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SARS-CoV-2, skin lesions and the need of a multidisciplinary approach

Editor

COVID-19 is a disease caused by severe acute respiratory syndrome coronavirus 2 of the genus Betacoronavirus (SARS-CoV-2). It was first described in Wuhan (China) on December 2019 and has spread to become a pandemic. Its clinical presentation is mainly characterized by cough, fever and dyspnoea, although many other symptoms have been described within its presentation pattern. In some cases, it causes an acute respiratory distress that has lead to the death of thousands of people around the world. Furthermore, different types of skin lesions have been described during the infection period of illness.[1] In this exceptional situation of global health emergency, physicians are undertaking research work in order to achieve notions on the aetiopathogenesis of these skin lesions. The first report of cutaneous manifestations described different forms of skin lesions such as erythematous rash, urticaria and chickenpox-like vesicles.[2] Further studies have classified 5 different type of skin lesions and associated them with patient demographics, timing in relation to symptoms of the disease, severity and prognosis.[1] Acro-ischaemic lesions have also been notified and attributed to disseminated intravascular coagulation and to the expression of secondary microthrombosis due to endothelial damage.[3-5] However, to date, there is no clear understanding on whether the skin lesions are secondary to the viral infection nor why there are different presentations of skin lesions for the same viral infection.

We present 4 patients with COVID-19, confirmed by positive polymerase chain reaction, who were referred to our service due to the appearance of skin lesions (Fig. 1). Two of them developed skin lesions during hospitalization whilst presenting respiratory symptoms, and the other two developed skin lesions many days after hospital discharge. Demographic data, description and histology of skin lesions, blood parameters, clinical symptoms and drugs administered are shown in Table 1. The algorithm of the spanish pharmacovigilance system (ASPS), which evaluates the possible implication of a drug reaction as a cause of the skin lesions,[6] was also applied. The ASPS analyzes i) the interval between drug administration and the apparition of skin lesions, ii) the degree of knowledge of the relationship between the drug and the effect described in literature, iii) the evaluation of drug withdrawal, iv) the rechallenge effect and v) alternative causes. Each item receives an individual subscore, and a total sum ≥6 indicates a probable causality.[6]

As mentioned above, skin lesions appear to be a sign within patients suffering from COVID-19. To date, no hypothesis has been proposed to explain if the lesions (including the different types) are attributable to the virus, to drug adverse reactions or to any other clinical condition. Histopathological study alone cannot conclude an aetiology, as it does not distinguish between a possible viral exanthema and a toxicoderma (Fig. 1). In our series, small enough to draw conclusions, we have found no differences between the multiple types of skin lesions and analytical or clinical features. Even in lesions with apparent vascular involvement, which have been associated with alterations in coagulation,[3-5] the analytical parameters did not differ from those with other types of skin lesions. Regarding drug involvement, since all the patients were exposed to multiple drugs at the same time, the ASPS was not able to differentiate the possibility of drug implication nor the immune mechanisms involved. Thus, further assays with selective (*in vitro* or *in vivo*) tests for each drug seem necessary in order to completely rule out drug involvement. In addition, since many patients worldwide are being infected with SARS-Cov-2, and many of them present similar medical history and receive the same treatments, it seems necessary to investigate the existence of an individual predisposition that facilitates the development of skin lesions. For all these reasons, in order to correctly study the aetiology of the skin lesions, a multidisciplinary approach should be carried out.

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The patients in this manuscript have given written informed consent to publication of their case details.

Conflicts of interest

Dr. Cabrera-Hernández, Dr Solano-Solares, Dr Chica-Guzmán, Dr Fernández-Guarino, Dr Fernández-Nieto, Dr Ortega-Quijano, Dr de-Andrés-Martín, Dr Moreno, Dr Carretero-Barrio, Dr García-Abellás, Dr González-de-Olano and Dr de-la-Hoz-Caballer have nothing to disclose.

