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TOXICODERMA AS AN ADVERSE EVENT IN A COVID-19 PATIENT: CASE REPORT

Keywords: COVID-19; Coronavirus Infections; Drug-Related Side Effects and Adverse Reactions; Medication Therapy; Lopinavir.

Palabras clave: COVID-19; Infecciones por coronavirus; Efectos colaterales y reacciones adversas relacionados con medicamentos; Hidroxicloroquina; Lopinavir.

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RESUMEN

Introducción. La infección por SARS-COV2, que en principio se pensó solo causaba manifestaciones respiratorias, también puede ocasionar síntomas gastrointestinales, renales, neurológicos, cardiovasculares e incluso cutáneos según algunos reportes.

Presentación del caso. Paciente femenina de 36 años quien asistió al servicio de urgencias por cuadro clínico consistente en disnea, astenia, adinamia, odinofagia leve y cefalea. Como antecedentes de relevancia se registró obesidad, tabaquismo y ocupación como trabajadora de la salud. Dados los síntomas, se indicó tratamiento antimalárico y antirretroviral para tratar COVID-19, diagnóstico que fue confirmado a los tres días de ingreso, pero al cuarto día de instaurado este manejo la mujer presentó polidipsia y *rash* macular, pruriginoso y generalizado. Por sospecha de toxicodermia, el tratamiento fue suspendido y con esto el cuadro cutáneo mejoró. Luego de 8 días de hospitalización, la paciente recibió el alta, junto con recomendaciones de bioseguridad y confinamiento durante 28 días.

Conclusiones. El caso descrito corresponde a un evento de toxicodermia en una paciente con COVID-19 en manejo con antirretroviral y antimalárico. A partir de los hallazgos, se establece que la exploración minuciosa de piel y mucosas en los pacientes con sospecha o diagnóstico confirmado de COVID-19 puede ser de gran ayuda para la correcta caracterización de esta nueva enfermedad.

Palabras clave: COVID-19; Infecciones por coronavirus; Efectos colaterales y reacciones adversas relacionados con medicamentos; Hidroxicloroquina; Lopinavir.

ABSTRACT:

Introduction: SARS-COV2 infection, which was initially associated with respiratory manifestations only, can also cause gastrointestinal, kidney, neurological and cardiovascular symptoms according to some reports.

Case presentation: A 36-year-old female patient attended the emergency department due to dyspnea, asthenia, adynamia, mild odynophagia and headache. The patient's medical history included obesity, smoking, and working as a health care worker. Considering the symptoms, antimalarial and antiretroviral treatment was indicated to treat COVID-19, a diagnosis that was confirmed three days after admission. However, on the fourth day of treatment, the patient presented with polydipsia and macular, pruritic, and generalized rash. Due to suspicion of toxicoderma, the treatment was suspended, and the skin condition improved. After 8 days of hospitalization, the patient was discharged with biosecurity recommendations and mandatory isolation for 28 days.

Conclusion: The described case is a report of toxicoderma in a patient with COVID-19 under treatment with antiretroviral and antimalarial drugs. Based on the findings, a thorough examination of skin and mucosa of patients with suspected or confirmed COVID-19 will undoubtedly contribute to the correct characterization of this new disease.

Keywords: COVID-19; Coronavirus Infections; Drug-Related Side Effects and Adverse Reactions; Medication Therapy; Lopinavir.

INTRODUCTION

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. The first cases were reported in December 2019 and it was declared a pandemic by the World Health Organization in March 2020 given the high rate of contagion and rapid global spread. Such is the impact of this condition that about 36.3 million cases and one million deaths had been reported by mid-October 2020 worldwide (1).

The SARS-CoV-2 infection has been characterized mainly by respiratory symptoms; however, since the onset of the pandemic, different manifestations of the disease have been reported, including gastrointestinal, kidney, neurological, and cardiovascular symptoms (2-4). Although less common, skin manifestations associated with COVID-19 have also been reported (5).

