Role of Drug Hypersensitivity in the Cutaneous Manifestations of SARS-CoV-2 Infection

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At the beginning of the SARS-CoV-2 pandemic, various types of skin lesions were reported during the infection period [1]. The first reports of cutaneous manifestations described 6 types of skin lesions: maculopapular exanthems, urticarial exanthems, vesicular exanthems, erythema multiforme, cutaneous vasculitis, and chilblain-like lesions [2]. Many affected patients had been exposed to different treatments. Consequently, we do not know whether some of the skin lesions that presented during the so-called first wave could be secondary to drug hypersensitivity [3].

We conducted a prospective, observational, and descriptive study whose main objective was to determine whether drug hypersensitivity could have been a cause of skin lesions in patients admitted to our hospital with SARS-CoV-2 infection between March and May 2020. A total of 72 patients with skin lesions were admitted to the Allergology Department and/or Dermatology Department (see Supplementary Material). According to the algorithm of the Spanish Pharmacovigilance System (ASPS) [4], which assess drug reaction as a possible cause of the skin lesions, drugs may have been involved in 37 of the 72 patients. All these patients had received azithromycin, hydroxychloroquine, lopinavir/ritonavir, and/or ß-lactam antibiotics. Sixteen of the 37 patients consented to remain in the study. The types of lesions observed and confirmed by histology were maculopapular exanthem (n=5), urticarial exanthem (n=5), vesicular exanthem (n=4), cutaneous vasculitis (n=1). and chilblain-like lesion (n=1). The mean time from initiation of treatment to skin manifestations was 7.5 days (range, 1-15 days). No patient presented an immediate reaction during treatment.

We designed a study protocol that included patch testing and a drug provocation test (DPT) with the drugs used during treatment. Patch tests with azithromycin 5% and 10% pet, hydroxychloroquine 5% and 10% pet, lopinavir/ritonavir 1% and 5% pet, and ß-lactam antibiotics (amoxicillin, clavulanic acid, and ceftriaxone; 1% and 5% pet) were performed 4-6 months after hospital discharge [5]. In the case of ß-lactam antibiotics, prick and intradermal skin tests with late readings were also performed prior to DPT. No positive results were found at the 24-, 48-, and 96-hour readings. DPT with the drugs involved were carried out on alternative days. Fifteen of the 16 patients studied underwent DPT with the drugs administered. One patient with cutaneous vasculitis did not undergo DPT. Results were positive for DPT in 3 patients (18.75%), azithromycin in 2 patients (one presented a late maculopapular exanthem and the other a vesicular exanthem), and clavulanic acid in 1 patient (maculopapular exanthem). The lesions were identical to those observed during the infection period (Table).

Recalcati et al [2] classified skin lesions into 3 groups, namely, exanthems, vascular lesions, and miscellaneous manifestations, reporting a prevalence of 67.3% for exanthems (maculopapular, 38.5%; urticarial, 11.5%; vesicular, 9.6%; erythema multiforme, 7.7%), 21.2% for vascular lesions (vascular, 13.5%; chilblain-like, 7.7%), and 11.5% for miscellaneous manifestations [2]. In our study, we observed a similar pattern of skin lesions, with 87.5% (14/16 patients) presenting with exanthems and 12.5% (2/16 patients) presenting with vascular lesions. It is not clear why patients with the same type of infection have very different presentations of skin lesions. Potential etiologic-pathogenic mechanisms have been described, especially for chilblain-like lesions that reflect perivascular and perieccrine inflammation with markers of significant interferon 1 activation [6] or cutaneous vasculitis due to thrombotic vasculopathy with involvement of interleukins such as IL-6 [7].

Patients with SARS-CoV-2 infection admitted to the hospital during the first wave were treated with a combination of mainly azithromycin, hydroxychloroquine, lopinavir/ritonavir, and/or ß-lactam antibiotics, all of which have the potential to trigger hypersensitivity reactions [8,9]. In our study, 3 patients presented with exanthematous skin lesions due to drug hypersensitivity confirmed by DPT. Patch tests were performed 4-6 months after discharge. It remains unclear whether this inappropriate timing of testing (according to the European Network on Drug Allergy guidelines) could have led to the negative results recorded for DPT-positive patients.