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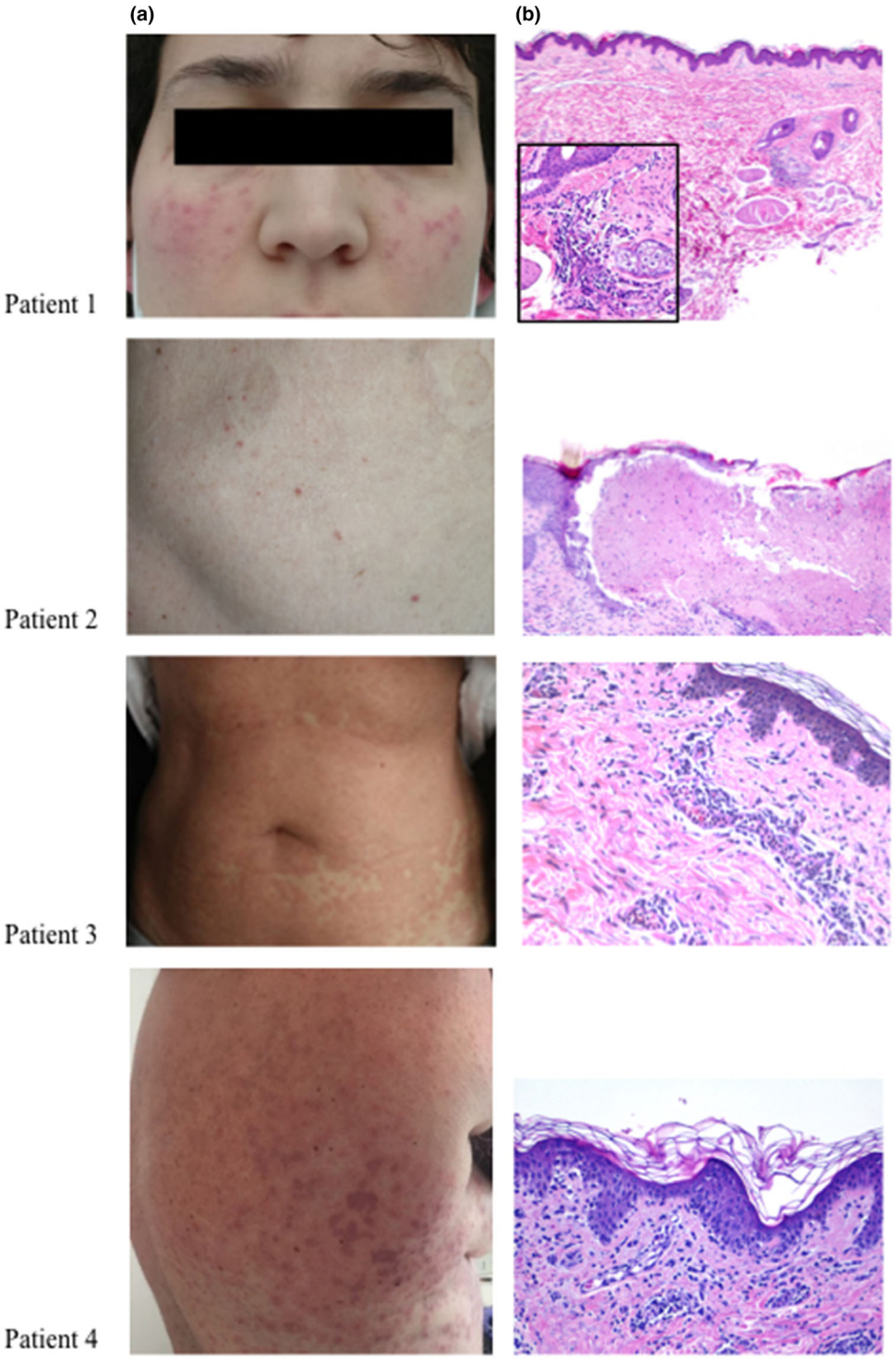

