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Manuscript title: Erythema annulare centrifugum with peri-eccrine inflammation triggered by SARS-CoV-2 infection.

Running title: EAC triggered by SARS-CoV-2 infection

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Dear editor,

Erythema annulare centrifugum (EAC) is a rare skin disease that typically presents with annular or polycyclic erythematous lesions on the trunk and proximal extremities, often with a trailing scale. The etiopathogenesis of EAC is still unknown, but it is thought to be a delayed-type hypersensivity response to a wide variety of antigens. Although in most cases no causative agent can be detected (idiopathic EAC), several trigger factors have been reported in indexed literature, including infections, malignancies, drugs, endocrine and autoimmune disorders. (1) A few cases of EAC triggered by SARS-CoV-2 infection (2) and COVID-19 vaccination (3) have also been described.

We report here a case of a 57-year-old woman with a 6 months history of a figurate rash. It started as a few erythematous papules on the abdomen which gradually enlarged centrifugally, then cleared centrally. Three weeks before the onset of the lesions, she was diagnosed with SARS-CoV-2 infection, confirmed by real-time polymerase chain reaction (RT-PCR). She had only mild symptoms of fever, sore throat, headache and malaise of 10 days duration, treated with paracetamol 500 mg/day, followed by a negative RT-PCR on nasopharyngeal swab sample performed one week later. The patient was otherwise in good health with no other significant medical conditions and she did not take any drug habitually.

Dermatological examination revealed multiple erythematous annular plaques with central clearing and a delicate peripheral scaling on the abdomen (Figure 1a, 1b) and upper arms. Potassium hydroxide examination of skin scrapping was negative for fungi.

Histopathology showed superficial perivascular lymphocytic infiltrate (Figure 1c, 1d) and perieccrine infiltrate (Figure 1d, 1e).

The clinicopathologic correlation led us to the diagnosis of EAC.

The patient was treated with a mild potency corticosteroid cream and a complete resolution of the lesions was obtained in 2 months.

EAC is a major figurate dermatitis categorized into superficial and deep variants. Histopathology of superficial EAC characteristically shows a dense lymphocytic infiltrate surrounding superficial vessels, which is known as a ‘coat sleeve’ appearance. Parakeratosis, spongiosis and basal layer vacuolization may be present. (2)

Peri-eccrine lymphocytic infiltration is not a histological feature of EAC, but it is commonly found in another figurate dermatitis: erythema papulatum centrifugum (EPC), which must be included in differential diagnosis. EPC differs from EAC in clinical manifestation, showing annular rings composed of grouped tiny papules (4), that in our case were not present.

Peri-eccrine lymphocytic infiltrate is a feature already described in other COVID-19 related cutaneous manifestations such as chilblain-like lesions, erythema multiforme-like eruption and

maculopapular eruption and can be explained as consequence of the presence of SARS-CoV-2 particles or antigens in the epithelial cells of the eccrine glands (5).

Herein we have described a unique case of superficial EAC with peri-eccrine inflammation. The temporal association with SARS-CoV-2 infection led us to believe they were associated. Although EAC has been observed in association with drugs (amitriptyline, cimetidine, finasteride, etizolam, aldactone, gold thiomalate, aceclofenac, immunotherapy agents, ustekinumab, chloroquine and hydroxychloroquine), paracetamol administration during viral infection is not a concausal molecule like triggering EAC. However, it is not possible to exclude that paracetamol may have had an initial role in the pathogenesis.(6)

SARS-CoV-2 infection may induce an immune response dysregulation, with release of tumor necrosis factor alpha (TNF-alpha) and other proinflammatory cytokines that could be involved the pathogenesis of EAC. (2) The presence, in our case, of peri-eccrine inflammation does not exclude the possibility of the direct involvement of the virus particles or antigens in the pathogenesis.

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All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

FIGURES

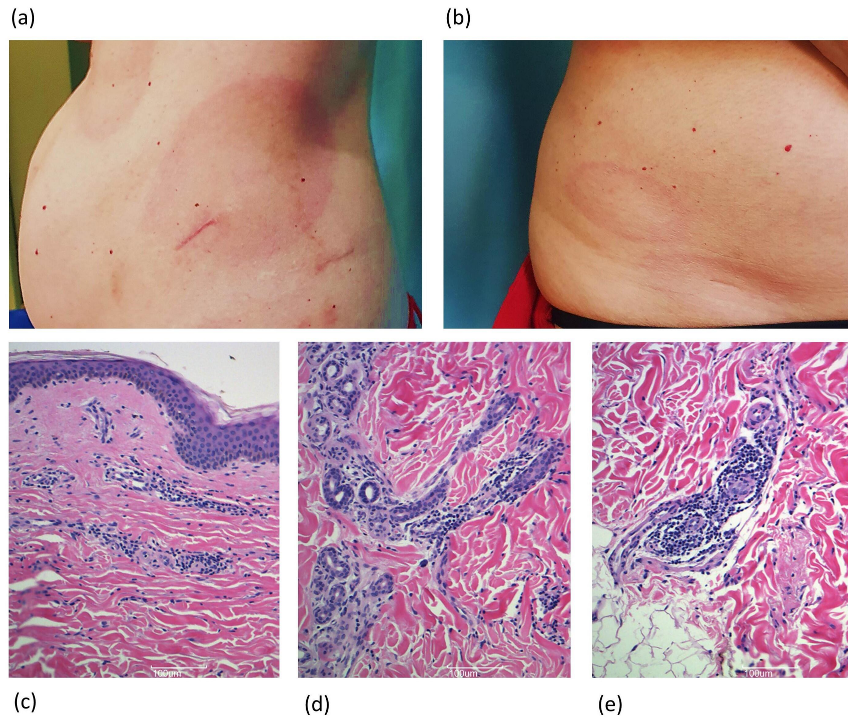

Figure 1. Erythematous annular plaques with central clearing on the abdomen (a,b); superficial perivascular lymphocytic infiltrate, Hematoxylin & Eosin stain, magnification ×4 (c); perivascular and perieccrine lymphocytic infiltrate, Hematoxylin & Eosin stain, magnification ×10 (d); perieccrine lymphocytic infiltrate, Hematoxylin & Eosin stain, magnification ×10 (e).