



Case Report

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Erythema Multiforme-Like Lesions: Covid-19? A Case Report

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Introduction

Cutaneous manifestations in patients with COVID-19 infection are being increasingly reported. Several patterns have been described, including erythematous maculo-papular, urticarial, chickenpox-like, purpuric peri-flexural, transient livedo reticularis, acro-ischemic or chilblain-like lesions, dengue-like petechial eruption and erythema multiforme-like lesions.

Erythema multiforme (EM) is an immune-mediated reaction that involves the skin and sometimes mucous membranes caused by infections, especially herpes simplex virus (HSV) and Mycoplasma pneumonia (MP), and medications such as hydroxychloroquine. It consists of a polymorphous eruption of macules, papules, and typical target lesions that are symmetrically distributed with a predilection for the distal extremities. MP-related EM has a distinct presentation compared with non-MP EM, with more diffuse and atypical targets, mucositis and respiratory tract sequelae. EM is a rare hydroxychloroquine-induced cutaneous adverse reaction with generalized distribution involving trunk, abdomen, back and mucous membranes [1-3].

The pathophysiological mechanism could be a cell-mediated immune reaction leading to pro-inflammatory cytokines production targeting Sars-Cov-2 antigens located in the skin [3]. COVID 19 positive patients often had localized acral targetoid lesions with no mucosal involvement and negative syphilitic serology. This clinical presentation, associated with cutaneous manifestations and their evolution, is suggestive of Sars-Cov-2-related EM rather than other causes [4].

Case Report

We report the case of a previously healthy 46 years old male, who required our medical attention during the last week of April because of the recent onset of erythema multiforme-like eruption, with no response to systemic corticosteroids. In March 2020, during the early phase of the COVID 19 pandemic, the patient developed low-grade fever, intense asthenia and chills, followed

by the appearance of chest tightness. Because of the persistence of symptoms, the 22th of March, the patient decided to go to the emergency room where he was subjected to nasopharyngeal swab and tested for SARS-CoV-2 RNA amplification, with positive result on the 23rd of March 2020. The patient was kept home, in solitary confinement, and after 10 days from the diagnosis, since there was no clinical improvement, on the advice of the general practitioner, he started therapy with azithromycin and hydroxychloroquine, the first one for the duration of seven days and the last one for the duration of ten days. 48 hours after stopping hydroxychloroquine administration, our patient showed skin lesions, specifically erythematous-oedematous papules first localized at the level of the face and palms, that progressively turned into erythematous-violaceous patches with a dusky center, with gradual appearance of typical target lesions, rapidly spreading to the whole skin area (Figure 1). General practitioner prescribed him oral corticosteroids (prednisone at the dosage of 50 mg/die) and oral antihistamines but there was no improvement for the following two weeks. During the first week of April, at the end of the 15-day isolation period, Two swabs for SARS-COVID-19 were performed (within 48 hours from each other), and both were negative. On the contrary, cutaneous lesions showed no improvement, requiring medical consultation (Figure 2). The patient had violaceous erythematous lesions with well-defined border and typical target features, especially on the palms and soles, some of them markedly coalescing mostly on the trunk and at the root of the limbs, minimally involving the face (Figure 3). Mucous membranes were spared. The patient also reported dysesthesia of hands and feet. Based on clinical features and medical history of recent viral infection as well as intake of drugs, we made the diagnosis of erythema multiforme. We decided to continue the ongoing therapy (prednisone 10 mg/die and oral antihistamines) and to perform PRIST, RAST for drugs, serology for cytomegalovirus, herpes simplex virus type 1 and type 2 and mycoplasma pneumoniae, together with a punch biopsy for histological examination, trying to understand if EM was due to SARS-COVID 19 infection or viral/atypical bacteria or drugs.



Figure 1: Skin rash with the characteristics of polymorphic erythema affecting the chest, upper limbs and hands. Erythematous patches with irregular, polycyclic contours.



Figure 2: Detail of the erythema in the forearm.



Figure 3: Detail of the erythema on the hand.

