Remdesivir-Induced Nonimmediate Cutaneous Hypersensitivity Reaction

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Remdesivir (GS-5734) is a prodrug of an adenosine nucleotide analogue with potent antiviral activity against filoviruses, paramyxoviruses, pneumoviruses, and coronaviruses. After being outperformed by monoclonal antibodies for the treatment of Ebola virus during the 2014-2016 Ebola outbreak in West Africa, it remained unused until the outbreak of the coronavirus disease 2019 (COVID-19) pandemic. Phase 3 trials of remdesivir in COVID-19 were initiated in February 2020 and received an emergency use authorization by the United States Food and Drug Administration [1,2]. Since the drug was first used for the treatment of COVID-19, the adverse events reported include increased hepatic enzymes, diarrhea, and skin reactions [3]. We report a case of maculopapular exanthema induced by remdesivir confirmed by patch tests (PTs) and intradermal skin tests (IDTs).

A 75-year-old woman with a medical history of asthma and obstructive sleep apnea-hypopnea syndrome was admitted to the hospital with double pneumonia and respiratory failure caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The absence of response to high-flow oxygen, continuous positive airway pressure, and an intravenous bolus of corticosteroids led us to initiate remdesivir (single loading dose of 200 mg on day 1 followed by once-daily maintenance doses of 100 mg). Since the first day of treatment with remdesivir, the patient reported burning and itching affecting her back, with no skin lesions. Twenty-four hours after the sixth dose of remdesivir, she developed an erythematous maculopapular exanthema on her back and submammary area. Remdesivir was discontinued, and treatment with parenteral antihistamines and corticosteroids was administered. The exanthema spread to the trunk, abdomen, and limbs during the following 4 days, with subsequent improvement and complete resolution 9 days after withdrawal of remdesivir. The lesions resolved without hyperpigmentation or desquamation. No systemic symptoms, vesicles, blisters, pustules, or mucous membrane involvement were observed. Laboratory tests revealed neither eosinophilia nor hepatic dysfunction.

A skin biopsy of the left arm revealed a superficial perivascular lymphocytic infiltrate, as well as an eosinophil-rich infiltrate throughout the dermis, compatible with toxicoderma (Figure, A).

During admission, the patient underwent a CT scan with iohexol, an intravenous iodinated contrast medium (ICM). The contrast was administered 24 hours before the exanthema spread. However, the skin lesions were already present when it was administered.

An allergy work-up was performed after obtaining the patient's written informed consent.

ICM allergy was ruled out by performing undiluted PTs, undiluted prick tests, and undiluted IDTs with optimal and nonirritant doses (0.1 and 1 mg/mL) of iohexol, iodixanol, ioversol, and iopromide. The results were negative in the immediate and delayed readings. A controlled intravenous challenge test was then carried out with the culprit ICM, iohexol. Increasing doses of iohexol administered at 1-hour intervals in 2 runs separated by 1 week (5-10-15 cc with a cumulative dose of 30 cc on the first day and 20-30-50 cc