The following is the first case of an adult patient diagnosed with COVID-19 in Bogotá, Colombia, who presented with skin manifestations due to an adverse dermatological reaction associated with the therapy established to treat this disease. It is worth mentioning that, at the time of writing this case report, there is no proven treatment for patients with COVID-19.

CASE PRESENTATION

A 36-year-old female patient from Bogotá, with low socioeconomic status and a health care worker, was admitted to the emergency department of a quaternary care center located in Bogotá due to dyspnea, asthenia, adynamia, mild odynophagia, and headache. The woman reported a history of obesity, smoking and epidemiological nexus with COVID-19.

Although the patient was alert and oriented on admission, tachycardia and tachypnea were observed; during the physical examination,

she had wet mucous membranes, anicteric sclerae, normochromic conjunctiva, no adventitious sounds, and skin in normal condition. Lab test results yielded the following values: lactate dehydrogenase: 191.8 U/L, hemoglobin: 14.2 g/dL, leukocytes: 6 130 (cells/mL), neutrophils: 64.5%, lymphocytes: 22.3% and platelets: 152 000 (cells/mL). Furthermore, computerized axial tomography of the chest was performed, which showed ground-glass opacity in the middle lobe medial segment. She was admitted to the hospital, and a nasopharyngeal swab was collected to perform an RT-PCR test and confirm the diagnosis of COVID-19; the result of this test was available 3 days later and was positive.

From the first day of hospital stay, compassionate drug treatment (6) was initiated with dual therapy (antimalarial and antiretroviral). Hydroxychloroquine 200mg every 12 hours prior to a 400mg intravenous loading bolus and lopinavir plus ritonavir 400mg every 12 hours were administered. On the fifth day of symptom onset and fourth day of treatment, the patient presented polydipsia and macular, pruritic, and generalized rash that started in the face and advanced to the trunk and limbs with macules and papules that disappeared when pressed, without mucosal involvement.

Given the new symptoms, a sample was taken for arterial blood gases. pH was 7.33, pCO₂ 68.3, pCO₃ 16.9, and lactate 4.03 mmol. A single dose of hydrocortisone 200mg IV was administered; however, pruritic rash and facial warmth persisted, so loratadine 10mg every 12 hours was prescribed for one day, followed by a switch to diphenhydramine hydrochloride 50mg every 12 hours orally for 2 days. On day six of hospitalization, and due to suspected toxicoderma, antimalarial and antiretroviral treatment was discontinued, resulting in improved skin symptoms.

The patient was discharged after eight days of hospitalization; during that period, no supplemental oxygen or ventilatory support was required, but she did present an episode of fever treated with ampicillin/sulbactam (3g every 6 hours) and piperacillin/tazobactam (4.5g every 6 hours). On discharge, recommendations were given for 28-day isolation and antibiotic treatment with oral moxifloxacin.

DISCUSSION

At the time of writing this case report, a dilemma arose as to whether to consider the patient's skin symptoms as a cutaneous manifestation associated with COVID-19 or as an adverse reaction to the use of hydroxychloroquine and lopinavir/ritonavir for the treatment of that disease. Given this scenario, the available literature was reviewed, and some case reports and case series were found documenting skin manifestations associated with COVID-19 and a single report of an adverse event due to chloroquine use.

The first series of cases published was prepared by Recalcati (7), who, from a cohort of 88 cases with COVID-19 treated at the Lecco Hospital in Lombardy, Italy, established that 18 patients developed skin manifestations, of which 8 had skin involvement on admission and 10 after hospitalization. The lesions identified in this study were erythematous rash (14 patients), generalized urticaria (3 patients), and varicelliform eruptions (1 patient). The most compromised body region was the chest with mild or absent pruritus and spontaneous resolution of the lesions within a few days.

