Research letter

Drug reaction with eosinophilia and systemic symptoms in patients hospitalized with COVID-19: a case series from a large US healthcare system

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Dear Editor, Patients hospitalized with COVID-19 often have prolonged admissions and are frequently exposed to multiple medications, putting them at risk for adverse drug reactions including drug reaction with eosinophilia and systemic symptoms (DRESS). This study presents the largest reported case series of hospitalized patients with concurrent COVID-19 and DRESS syndrome.

A retrospective chart review was performed of 9330 polymerase chain reaction (PCR)-positive patients with COVID-19 and 144 cases of DRESS between 20 January 2020 and 20 May 2021. Patients with DRESS syndrome occurring concurrently with COVID-19 were assessed for clinical characteristics, culprit drugs, treatments and outcomes by a board-certified dermatologist and an allergist/immunologist. The RegiSCAR score was calculated for each patient using available documentation.[1]

The six confirmed cases of concurrent DRESS and COVID-19 (incidence 6·43 per 10 000 inpatients with COVID-19) were admitted to the intensive care unit and survived to discharge (Table 1). Their mean length of hospitalization was 68 days (SD 42; median 58). All patients developed hypoxaemic respiratory failure and acute respiratory distress syndrome requiring endotracheal intubation. For the treatment of COVID-19 and/or empirical treatment for secondary bacterial pneumonia, treatment included vancomycin (100%), cefepime (83%), corticosteroids (67%), remdesivir (50%), azithromycin (50%), hydroxychloroquine (50%), tocilizumab (50%) and meropenem (50%). The median times to rash onset from admission and from COVID-19 symptom onset were 19 days (range 8–39) and 32 days (range 13–46), respectively. The mean time to rash onset from probable culprit drug exposure was 17 days (range 6–34): this occurred at 0–7 days (17%), 8–14 days (33%) and > 15 days (50%). The most likely culprit drugs were vancomycin, cefepime and meropenem. Because four patients (67%) were started on vancomycin and cefepime concurrently, both drugs were considered probable culprits. The mean absolute eosinophil count was $4{\cdot}47 \times 10^9$ cells L^{-1} (range $2{\cdot}97–5{\cdot}83 \times 10^9$). Cases had involvement of the kidney (100%) and liver (83%); all patients had mild troponin elevations that were not consistent with myocardial injury associated with DRESS syndrome. Five patients (83%) were treated with corticosteroids for a mean duration of 29 days, and one patient (17%) recovered without treatment.

Historically, the most commonly identified DRESS culprits from the literature include allopurinol, antiepileptics, sulfonamides and vancomycin. In this study, case of COVID-19 with DRESS were caused by antibiotics. In those with COVID-19 DRESS, hydroxychloroquine, vancomycin, piperacillin/tazobactam, ceftriaxone and azithromycin have previously been identified as culprits.[2–4] Approximately 70% of patients with COVID-19 who are hospitalized receive antibiotics, but < 10% have secondary bacterial infections.[5] Given that antibiotics are not the primary treatment of COVID-19 pneumonia but are instead often used empirically for a complicating bacterial pneumonia, improved measures to limit unnecessary antibiotic use in COVID-19 may prevent the development of DRESS.

The DRESS diagnostic criteria are notably similar to COVID-19 infection signs; for example, fever and/or multiorgan dysfunction may be due to either DRESS or COVID-19. However, skin rashes in response to viral infection (viral exanthems) typically present within 14 days of symptom onset.[6] No patients included in the series had rash onset within 13 days from COVID-19 symptom onset, suggesting that the rash was drug induced and part of DRESS, and not the result of viral infection.

Notably, all patients in this study had markedly high eosinophilia, with most values peaking at more than $3{\cdot}00 \times 10^9$ cells L^{-1}. This is despite use of corticosteroids in four patients (67%), who could have had lysed, masked or attenuated peripheral eosinophilia. The current data do not support that eosinophils play either a protective or pathogenic role in COVID-19 under normal circumstances.[7] While the estimated mortality of DRESS syndrome is 5–10%, and the in-hospital mortality from COVID-19 is 15·2–24·5%,[8] none of the patients with DRESS and COVID-19 died in this study.