Cutaneous findings were scarcely reported during the second wave of the pandemic in June 2020. The 3 potential

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Table. Clinical and Analytical Characteristics of the Patients Who Underwent an Allergy Study

Patient	Skin lesions during SARS-CoV-2 infection	Histopathological study	Drugs administered	Patch test[a]	DPT[b]	Skin lesions after DPTX
1	Maculopapular exanthem	Perivascular infiltrate of lymphocytes and eosinophils, epidermal spongiosis, hematic extravasation, and necrotic keratinocytes	A, H, L/R	-	-	NA
2	Maculopapular exanthem		A, H, L/R, Cef	-	-	NA
3	Maculopapular exanthem		A, H, L/R, Cef	-	-	NA
4	Maculopapular exanthem		A, H, L/R, Cef	-	+ (A)	Maculopapular exanthem
5[c]	Maculopapular exanthem		A, H, L/R, Ax, Cla	-	+ (Cla)	Maculopapular exanthem
6	Urticarial exanthem	Perivascular infiltrate of lymphocytes, intravascular neutrophils, and upper dermal edema	A, H, Cef	-	-	NA
7	Urticarial exanthem		A, H, L/R, Cef	-	-	NA
8	Urticarial exanthem		A, H, L/R, Cef	-	-	NA
9	Urticarial exanthem		A, H, L/R, Cef	-	-	NA
10	Urticarial exanthem		A, H, L/R	-	-	NA
11	Vesicular exanthem	Epidermal necrosis with acantholysis, swelling of keratinocytes, and intraepidermal vesicles	A, H, L/R	-	+ (A)	Vesicular exanthem
12	Vesicular exanthem		A, H	-	-	NA
13	Vesicular exanthem		A	-	-	NA
14	Vesicular exanthem		A, H	-	-	NA
15	Chilblain-like	Ischemic epidermal necrosis of keratinocytes and vascular ectasia	A, H, L/R	-	-	NA
16	Cutaneous vasculitis	Leukocytoclastic vasculitis with perivascular neutrophilic infiltrate	A, H, L/R	-	NP	NA

Abbreviations: A, azithromycin; Ax, amoxicillin; Cef, ceftriaxone; Cla, clavulanic acid; DPT, drug provocation testing; H, hydroxychloroquine; L/R, lopinavir/ritonavir; NA, not applicable; NP, not performed.
[a]Performed with the drugs administered. Concentrations: azithromycin 5% and 10% pet, hydroxychloroquine 5% and 10% pet, lopinavir/ritonavir 1% and 5% pet and amoxicillin, clavulanic acid and ceftriaxone 1% and 5% pet.
[b]Performed with the drugs administered. In case of ß-lactam antibiotics, prick and intradermal skin tests with late readings were performed prior to DPT.
[c]DPT with Ax was negative. Intradermal test performed 10 days after positive DPT to clavulanic acid was positive at the 48-hour reading.

explanations for this finding are less severe reactions, variations in SARS-CoV-2 antigenicity, and a change in the treatment combination from azithromycin, hydroxychloroquine, and lopinavir/ritonavir to other options [10]. In addition, the change could have led to fewer cases of hypersensitivity reactions to these drugs. Although the number of patients in our series is small and prevents definitive conclusions from being drawn, we provide the first report of the role of drug hypersensitivity in exanthematous skin lesions in patients with SARS-CoV-2 infection confirmed by DPT. Consequently, drug hypersensitivity should be taken into account in the differential diagnosis of these types of lesions. Recent studies have suggested the need for a multidisciplinary approach [3] to diagnosis of skin lesions in patients with SARS-CoV-2 infection owing to the possibility of drug hypersensitivity reactions (with a positive lymphocyte transformation test result), HLA-associated genetic predisposition, disease severity, a prothrombotic state, immunologic mechanisms, possible interactions between medications, and viral infection [11-13]. Therefore, it is important to adopt a joint approach between allergists, dermatologists, immunologists, infectious diseases specialists, and pathologists in order to ensure better understanding and management of cutaneous manifestations in patients with SARS-CoV-2 infection.

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Conflicts of Interest

The authors have no conflict of interest to declare.

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