Conflict of interest

The authors have no conflict of interest to disclose.

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Drug reaction with eosinophilia and systemic symptoms syndrome in a patient with COVID-19

Dear Editor

Skin rashes associated with COVID-19 include eruptions induced by drugs prescribed for management of this infection. We report a case of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome in a patient with COVID-19.

A 50-year-old man was admitted to the intensive care unit for pneumonia with acute respiratory distress syndrome. COVID-19 was confirmed by positive RT-PCR SARS-CoV-2 on nasopharyngeal swabs and later by positive IgM and IgG antibodies against SARS-CoV-2 (114.5 AU/mL). In the context of fever >38.5°C, nine days after admission, the patient developed a generalized maculopapular rash on more than 70% of his body surface area with oedema of hands and face (Fig. 1). Azithromycin and hydroxychloroquine had been initiated 18 and 17 days, respectively, prior to the skin eruption. The patient had also received the following drugs: heparin, propofol, clonidine, norepinephrine, sufentanil and rocuronium (at admission); pantoprazole (9 days before); sevoflurane (8 days before); cefuroxime (6 days before); and flucloxacillin (4 days before). Laboratory tests revealed a new elevation of C-reactive protein (CRP) level (349 mg/L; nl. <5 mg/L), high absolute blood eosinophilia (950/μL; nl. <600/μL), atypical lymphocytes (120/μL) and elevated D-dimer (7343 ng/mL; nl. <500 ng/mL). Moreover, patient presented abnormal renal function (blood urea nitrogen 93 mg/mL, serum creatinine 1.37 mg/dL) and altered liver tests [elevated serum aspartate amino transferase (ASAT): 59 U/L; nl. <35, and gamma glutamyl transferase (GGT): 579 U/L; nl. <60]. Serologic investigations carried out 8 days after the beginning of the eruption for Epstein-Barr virus (EBV) and cytomegalovirus (CMV), and after 11 days for human immunodeficiency virus (HIV), and hepatitis B and C were negative. Histopathological analysis of skin biopsy specimens showed oedema of the dermis associated with moderate perivascular infiltrate including lymphohistiocytic cells and eosinophils, suggestive of a DRESS. According to the scoring system for classifying DRESS cases (RegiSCAR) reported by Kardaun *et al.*,[1] a drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome was diagnosed as follows: fever ≥38.5°C (0), enlarged lymph nodes (0), eosinophilia (1), atypical lymphocytes (1), skin rash extent >50% body surface area (1), skin rash suggesting DRESS (1), biopsy suggesting DRESS (0), organ involvement (liver, kidney, lung) (2), resolution ≥15 days (0), viral titers (HBV/HCV) negative (1). The prognosis of DRESS in our patient was considered severe according to the severity and prognosis scoring system proposed by Mizukawa *et al.*[2] with a total score in the early phase (calculated during the first 3 days of the eruption) of 8 (>4) as follows: age (0), duration of drug exposure after onset (1), erythema >70% BSA (1), erosion, <10% BSA (0), fever >38.5°C during >7 days (2), appetite loss (<70% of regular food intake) (1), renal dysfunction (creatinine) (1), liver dysfunction (ALT) (0), C-reactive protein (2).

All suspected drugs (in particular azithromycin and hydroxychloroquine) had already been stopped and intravenous corticosteroids were administered (methylprednisolone 1 mg/kg/day).

Progressive resolution (over more than 15 days) of the exanthema and systemic involvement (inflammatory, haematological, hepatic, renal) was observed with gradual tapering of corticosteroid therapy (80 mg/day for 9 days; 40 mg/day for 11 days; 20 mg/day for 11 days; 8 mg/day for 5 days), and the patient was discharged from ICU 3 weeks later.

RT-PCR SARS-CoV-2 RNA performed on skin samples as well as sequential RT-PCR SARS-CoV-2 RNA performed on nasopharyngeal swabs after the resolution of the symptoms was negative.

