Drug hypersensitivity in cutaneous manifestations of SARS-CoV-2 infected patients

Solano-Solares E[1*], Chica-Guzmán V[1*], Pérez-Allegue I[1], Cabrera-Hernández R[1], Fernández-Guarino M[2], Fernández-Nieto D[2], Moreno-García-del-Real C[3], de-Andres-Martin A[4], García-Bermejo L[5], González-de-Olano D[1,6,**], de-la-Hoz-Caballer B[1,6,**]

[1]Allergology Department, Hospital Universitario Ramón y Cajal, IRYCS, Madrid, Spain.
[2]Dermatology Department Hospital Universitario Ramón y Cajal, IRYCS, Madrid, Spain.
[3]Pathological Anatomy Department Hospital Universitario Ramón y Cajal, IRYCS, Madrid, Spain.
[4]Immunology Department Hospital Universitario Ramón y Cajal, IRYCS, Madrid, Spain.
[5]Biomarkers and Therapeutic Targets Group, RedinRen, Hospital Universitario Ramón y Cajal, IRYCS, Madrid, Spain.
[6]Spanish Thematic Network and Co-operative Research Centres, ARADyAL, Spain.

*Both authors have equally contributed and should be both considered as first authors
**Both authors should be considered as senior authors.

Corresponding Author

David Gonzalez de Olano
Carretera Colmenar Viejo, km. 9, 100, 28034 Madrid
Email: dgolano@yahoo.es

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0744

doi: 10.18176/jiaci.0744

Key Words: Cutaneous Manifestations; Drug Provocation Ttest; First Wave, SARS-CoV-2; Drug Hypersensitivity

Palabras clave: Manifestaciones Cutáneas. Prueba de Provocación con Medicamentos. Primera Ola. SARS-CoV -2. Hipersensibilidad con Medicamentos

At the beginning of the Pandemia of SARS-CoV-2, different types of skin lesions were described in patients during the infection period [1]. The first reports of cutaneous manifestations described 6 patterns of skin lesions: maculopapular exanthems, urticarial exanthems, vesicular exanthems, erythema multiforme, cutaneous vasculitis and chilblain-like lesions [2]. Many of this patients were exposed to different treatments and to date, there is no clear understanding on whether some of this skin lesions presented during the so-called "first wave" could be secondary to drug hypersensitivity.

We conducted a prospective, observational and descriptive study which main objective was to determine if drug hypersensitivity could be a cause of skin lesions in patients admitted to our hospital due to SARS-CoV-2 infection during the months of march to may 2020. A total of 72 patients with skin lesions were admited to the Allergology and/or Dermatology Department (see supplementary material) during this period of time. Out of this 72 patients, 37 presented possible drug implication following the algorithm of the spanish pharmacovigilance system (ASPS) [4], which evaluates the possible implication of a drug reaction as a cause of the skin lesions. All of these patients had received treatment with azithromycin, hydroxychloroquine, lopinavir/ritonavir and/or betalactam antibiotics. Of the 37 patients, 16 patients consented in continuing the study. The types of lesions observed and reported 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 of days since beginning of treatment to skin manifestations was 7.5 days (1-15 days). No patient presented an immediate type reaction during their treatment.

doi: 10.18176/jiaci.0744

We designed a study protocol that included patch testing and a drug provocation test (DPT) with the drugs used during the treatment. Patch tests with azithromycin 5% and 10% petrolatum, hydroxychloroquine 5% and 10% petrolatum, lopinavir/ritonavir 1% and 5% petrolatum and betalactam antibiotics (amoxicillin, clavulanic acid and ceftriaxone) 1% and 5% petrolatum) were performed 4-6 months after hospital discharge [5]. With betalactam antibiotics, prick and intradermal skin tests with late readings, were also performed prior to DPT. No positive results were found after 24h-48h-96h readings. DPT with the implicated drugs were carried out in alternative days. Out of the 16 patients studied, 15 patients underwent DPT with the administered drugs. One patient with cutaneous vasculitis didn´t underwent DPT. DPT was positive in 3 patients (18.75%); two patients were positive to azythromicine (one presented a late maculopapular exathem and the other a vesicular exanthem) and one patient to clavulanic acid (maculopapular exanthem). The patients presented the same lesions as the ones presented during the infection period (see table I).

