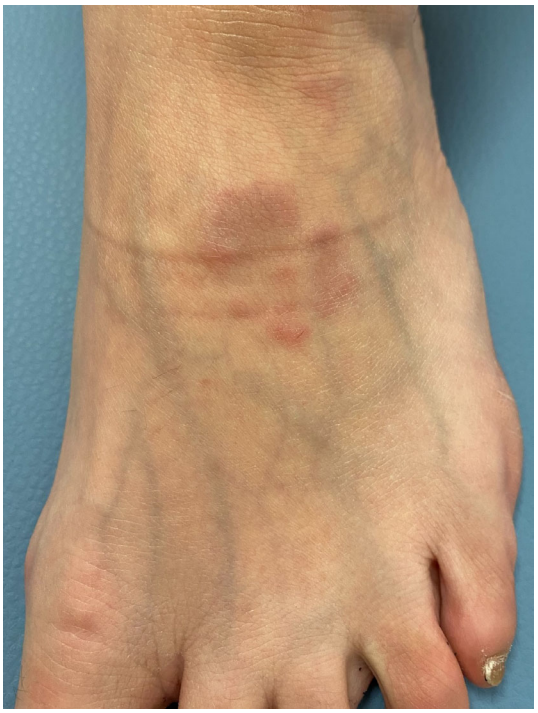

FIGURE 1 3 × 4 cm papular lesion on the dorsum of the foot

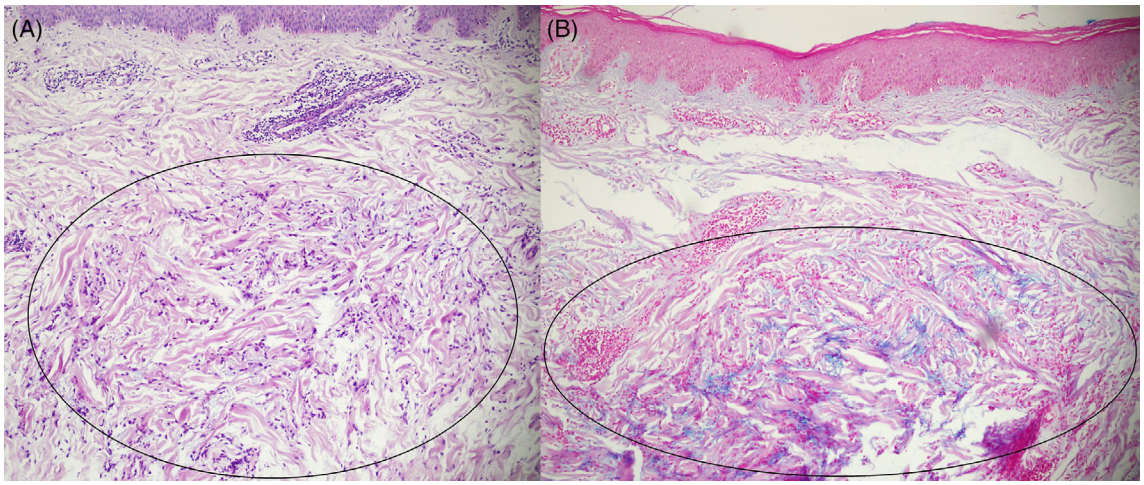

FIGURE 2 (A) In the upper dermis, histiocytic inflammation is noted between mononuclear cells and collagen bundles around the vessels. (B) Increased dermal mucin with Alcian blue is observed in the dermis

SARS-CoV-2 spike proteins. GA is thought to occur with the activation of the immune system triggered by the virus, rather than the direct effect of the virus on the skin.[3] In our patient, the lesion disappeared within 10 days following the skin biopsy. Therefore, the virus could not be detected through a PCR test or immunohistochemical study by performing fresh skin biopsy from the skin. This is the second known case of GA associated with SARS-CoV-2 infection. As in the first reported incident, an interstitial pattern was also observed in the histopathology of our case. It has been suggested recently that interstitial granuloma anulare 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 infections and is self-resolving.[4] 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.

Many cutaneous findings related to the SARS-CoV-2 virus have been observed but their etiopathogenesis has not been explained. Dermatological findings reported to be associated with SARS-CoV2 during the COVID-19 pandemic include maculopapular rash, urticaria, vesicular rash, petechiae, purpura, chilblains, livedo racemosa, and distal ischemia. Specific skin manifestations of the COVID-19 pandemic are gaining attention as they may be useful in the triage and risk stratification of COVID-19 positive patients.[5] Our case as well as the previous reported case support the idea that GA may be one of the reactive dermatoses that can occur after a SARS-COV-2 infection.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Selma Emre: The corresponding author; writing and reviewing manuscript. **Esranur Unal:** Collecting patient information. **Burak Celik:** Writing manuscript. **Nuran Sungu:** Performing histopathological examination.

INFORMED CONSENT

Written informed consent was obtained from the patient for the use of image.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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