Drug-induced severe cutaneous adverse reactions in a patient after COVID-19 infection. Case report

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ABSTRACT

During the COVID-19 pandemic, various adverse drug reactions were observed. This could have been related to a greater immunological susceptibility of patients with SARS-CoV-2 to present this type of symptoms, as well as exposure to multiple drugs used in their treatment. We report the case of a patient with a severe respiratory infection due to COVID-19, who presented 2 serious adverse drug reactions associated with paracetamol in a short period of time.

Key words: toxic epidermal necrolysis, acute exanthematous pustulosis, adverse drug reaction, SARS-CoV-2, COVID-19.

INTRODUCTION

In December 2019, Wuhan, China, became the center of an outbreak of pneumonia of unknown cause, which the World Health Organization (WHO) later named severe acute respiratory syndrome coronavirus 2 SARS-CoV-2 caused by coronavirus-2019 (COVID-19). This disease was declared a pandemic on March 12, 2020, due to increased infection rates outside China[1].

With the spread of the disease, multiple adverse drug reactions (ADRs) were reported in patients infected with COVID-19, which occurred concomitantly or consecutively. That may be related to the high number of drugs to which patients with severe disease were exposed, since during the first months of the pandemic, there was no standardized treatment for severe forms of the disease1-3. Likewise, SARS-CoV-2 has been reported to be associated with increased susceptibility to adverse drug reactions due to the immune system deregulation it causes[1,2].

CASE REPORT

A male patient, 40 years old, healthy, with no allergic history, of Chinese descent, was admitted for severe pneumonia due to COVID-19. Twenty-one days after hospitalization, he developed a confluent, erythematous, maculopapular, confluent exanthem with multiple pustules, involving the dorsum, flanks, buttocks, and inguinal region. Suspecting acute generalized exanthematous pustulosis (AGEP), it was decided to stop the suspicious drugs (colistin, midazolam, enoxaparin, omeprazole, and paracetamol), to perform laboratory studies and a skin biopsy. The laboratory showed leukocytosis (20 229/mm^3), neutrophilia (75.8%), and eosinophilia (7.5%, absolute count of 1523/cm^3), and the histopathological study showed the presence of subcorneal pustules, confirming the diagnostic suspicion. Due to the extensive involvement of the cutaneous surface, meprednisone 1 mg/kg/day was prescribed, and the patient evolved with a rapid involution of the cutaneous lesions and complete resolution after nine

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days. Due to this favorable evolution of the cutaneous involvement together with the resolution of pneumonia and because of the epidemiological discharge due to COVID-19, it was decided to discharge the patient. Three days later he consulted again for fever and erosions in the genital region. Physical examination revealed a non-pruritic erythematous maculopapular rash, flaccid blisters, typical and atypical targets on the trunk, and upper and lower limbs (Figs. 1 and 2).

In the genital region, there were mucosal erosions, irregular in shape and with an erythematous background. There were also Nikolsky's and Asboe-Hansen's signs. The denuded and potentially denudable skin surface was 10%. The patient reported that this condition began 24 hours after being discharged from the hospital after having decided to self-medicate with paracetamol and cephalexin because he had a fever at home. On interrogation, he mentioned that his brother had presented a similar condition with paracetamol years before. We decided to hospitalize the patient. Swabs of genital mucosal erosions were performed to detect antigens by immunofluorescence of herpes viruses I, II, and zoster, which were negative. The laboratory revealed leukocytosis (15,064/mm^3) with neutrophilia (83%) and eosinophilia (5.9%, absolute count 894/cm^3). Serologies for HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV) proved negative. A new skin biopsy was taken for histopathologic study, which revealed dermoepidermal detachment with confluent necrotic keratinocytes, findings compatible with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) (Fig. 3).