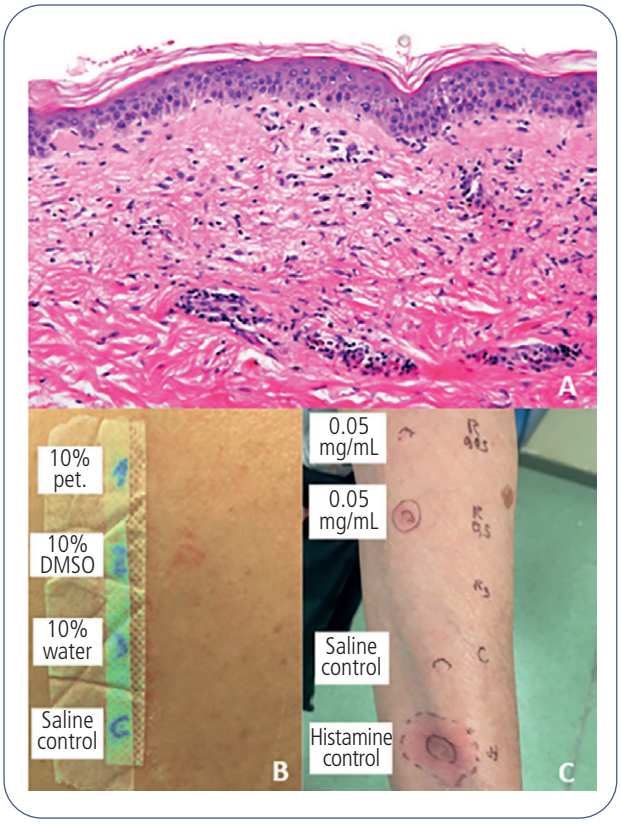

Figure. A, Skin biopsy. Perivascular lymphocytic infiltrate and eosinophil-rich infiltrate throughout the dermis, consistent with toxicoderma (hematoxylin-eosin, ×200). B, Patch tests with remdesivir at 10% in petrolatum, DMSO, and water at 96 hours after application: micropapules were observed in chamber 2 (remdesivir 10% in DMSO). C, Intradermal tests with remdesivir at 0.05 mg/mL and 0.5 mg/mL in the immediate reading: a positive result with a wheal diameter >3 mm and surrounding erythema can be observed at the concentration of 0.5 mg/mL.

with a cumulative dose of 100 cc on the second day) yielded a negative result.

The patient subsequently underwent PTs and IDTs with remdesivir. According to the European Society of Contact Dermatitis and the European Network on Drug Allergy, PTs were prepared at 10% in petrolatum, 10% in dimethyl sulfoxide (DMSO), and 10% in water and placed on the skin of the upper back [4]. Readings at 48 and 96 hours revealed a positive result for DMSO (Figure, B). IDTs at 0.05 mg/mL yielded a negative result, whereas the concentration of 0.5 mg/mL elicited a positive result 20 minutes after application (Figure, C). Delayed readings of IDTs were negative at both concentrations. IDTs with remdesivir at 0.5 mg/mL were negative in 5 healthy volunteers.

The condition was diagnosed as remdesivir-associated nonimmediate hypersensitivity reaction, and the patient was advised to avoid remdesivir.

Since COVID-19 was first reported in Wuhan, China, remdesivir has seldom been responsible for hypersensitivity reactions. Heck et al [5] reported symmetrical drug-related intertriginous and flexural exanthema due to remdesivir in a 67-year-old man with COVID-19. The likelihood of remdesivir being the culprit drug was established by applying the Naranjo Adverse Drug Reaction Probability Scale [6]. Azmy et al [7] reported idiopathic nonhistaminergic acquired angioedema as a complication of SARS-CoV-2 infection in a 29-year-old woman admitted to the intensive care unit. Although the suspected etiology was the hyperinflammatory syndrome seen in severe COVID-19, the patient had received remdesivir, among other drugs, until 3 days before onset of angioedema.

We report a case of nonimmediate hypersensitivity reaction to remdesivir, which manifested as maculopapular exanthema. The clinical course, skin biopsy, and positive PT and IDT results confirmed the diagnosis.

We acknowledge that the positive IDT result in the immediate reading was not consistent with the delayed positive result in PT. Initially, we thought this could be due to an irritant response to a high concentration of remdesivir or a possible IgE-mediated mechanism. However, IDTs performed at the same concentrations in healthy volunteers ruled out the possibility of an irritant response, and the clinical manifestations, histopathological findings, and PT result suggested a delayed hypersensitivity mechanism.

To the best of our knowledge, we report the first case of remdesivir allergy confirmed by positive results in PT and IDT. Distinguishing between cutaneous manifestations of COVID-19 and adverse reactions to remdesivir can be challenging. Therefore, it is important to perform an allergy work-up to clarify the etiology of skin lesions [8].

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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