DRESS syndrome is a severe cutaneous adverse drug reaction. Usually, the rash appears 3–8 weeks after the initial administration of the drug. In the present case, many drugs were administered. However, from a chronological point of view, hydroxychloroquine and azithromycin, used for their probable antiviral activity against SARS-CoV-2, were most likely

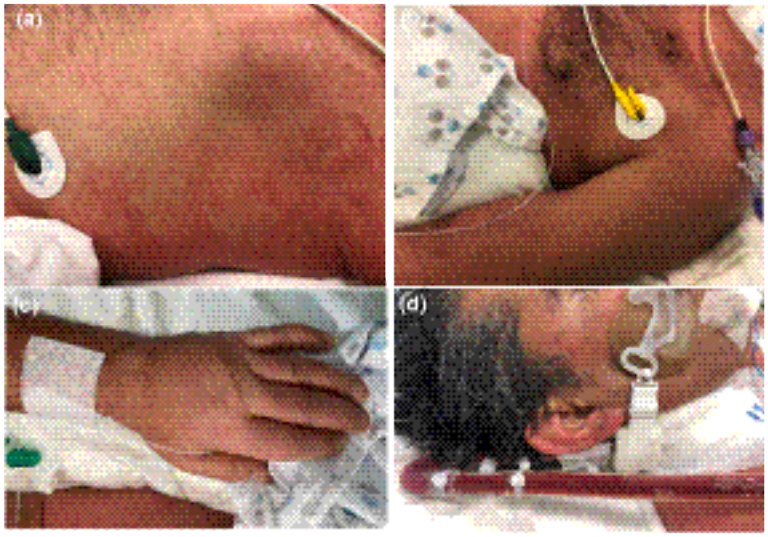

Figure 1 Generalized erythematous maculopapular rash (a,b) with hand (c) and face oedema (d).

responsible for the syndrome. In this case, the latency period between therapy and onset of the adverse reaction might seem quite short (17–18 days). This could result from repeated use of the same drug; however, it was not the case for this patient. A few cases of DRESS have already been reported with hydroxychloroquine,[3,4] including one case with EBV reactivation.[5] Rare cases of DRESS linked to azithromycin have also been described,[6,7] including one case in a child also associated with primary EBV infection.[8] The pathophysiology of DRESS syndrome is complex and not completely defined. On the one hand, a delayed hypersensitivity to drugs suggests a T-cell-mediated reaction, but viral reactivations or antiviral immunity also seem to be implicated. However, the interaction and role of viral infections on the drug metabolism as well as onset and amplification of the culprit drug-specific T lymphocyte response remain incompletely defined.

The most frequently associated viruses are human herpes virus (HHV) 6 and 7, EBV and CMV. One case of DRESS has been reported associated with the influenza A and B virus.[9] Due to negative RT-PCR SARS-CoV-2 on nasopharyngeal swabs after the eruption in our patient, viral reactivation seems unlikely. Lymphocyte transformation tests will be performed 4–6 weeks after onset of the eruption and patch tests will only be performed within 3–6 months to confirm the imputability of either drug, However, it is important to make clinicians aware of such reactions with severe inflammatory effects and end organ involvement could become more frequent during the current pandemic and could complicate the management of COVID-19 patients.[4] However, it remains plausible that that the high dose of systemic corticosteroid administrated for the DRESS syndrome could have had a positive impact on the clinical course of the critical COVID-19 of this patient.

To conclude, we report a case of DRESS syndrome possibly due to hydroxychloroquine or azithromycin in a patient with COVID-19.

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The patient in this manuscript has given written informed consent to the publication of their case details.

Conflicts of interest

The authors disclosed any financial association or other conflicts of interest.

