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

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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.

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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

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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

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