Discussion

We received medical test results after 10 days showing important data: Total serum IgE were 422.00 kUA/l (normal range

0-100), specific IgE were positive for ampicillin and amoxicillin, while IgM for CMV, HSV 1/2 and mycoplasma were all negative. Histological examination revealed a large area of edema in medium and deep dermis, accompanied by diffuse and accentuated fragmentation of collagen and elastic fibers. Small sized vessels were thrombotic having wall with sclerohyalinosis. purpuric, haemorrhagic suffusion and reactive fibroblasts were seen around extensive dermal mucinosis (Figure 4). There was also a mild inflammatory infiltrate in the absence of leukocytoclastic vasculitis. The histological findings were reminiscent of an Arthus-like type reaction of acute hypersensitivity mediated by antibodies directed against soluble antigens.

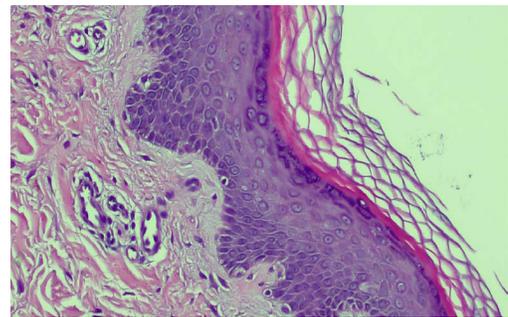


Figure 4: Preparation prepared and stained with Hematoxylin-Eosin showing small blood vessels with prominent “Hobnail” endothelium, mild chronic inflammatory infiltration, mainly perivascular lymphomonocyte.

The picture described is consistent with polymorphic Erythema because of phenomena of vacuolization of the keratinocytes of the basal layer typical of interface dermatitis. Differential diagnosis should be made with diseases such as Erythema Elevatum Diutinum (EED), Deep Annular Granuloma (GAP), and Pernial Erythema. From a histopathological point of view, our case did not present signs of leukocytoclastic vasculitis, the diagnostic clue of EED. The lesion showed an extensive damage to collagen and elastic fibers in the medium-deep dermis, similarly to GPA, but it lacks a real granuloma made up palisading histocytes and neighboring lymphocytes. It is certainly correct to put in place the similarities between our injury and the Erythema Pernio. Infact we also described a localized inflammatory lesion, with lymphocytic vasculitis, edema of the dermis, thickening of the vessel walls appearing as “fluffy edema” in the vessels (lymphocytes in the musculature of the vessels and around the glandular ducts).

We performed medical examination of the patient ten days after performing skin biopsy, during the removal of surgical staples: skin lesions were almost resolved with superficial desquamation and mild residual erythema. The patient did not complaint dysesthesia of palmo-plantar regions. We started oral corticosteroids withdrawal while suspending oral antihistamines.

Conclusions

New information and cutaneous manifestations possibly related to COVID-19 are emerging every day. Further studies are needed to evaluate whether these lesions are associated with the virus, the drug intake or any other conditions [1]. The vast majority of the studies reported no correlation between COVID-19 severity and skin lesions [5]. Keratinocytes may be a secondary target after Langerhans cells activation, inducing a spectrum of different clinical manifestations. It could be postulated that the virus does not target keratinocytes, but probably the immune response to infection leads to Langerhans cells activation, resulting in a state of vasodilation and spongiosis [5,6].

Erythema multiforme (EM) is triggered by infectious agents in 90% of the cases, while drug-associated EM is reported in less than 10% of cases. Herpes simplex virus (HSV) and *Mycoplasma pneumoniae* are the main agents, but other viruses have been reported, such as Adenovirus, Coxsackie, Parvovirus B19. Some studies suggest that this EM-like or target-like exanthema might be another pattern of COVID-19 associated exanthema. Recent papers also highlight targetoid lesions in patients with COVID-19 infection. In addition, the presence of pseudo-vesicles and enanthem are the two clues that suggest an infectious origin rather than a drug reaction [1], but hydroxychloroquine-induced erythema multiforme after 12 days of exposure [7]. However, we

cannot exclude the (role played by the several drugs administered to the patients?) involvement of several drugs administered to the patients [1].

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