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Management of biological therapies for chronic plaque psoriasis during COVID-19 emergency in Italy

Dear Editor,

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is creating an unprecedented global public health emergency with the continuous growth of infected individuals worldwide.[1] Italy was one of the first European countries to face the first wave of infection outside mainland China.[2] The first case of COVID-19 was confirmed in Lombardy on 20 February 2020, and subsequently, a rapid increase in the number of detected cases was observed, spreading through Italy and the rest of Europe.[3] As of 22 April, confirmed COVID-19 cases in Italy were 183 957.[2,4]

Because of the impaired immunologic status of patients with psoriasis, their clinical management is challenging in the pandemic, particularly for those using biologics inhibiting key pathogenic cytokines such as TNF-α, IL-17, IL-12/23 or IL-23.[5–6]

To date, there is neither an agreement nor a study sustaining the impact of continuing or stopping biologics in psoriatic patients during the COVID-19 pandemic.[7–10]

The PSO-BIO-COVID is an observational, multicentric study, supported by the Italian Society of Dermatology (SIDeMaST), aimed at evaluate the impact of SARS-CoV-2 infection on the management of patients with psoriasis in Italy, during the first year of the pandemic.

Patients with moderate-to-severe chronic plaque psoriasis, aged >18 years, undergoing treatment with any biological agent as of 22 February 2020, were eligible.

Data on biological agent used for treatment and any suspension and/or lengthening of time intervals (LTIs) for treatment administration between 22 February and 22 April 22 2020 have been collected in a standardized data collection system through face-to-face, remote visits or via email. Frequency and percentages on the total number of centres and patients were the analyses performed.

The study was approved by the National Ethical Committee for COVID-19-related studies at INMI Lazzaro Spallanzani IRCCS, with the Dermatology Unit-Fondazione Policlinico Tor Vergata as the coordinating centre.

A total of 12 807 psoriatic patients from 33 specialized dermatologic centres were included in the study. 328 patients (2.6%) stopped treatment during the observation period without consulting their dermatologist mainly because of fearing high contagious risk; 233 (1.8%) interrupted their therapy after

Table 1 Number and percentage of psoriatic patients treated with a biological agent in Italy. Period: 22 February 2020–22 April 2020

	ADA	ETA	INF	UST	SEC	IXE	BRO	GUS	TIL	RIS	Total
Total patients	**3045**	**1645**	**343**	**2638**	**2417**	**1586**	**297**	**628**	**16**	**192**	**12 807**
Mean % of treated patients for each biological drugs	23.8%	12.8%	2.7%	20.6%	18.9%	12.4%	2.3%	4.9%	0.1%	1.5	100%
Patients stopping therapy autonomously†	90 (3.0%)	49 (3.0%)	19 (5.5%)	72 (2.7%)	49 (2.0%)	32 (2.0%)	5 (1.7%)	9 (1.4%)	0	3 (1.6%)	**328 (2.6%)**
Patients stopping therapy after consulting with the physician†	85 (2.8%)	30 (1.8%)	10 (2.9%)	21 (0.8%)	36 (1.5%)	8 (0.5%)	5 (1.7%)	13 (2.1%)	0	4 (2.1%)	**233 (1.8%)**
Patients' LTIs of therapy autonomously†	47 (1.5%)	61 (3.7%)	5 (1.5%)	28 (1.1%)	27 (1.1%)	9 (0.6%)	2 (0.7%)	4 (0.6%)	0	2 (1.0%)	**185 (1.4%)**
Patients' LTIs of therapy after consulting with the physician†	25 (0.8%)	6 (0.4%)	11 (3.2%)	26 (1.0%)	10 (0.4%)	26 (1.6%)	1 (0.3%)	5 (0.8%)	0	4 (2.1%)	**114 (0.9%)**

ADA, adalimumab; BRO, brodalumab; ETA, etanercept; GUS, gusesslkumab; INF, infliximab; IXE, ixekizumab; LTIs, lengthening of time intervals; RIS, risankizumab; SEC, secukinumab; TIL, tildrakizumab; UST, ustekinumab.
†Percentages are calculated on the total number of patients.