Figure 1 a) Clinical presentation: Patient 1: Dispersed hives over the face, trunk and lower limbs. Patient 2: Scattered, non-confluent papules and vesicles disseminated on trunk. Patient 3: Confluent, erythemato-oedematous plaques located on the trunk, neck and lower limbs. Patient 4: Confluent, erythematous macules and plaques with a violaceous targetoid appearance, predominantly on the trunk and proximal limbs, with scarce facial involvement. b) Histology. Patient 1: Urticarial pattern with mild oedema, perivascular inflammation and dilated vessels in the upper dermis. Inset: Vessels filled with neutrophils and mixed perivascular inflammation. Patient 2: Intraepidermal vesicle with fibrin debris, some necrotic cells and discrete ballooning keratinocytes in the margins. Immunohistochemistry against human herpes virus 1 was negative. Patient 3: Urticarial pattern that shows dilated vessels filled with neutrophils, mild perivascular lymphocytic inflammation and minimal blood extravasation. Patient 4: Mixed interface pattern with dilated vessels filled with neutrophils, frequent blood extravasation and scattered necrotic keratinocytes.

Table 1 Clinical and analytical characteristics of the patients

	Patient 1	Patient 2	Patient 3	Patient 4
Demographic characteristics				
Gender	Female	Male	Female	Female
Age (years)	32	64	59	58
Clinical manifestations	F, P	C, D, F, M, P	Ag, An, F, H, M, N	C, D, Di, F, M, P
Skin lesions				
Onset† (days)	6	15	16	25
Duration (days)	5	7	17	19
Analytical parameters‡				
Creatinine (mg/ml)	0.88/0.73	1.01/0.81	0.65§	0.81/0.79
LDH (U/l)	169/202	264/242	247§	474/314
GOT-GPT (U/l)	18–16/21–15	23–20/27–31	15–11§	41–62/17–53
CRP (mg/L)	32/13.9	57.4/75.8	154.4§	187.7/1
D-dimer (ng/mL)	321/578	1034/721	1687§	1186/1098
Lymphocytes ($10^3/\mu L$)	1/1.47	2.36/3.32	1.57§	0.9/1.94
Eosinophils ($10^3/\mu L$)	0.02/0.01	0.01/0.017	0.73§	0.0/0.02
IL-12 (pg/mL)	NP/NP	0.21/ NP	0.0§	2.88/NP
IL-10 (pg/mL)	NP/NP	0.64/NP	0.0§	NP/NP
IL-6 (pg/mL)	NP/NP	1.75/NP	1.58§	29/NP
Ferritin (ng/mL)	12.97/NP	788.6/NP	428§	43.94/NP
Total IgE (kU/L)	NP/NP	NP/NP	1476§	NP/50
Drugs¶				
	Time (days)**/ ASPS††	Time (days)**/ASPS††	Time (days)**/ASPS††	Time (days)**/ ASPS††
Hydroxycloroquine	14/5	3/5	14/1	16/1
Azithromycin	15/4	3/0	5/0	16/-1
L + R	NP/NA	2/4	NP/NA	11/4
Other:				
Ceftriaxone	NP/NA	0/5	NP/NA	NP/NA
Tocilizumab	NP/NA	NP/NA	NP/NA	10/-3

Ag, ageusia; An, anosmia; C, cough; CRP, c-reactive protein; D, dyspnoea; Dh, diarrhoea; F, fever; GOT, glutamic oxaloacetic transaminase; GPT, glutamate pyruvate transaminase; H, headache; IL, interleukin; LDH, lactate dehydrogenase; L + R, Lopinavir–Ritonavir; M, myalgia; N, nasal congestion; NA. not applicable; NP, not prescribed; P, pneumonia.

†Time interval between the onset of clinical symptoms and the development of skin lesions.