The different types of skin lesions have been classified in 3 groups: 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 (vasculitic 13.5%, chilblain-like 7.7%) and 11.5% for miscellaneous manifestations [2]. In our patients we saw a similar pattern of skin lesions with 87.5% (14/16 patients) presenting with exanthem lesions and 12.5% (2/16 patients) presenting with vascular lesions. There is no clear understanding on why patients with the same type of infection have very different presententations of skin lesions. Some possible aetiopathogenic mechanisms have been described especially for chilblain-like pattern lesions that reflect perivascular and peri-eccrine inflammation with markers of significant Interferon 1 activation [6] or some cutaneous vasculitis due to thrombotic vasculopathy with involvement of interleukins such as IL6 [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 betalactam antibiotics. All of which have a potential to develop hypersensitivity reactions [8,9]. In our population 3 patients presented with

doi: 10.18176/jiaci.0744

exanthematous skin lesion reactions due to drug hypersensitivity confirmed by DPT. Patch tests were performed 4-6 months after hospital discharge. Wether this innapropiate timing of testing (according to the ENDA Guidelines) could have result in the negative results of DPT positive patients, might be taken into account.

During the "Second Wave" of the pandemia in june 2020, cutaneous findings have scarcely been reported, mentioning 3 possible causes: less severity reactions in patients, variations in SARS-CoV-2 antigenicity and change in treatment combination from azithromycin, hydroxychloroquine and lopinavir/ritonavir to other treatments [10]. This change in treatment could also had contributed to less cases of hypersensitivity reactions to this drugs. Although the number of patients in our series is small and limits definitive conclusions, it is reported for the first time the involment of drug hypersensitivity in exanthematous skin lesions of SARS-CoV-2 infected patients confirmed by DPT. That brings the necessity to take into account drug hypersensitivity in the differential diagnosis of these types of lesions. Recently it has been reported the need of a multidiscplinary approach [3] for diagnosis of skin lesions in patients with SARS-CoV-2 infection due to the possibility of drug hypersensitivity reactions (with positive lymphocyte transformation test), HLA associated genetic predisposition, disease severity, a prothrombotic state, inmunologic mechanisms and posible interactions between medication and viral infection [11, 12, 13]. Therefore it is important to have a joint approach between allergist, dermatologist, immunologist, infectious disease and pathologist in order to have a better understanding and management of cutaneous manifestations in patients with SARS-CoV-2 infection.

Conflicts of interest

The authors have no conflict of interest to declare

Funding sources

This was supported by SANTANDER grant

References

1. Galván Casas C, Català A, Carretero Hernández G, Rodriguez-Jimenez P, Fernandez-Nieto D, Rodriguez-Villa Lario A, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020;183(1):71-7.
2. Recalcati S, Gianotti R, Fantini F. COVID-19: The experience from Italy [published online ahead of print, 2020 Dec 17]. Clin Dermatol. 2020.
3. Cabrera-Hernández R, Solano-Solares E, Chica-Guzmán V, Fernandez-Guarino M, Fernandez-Nieto D, Ortega-Quijano D, et al. SARS-CoV-2, skin lesions and the need of a multidisciplinary approach. J Eur Acad Dermatol Venereol. 2020;34(11):e659-e662.
4. Cabañas R, Ramírez E, Sendagorta E, Alamar R, Barranco R, Blnca-López N, et al. Spanish Guidelines for Diagnosis, Management, Treatment, and Prevention of DRESS Syndrome. J Investig Allergol Clin Immunol. 2020;30(4):229-253.
5. Romano A, Viola M, Gaeta F, Rumi G, Maggioletti M. Patch testing in non-immediate drug eruptions. Allergy Asthma Clin Immunol. 2008;4(2):66-74. doi:10.1186/1710-1492-4-2-66
6. Colmenero I, Santonja C, Alonso-Riaño M, Noguera-Morel L, Hernández-Martín A, Andina D, et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases. Br J Dermatol. 2020 Aug 5
7. Magro C, Mulvey JJ, Laurence J, Sanders S, Crowson N, Grossman M, et al. The differing pathophysiologies that underlie COVID-19 associated perniosis and thrombotic retiform purpura: a case series. Br J Dermatol. 2020 Jul 22

