

## Remdesivir-induced non-immediate cutaneous hypersensitivity reaction

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Remdesivir (GS-5734) is a prodrug of an adenosine nucleotide analogue with a 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 novel coronavirus disease 2019 (COVID-19) pandemic broke out. Phase III trials of remdesivir in COVID-19 were initiated on February 2020 and received an emergency use authorization by FDA [1,2]. Since its use for the treatment of COVID-19 began, adverse events were reported, such as increased hepatic enzymes, diarrhea, and skin reactions, among others [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 due to double pneumonia and respiratory failure caused by severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) infection. Because of a lack of response to high-flow oxygen, continuous positive airway pressure and intravenous bolus of corticosteroids, remdesivir treatment

was initiated with a 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, she reported burning and itching in her back without appearance of any skin lesions. Twenty-four hours after the sixth dose of remdesivir, she developed an erythematous maculopapular exanthema on her back and submammary area. Remdesivir treatment was discontinued and she was treated with parenteral antihistamines and corticosteroids. Exanthema spread to the trunk, abdomen and limbs during the next four days, with subsequent improvement and complete resolution nine days after remdesivir withdrawal. The lesions resolved without hyperpigmentation or desquamation. No systemic symptoms, vesicles, blisters, pustules or mucous membrane involvement were observed. Neither eosinophilia nor hepatic dysfunction appeared in laboratory tests.

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

During the hospital admission, the patient underwent a CT scan imaging with iohexol, an intravenous iodinated contrast media (ICM). The contrast was administered twenty-four hours before the exanthema spread. However, the patient already presented the skin lesions when it was administered.

After obtaining the patient written informed consent, an allergy work-up was started.

Iodinated contrast media (ICM) allergy was ruled out by performing undiluted patch tests (PTs), undiluted prick tests and intradermal skin tests (IDTs) with optimal and

nonirritant doses (0.1 and 1 mg/mL) of ICM iohexol, iodixanol, ioversol and iopromide with a negative result at immediate and delayed readings. Subsequently, a controlled intravenous challenge test with the culprit ICM, iohexol, was carried out. Increasing doses of iohexol at 1-hour intervals in two 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 with a cumulative dose of 100 cc on the second day) were administered, yielding a negative result.

Later on, the patient underwent PTs and IDTs with remdesivir. According to the ESCD (European Society of Contact Dermatitis) and the ENDA (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 upper back skin [4]. Readings at 48 and 96 hours revealed a positive result in DMSO (Figure B). IDTs at 0.05 mg/mL showed a negative result while the concentration of 0.5 mg/mL elicited a positive result twenty minutes after its application (Figure C). Delayed readings of IDTs were negative at both concentrations. IDTs with remdesivir at 0.5 mg/mL were negative in five healthy control volunteers.

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

Since the novel coronavirus disease 2019 (COVID-19) was first reported in Wuhan, remdesivir has been seldom responsible for hypersensitivity reactions. Heck et al. [5] described a SDRIFE due to remdesivir on a 67-year-old male suffering from COVID19. 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 an

idiopathic nonhistaminergic acquired angioedema as a complication of SARS-CoV-2 infection, in a 29 year-old woman admitted in the intensive care unit. Although the etiology was suspected to be due to the hyperinflammatory syndrome seen in severe COVID19, the patient had received remdesivir, among other drugs, until three days before the development of the angioedema.

We report a case of non-immediate hypersensitivity reaction to remdesivir manifested as a maculopapular exanthema. The clinical course, skin biopsy and positive PTs and IDTs results confirmed the diagnosis.

We acknowledge that the positive IDT result on 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 Ig E-mechanism involved. 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 highly suggested a delayed hypersensitivity mechanism.

To the best of our knowledge, we describe the first case of remdesivir allergy confirmed with positive PTs and IDTs. Distinguishing between cutaneous manifestations of COVID-19 and remdesivir adverse reactions can be a challenge, which is why we consider important to perform an allergy evaluation 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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**Figure A.**

A) Skin biopsy. Perivascular lymphocytic infiltration and eosinophil-rich infiltrate throughout the dermis, consistent with toxicoderma (HE x200). B) PTs with remdesivir at 10% in petrolatum, DMSO and water at 96 hours after application: micropapules were observed at chamber 2 (remdesivir 10% in DMSO). C) IDTs with remdesivir at 0.05 mg/mL and 0.5 mg/mL at immediate reading: a positive result with a wheal diameter higher than 3 mm and a surrounding erythema can be regarded at the concentration of 0.5 mg/mL.