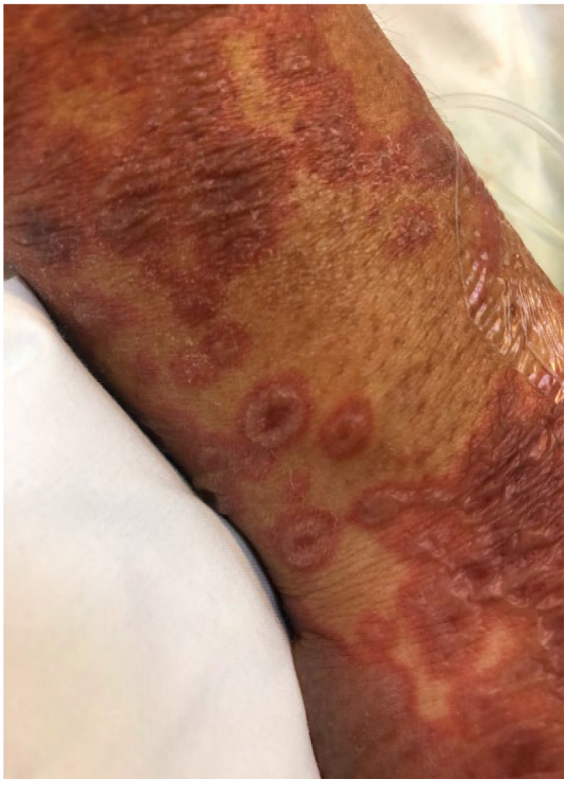

Figure 2. Presence of typical targets associated with morbilliform exanthema on the ventral aspect of the left wrist.

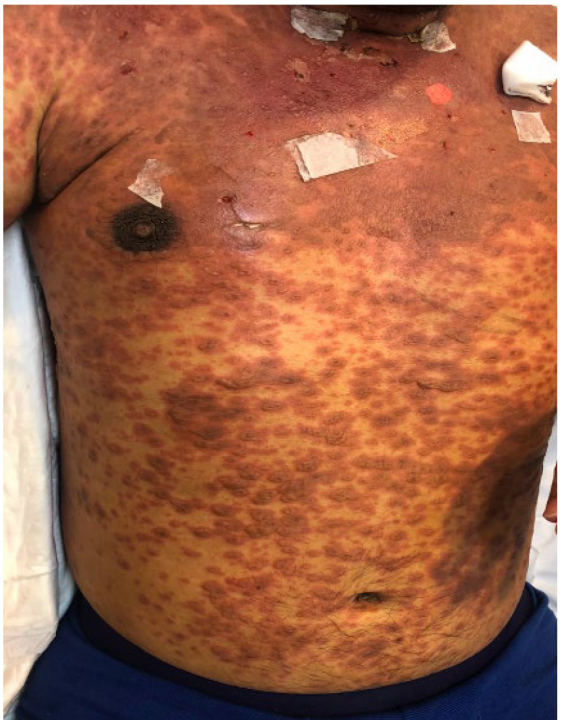

Figure 1. Erythematous morbilliform exanthem involving the patient's trunk showing target-like lesions and areas of cutaneous denudation.

The mortality score –ScoreTEN on day 1– was 3.2%. Methylprednisolone 1 g/day was prescribed for 3 days. The patient evolved with a rapid progression of the condition, with 90% of the body surface area involved 48 hours after admission, so it was decided to add cyclosporine 4 mg/kg/day intravenously. Ten minutes after the first infusion of this drug, he presented a diffuse erythematous rash, dyspnea (pulse oximetry normal), and pruritus, so we administered oxygen with a low-flow cannula, intravenous diphenhydramine, and discontinued cyclosporine. The condition appeared compatible with an infusion reaction caused by a cytokine storm and, more distantly, anaphylaxis. Because of this situation, it was decided –in an interdisciplinary manner with the medical clinic, allergy, and dermatology team– to change the treatment to intravenous gammaglobulin, 1 g/kg/day associated with methylprednisolone 1 mg/kg/day for 3 days[4-6]. The patient evolved favorably with complete re-epithelialization of the lesions in 5 weeks.