doi: 10.18176/jiaci.0744

8. Dordal Culla MT, Herrera-Lasso Regás V, Martí-Garrido J, Rodríguez Cumplido D, Vázquez-Revuelta P, Lleonart Bellfill R. Treating COVID-19: Review of Drug Hypersensitivity Reactions. J Investig Allergol Clin Immunol. 2020;30(6):385-399. doi:10.18176/jiaci.0588
9. Gelincik A, Brockow K, Çelik GE, Doña I, Mayorga C, Romano A, et al. Diagnosis and management of the drug hypersensitivity reactions in Coronavirus disease 19: An EAACI Position Paper. Allergy. 2020;75(11):2775-2793.
10. Fernandez-Nieto D, Ortega-Quijano D, Suarez-Valle A, Jimenez-Cauhe J, Jaen-Olasolo P, Fernandez-Guarino, M. Lack of skin manifestations in COVID-19 hospitalized patients during the second epidemic wave in Spain: a possible association with a novel SARS-CoV-2 variant – a cross-sectional study. J Eur Acad Dermatol Venereol, 35: e183-e185.
11. Mascitti H, Bonsang B, Dinh A, Assan F, Perronne V, LeBlanc T, et al. Clinical Cutaneous Features of Patients Infected With SARS-CoV-2 Hospitalized for Pneumonia: A Cross-sectional Study. Open Forum Infect Dis. 2020;7(11):ofaa394. Published 2020 Oct 18.
12. Pretti MAM, Galvani RG, Vieira GF, Bonomo A, Bonamino MH, Boroni M. Class I HLA Allele Predicted Restricted Antigenic Coverages for Spike and Nucleocapsid Proteins Are Associated With Deaths Related to COVID-19. Front Immunol.2020;11:565730. Published 2020 Dec 16.
13. Hayakawa, J., Takakura, H., Mizukawa, Y. and Shiohara, T. (2020), COVID-19-related cutaneous manifestations associated with multiple drug sensitization as shown by lymphocyte transformation test. J Eur Acad Dermatol Venereol, 34: e779-e781.

Supplementary Figure 1. Study Flowchart

ASPS: algorithm of the spanish pharmacovigilance system; DPT: Drug Provocation Test;

DPT +: Positive drug provocation test; DPT -: Negative drug provocation test;

Table I. Clinical and analytical characteristics of the patients who underwent allergy study

Patient	Skin lesions During SARS-CoV-2 infection	Histopathological Study	Drugs Administered	Patch Test*	DPT**	Skin lesions After DPT
1	Maculopapular Exanthem	Perivascular infiltrate of lymphocytes, 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¶	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

A: Azithromycin; H: hydroxychloroquine; L/R: lopinavir/ritonavir; Ax: Amoxicillin; Cla: clavulanic acid; Cef: ceftriaxone; NP: not performed; NA: not apllicable.

*Performed with the drugs administered. Concentrations: Azithromycin 5% and 10% petrolatum, hydroxychloroquine 5% and 10% petrolatum, lopinavir/ritonavir 1% and 5% petrolatum and amoxicillin, clavulanic acid and ceftriaxone 1 and 5% petrolatum.

** Performed with the drugs admministered. In case of betalactam antibiotics prick and intradermal skin tests with late readings were performed prior to DPT.

¶ DPT with Ax was negative. Intrademal test performed 10 days after positive DPT to Clavulanic Acid was positive at 48h reading.

doi: 10.18176/jiaci.0744