‡The results are expressed at the time of hospital admission and the determination closest to the development of the skin lesions, separated by a forward slash.

§The development of the skin lesions occurred the same day of hospital admission.

¶Drugs used in the treatment of the disease which might be suspicion of being related to the development of skin lesions.

**Development of the lesions as compared to the beginning of treatment with the drug.

††ASPS score: algorithm of the spanish pharmacovigilance system. Final score: <0, not related; 1–3 conditional; 6–7 probable; 8 definite.

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Teledermatology for acne during COVID-19: high patients' satisfaction in spite of the emergency

Editor

Acne is a chronic inflammatory skin disease affecting the 9.4% of global population.[1] Although it usually occurs in adolescents aged from 15 to 24 years old, it is not uncommon to develop in adults either.[2] Boys are more frequently affected, particularly with severe forms of the disease. An adequate and continuous treatment of the disease is required in order to reduce acne lesions, prevent permanent scarring and limit the duration of the disorder.[3] Disease severity could also affect patients' quality of life, sometimes causing anxiety, depression and even suicide.[4] With the implementation of new technologies, particularly mobile technologies, there is a growing use of smartphones and personal computers among the whole population, especially among teens and younger adults. Since the coronavirus disease 2019 (COVID-19) outbreak, different measures have been applied in hospitals in order to avoid or limit as much as possible coronavirus infection spread, including the reduction of face-to-face visits and the implementation of teledermatology.[5,6] Objective of our study was to assess how teledermatology visits were subjectively experienced by the patient as well as to identify how to improve the doctor–patient relationship and to satisfy patients' expectations. An observational prospective study was conducted at the Dermatology Unit of the University of Naples Federico II, Italy. Patients aged >18 years and already attending the Acne Care Centre before COVID-19 outbreak, who received their control visit through live interactive video-call visits, were asked to complete a 6-item questionnaire using a 0-10 scale (score 0-3: negative; 4-6: not bad not good; 7-10: positive) to assess how teledermatology visits were subjectively experienced. Informed consent was obtained during the visit, and the questionnaire was completed anonymously. Fifty-two patients (24 males and 28 females; aged 18–27 years; mean 22.5 years) were consecutively enrolled in the study. Overall, 48 (92.3%) out of 52 patients rated the attention paid by the dermatologist regarding their disease as favourable (score = 7–10). Similar outcomes (86.5%) were also reported from data regarding the evaluation of the time spent by the dermatologist for the visit.

Regarding the treatment received, 71% (37/52) of patients were satisfied with the treatment they received (score = 7–10), while 80.7% (n = 42; score = 7–10) reported high well-being after treatments. 46.1% of the patients (n = 24; score = 0–3) reported that side-effects did not represent a significant obstacle to continue the systemic therapies, and 50 patients (96.1%) related they will continue to consult the same dermatologists (score = 7–10). All the scores reported for each question and the complete questionnaire are reported in Table 1. Data from literature indicate teledermatology as a popular service among both patients and clinicians.[7] Merthens et al.[4] in their 14-year retrospective study in UK, based on 40201 teleconsultations, revealed that teledermatology service had been useful to prevent 16 282 face-to-face appointments. In line with literature,[8–10] our questionnaire showed that the majority of patients (92.3%) appreciated the visits and the attention that physicians gave them, as well as the treatment received, with 90.3 % assessing they will continue to consult the same dermatologists. This is the first study assessing the grade of satisfaction of patients affected by acne disease after video-call visits. Limitations of our study were the lack of a validated questionnaire assessing the grade of patients' satisfaction for telemedicine services and the lack of randomization. Further studies on larger sample size regarding teledermatology in acne patients should extend beyond satisfaction and agreement to health outcomes and cost-effectiveness. However, because guidelines or official recommendations about the use and the efficacy of these new technologies are lacking, different experiences and strategies applied in different hospitals should be shared in order to find a common method well appreciated from both patients and physicians.