This study involved case finding through informatics methods for DRESS syndrome and COVID-19 PCR-positive testing. As such, we may not have captured all cases of both COVID-19 and DRESS concurrently. Data collection was retrospective, which may have resulted in missing or biased data. However, given that inpatient COVID-19 diagnosis and management were harmonized across our health system, we do not suspect misclassification.

It is not surprising that DRESS syndrome can occur in patients with COVID-19, given that patients are severely ill with long lengths of stay and antibiotic exposure. Patients with DRESS and COVID-19 had longer lengths of

Table 1 Case descriptions of patients with concurrent drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome and COVID-19

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Demographics						
Age (years)	75	80	57	61	31	39
Gender	Male	Male	Female	Male	Female	Female
Comorbidities	DM, HTN, COPD	HTN, cancer, CAD	HTN, COPD	DM, HTN	Asthma	DM, asthma
Features of COVID-19						
COVID-19 symptoms	SOB	Cough, SOB, malaise	Cough, fever, SOB	Cough, SOB, malaise	Headache, fever, malaise	Cough, SOB, N/V, anosmia
Intubation	Yes	Yes	Yes	Yes	Yes	Yes
Intensive care unit	Yes	Yes	Yes	Yes	Yes	Yes
Time from COVID-19 to admission (days)	6	7	5[a]	23[a]	10[a]	9[a]
Features of DRESS syndrome						
RegiSCAR validation criteria	3 (possible)	4 (probable)	7 (definite)	8 (definite)	4 (probable)	7 (definite)
Naranjo score[b]	7, 7	4, 4	10	7, 8	8, 8	7, 7
Skin rash						
Extent (skin surface %)	28%	26%	94%	52%	Unknown	100%
Appearance	Morbilliform	Morbilliform	Morbilliform	Morbilliform	Morbilliform	Morbilliform
Onset (days from COVID-19 onset)	25	46	13	42	39	17
Onset (days from admission)	19	39	8[a]	18[a]	29[a]	8[a]
Onset (days from suspect drug initiation)	13	34	8	15	26	6
AEC peak ($\times 10^9$ cells L^{-1})	4·73	3·49	5·83	5·06	4·75	2·97
Fever (> 38·5 °C)	Yes	Yes	Yes	Yes	Yes	Yes
Involved organs	Kidney	Liver, kidney	Liver, kidney	Liver, kidney	Liver, kidney	Liver, kidney
Potential culprit drugs[c]						
Probable	Cefepime, vancomycin	Cefepime, vancomycin	Vancomycin	Cefepime, vancomycin	Vancomycin, meropenem	Cefepime, vancomycin
Virological studies						
Positive	COVID-19	COVID-19, HBV	COVID-19, HHV-6	COVID-19	COVID-19	COVID-19
Negative	HHV-6, HBV, HCV, HIV	HCV	EBV, CMV, HAV, HBV, HCV, HIV	CMV	HSV-1, HSV-2, VZV, EBV, CMV, HAV, HBV, HCV, HIV	HSV-1, HSV-2, VZV, CMV, HHV-6, HBV, HCV, HIV
DRESS treatment	None	Methylprednisolone (3 mg kg^{-1}) × 2 days, prednisone (1 mg kg^{-1}) × 25 days	Methylprednisolone (1 mg kg^{-1}) × 12 days	Methylprednisolone (0·5 mg kg^{-1}) × 19 days	Prednisone (1 mg kg^{-1}) × 66 days	Methylprednisolone (2 mg kg^{-1}) × 21 days
Time to DRESS resolution (days)	8	25	31	25	55	43

AEC, absolute eosinophil count; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CMV, cytomegalovirus; DM, diabetes mellitus; EBV, Epstein–Barr virus; HAV, hepatitis A; HBV, hepatitis B; HCV, hepatitis C; HHV, human herpesvirus; HSV, herpes simplex virus; HTN, hypertension; N/V, nausea/vomiting; SOB, shortness of breath; VZV, varicella zoster virus. [a]Based on admission date to an outside hospital. [b]The scores correspond in order to the drugs listed under 'Potential culprit drugs'. [c]Based on provider assessment.

hospitalization than those with COVID-19 alone.[8] Cases may be associated with significantly high eosinophil counts and multiorgan involvement, but may not be associated with worse outcomes from DRESS or COVID-19. It is necessary to expand this study over time, to different health systems and with longitudinal follow-up to assess long-term sequelae, to improve the characterization of DRESS in COVID-19.

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.