Another case series in 8 dermatological units reported skin lesions in 22 patients with COVID-19, who presented with slightly pruritic papulovesicular varicelliform exanthem, predominantly thoracic, with a range of 4 to 15 days of duration and without facial or mucosal

involvement. Other associated symptoms were fever (95.5%), cough (73%), headache (50%), asthenia (50%), rhinorrhea (45%), dyspnea (41%), hyposmia (18%), hypogeusia (18%), odynophagia (4.5%), diarrhea (4.5%), and myalgia (4.5%) (8).

Magro *et al.* (9) attempted to define the role of complement system activation and microvascular thrombosis in 5 patients with severe and persistent manifestations of COVID-19. To this end, they studied lung and skin tissue with lesions (retiform purpura) and without lesions, finding deposits of terminal complement components C5b-9 and C4d in the microvasculature. This suggested that some serious cases of this disease may have a microvascular lesion syndrome mediated by the pathways of complement activation and an associated procoagulant state.

Also, some case reports describe skin manifestations in adults and children such as petechiae, erythema, rash, urticaria, and livedo reticularis in the presence of COVID-19, although most of these patients are asymptomatic and have no histologic support (10-13). Finally, Hunt & Koziatek (14) published the case of a patient with SARS-CoV-2 infection who had generalized fever and rash, maculopapular and non-pruritic morbilliform eruptions, and required ICU management.

Toxicoderma is an adverse skin reaction associated with the use of medicines. Its clinical presentation may vary in terms of injury types and severity, so the diagnosis must be rapid and accurate to establish appropriate treatment (15). Maculopapular rash is a common manifestation of toxicoderma located mainly in the limbs and trunk and does not affect the mucous membranes. Toxicoderma lesions resolve with discontinuation of the causal drug (16). It should be noted that Huang *et al.* (17) reported the presentation of rash as

an adverse event in a patient with COVID-19 who received chloroquine.

With this in mind, and in the face of the clinical case presented, it was established that the dermatological manifestation of the patient was an adverse event to treatment with hydroxychloroquine and lopinavir/ritonavir since there was initial facial involvement, accompanied by flushing and heat, which improved after discontinuation of this treatment.

It is worth remembering that the use of hydroxychloroquine and lopinavir/ritonavir for the compassionate management of COVID-19 was initially based on the compatibility of SARS-CoV-2 with other viruses (studied *in vitro* and modeled). However, its use is not recommended currently due to the adverse cardiovascular events that they may cause (18).

Currently, physicians and scientists are investigating the skin manifestations of COVID-19, their physiopathological mechanism, and characteristics in different population groups. They emphasize the importance of promoting among clinicians the identification of skin lesions without apparent cause, as they may be diagnostic tools that guide the clinical suspicion of COVID-19 and the implementation of preventive isolation measures that contribute to reducing virus transmission (19-21). In this way, a thorough examination of the skin and mucous membranes of patients with confirmed or suspected COVID-19 helps to correctly characterize this new disease and establish its possible relationship with adverse drug reactions, as happened in the present case.

In summary, the authors consider it necessary for health professionals to report adverse events associated with compassionate drugs since this information will guide clinical practice, at least while drug efficacy and safety results for COVID-19 are available.

This report recognizes as a limitation that no confirmatory biopsy of the skin manifestation was performed.

CONCLUSIONS

According to the findings and the literature, the case described is an event of toxicoderma in a patient with COVID-19 under antiretroviral and antimalarial treatment. However, it is clear that there is still much to be said about this disease, and further research on its manifestations is needed.

In this sense, a thorough examination of the skin and mucous membranes of patients with suspected or confirmed diagnosis of COVID-19 will be useful to characterize the disease correctly.

ETHICAL CONSIDERATIONS

The present report did not pose any risk to the patient because it synthesized retrospective information. The patient consented to the review of her medical records and authorized the publication of her case for academic and scientific purposes.

CONFLICTS OF INTEREST

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