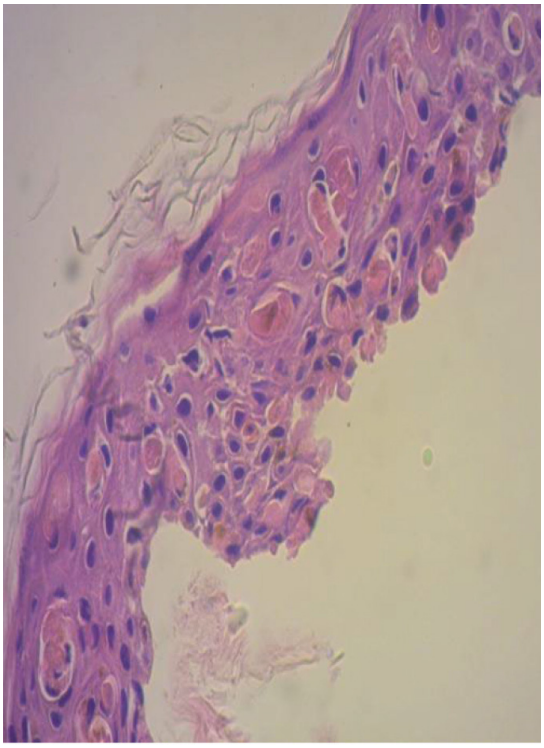

Figure 3. Dermoepidermal detachment with multiple necrotic keratinocytes.

DISCUSSION

The incidence of severe ADRs in patients with COVID-19 is unknown, although cases of AGEP, sensitivity to drugs with eosinophilia and systemic symptoms (DRESS), and SJS/TEN have been reported. The diagnosis of these reactions can be complex, since virus cutaneous manifestations have been described which may be indistinguishable from these. In such cases, the history of drug exposure, the clinical picture, complementary tests such as laboratory studies and skin biopsy may be useful to identify severe drug-related cases as in the reported patient[7].

We propose that SARS-CoV-2 infection produces an inflammatory environment that may lower the threshold for ADRs development. The reasons for this susceptibility are not fully understood, although multiple drug exposure, immune deregulation, presence of concomitant infections, genetic polymorphism, association with specific human leukocyte antigens (HLA), T-cell and monocyte involvement may be critical components of this link[6,7]. In turn, it has been reported that infections not only increase the risk of ADRs but also lead to more severe phenotypes, with a greater risk of systemic involvement and sequelae. This immunological dysregulation could explain the sequential occurrence of three types of severe ADRs in the same patient, something that has been exceptionally reported in the literature[8].

On the other hand, it has been reported that paracetamol or acetaminophen can trigger SJS/ TEN in patients with viral infections. This clinical scenario was studied in patients with HIV infection, who have been identified as having a higher probability of developing ADRs and a 100-fold higher risk of developing SJS/ TEN than the general population[9]. In relation to this, ethnic differences in HLA associated with SJS/TEN secondary to acetaminophen have been demonstrated. In Thai patients with SJS/TEN and severe ocular involvement, there was evidence of association with haplotypes HLA-B*44:03 - HLA-C*07:014-6 . The reported case highlights the fact that the patient had received paracetamol on multiple occasions without adverse effects and had a family history of ADRs secondary to paracetamol that had not been reported in the first evaluation. For this reason, we consider the possibility that –although the patient may carry an unstudied genetic predisposition that makes him susceptible– COVID-19 infection, through a complex interaction, may have been responsible for its clinical expression[4].

The specific treatment of severe cutaneous ADRs is supported by expert recommendations, mainly that of the SJS/TEN; however, it has been the object of controversy. Current evidence supports using intravenous gammaglobulin associated with corticosteroids, parenteral cyclosporine, and, more distantly, anti-TNF[6]. Although –in this patient– the response to methylprednisolone in association with intravenous gammaglobulin was favorable, the utility and safety of these drugs in the context of coexisting or recent COVID-19 infection have not yet been reviewed[2,6-11].

CONCLUSION

The incidence of severe ADRs in patients with COVID-19 is unknown, although AGEP, DRESS, and SJS/TEN have been reported. The relevance of this case lies in considering that a recent history of SARS-CoV-2 infection may be a risk factor for developing this type of symptoms, although we emphasize that further studies are needed to confirm this hypothesis.

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Conflict of interest: the authors declare that they have no conflict of interest.

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