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Case Series

Pharmacovigilance of cutaneous adverse drug reactions-a focused research in times of COVID pandemic

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ABSTRACT

Severe cutaneous adverse drug reactions are limiting, ranging from 5 cases per million including acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia systemic symptoms (DRESS) to 1 case per million of toxic epidermal necrolysis. Cutaneous adverse drug reactions following drug therapy of COVID-19 are not uncommon. Viral infection and drug interactions predisposes to the development of cutaneous adverse drug reactions, as already documented with Epstein-Barr virus, cytomegalovirus, human herpesvirus 6, and HIV. The Adverse drug reaction monitoring center of CNMCH has actively participated in pharmacovigilance programme of India by reporting few adverse drug reactions including the following cases. It is iterated that pharmacovigilance programme extends beyond just mere detection and reporting of adverse drug reactions and also should involve in assessment and understanding the cases, thus facilitating control and prevention of these cases. Particularly in times of COVID pandemic there has been continuous amendment in the treatment guidelines both at the central and state level. Incorporation of various antibiotics, antiparasites and antiviral drugs for the treatment of COVID, has potentiated the risk of development of drug allergies. Admittedly, the detailed understanding of drug allergy cases has been in general constrained with a relative lack of access to standardized laboratory diagnostic tests. Focused research is the need of the hour in order to understand the drug allergies better. In this study we have included those cases reported by department of medicine and dermatology of Calcutta national medical college and hospital in the past six months. All the cases were COVID positive and were treated conservatively by de-challenging the culprit drug and administration of antihistamines, topical steroids, while a few was put on systemic steroid therapy. There were six such reported cases of cutaneous adverse drug reaction following COVID treatment. There were four cases of maculopapular drug eruptions, while the other cases were diagnosed with fixed drug eruptions and acute generalized exanthematous pustulosis respectively. All the cases were reported under pharmacovigilance programme of India.

Keywords: Pharmacovigilance programme of India, Cutaneous adverse drug reaction, Acute generalized exanthematous pustulosis, DRESS, Maculopapular rash, Fixed drug eruptions

INTRODUCTION

Coronavirus disease caused by severe acute respiratory syndrome virus has spread widely and become a globally pandemic. It is associated with multiorgan disorders, among which dermatological manifestations are commonly diagnosed. Viral infection and drug interactions predisposes to the development of cutaneous adverse drug reactions, as already documented with Epstein-Barr virus, cytomegalovirus, human herpesvirus 6, and HIV. Non-classical activation of the immune system results in 'intolerance' or 'pseudo allergic' reactions. In these cases, the drugs act as hapten or prohapten may directly induce mast cell degranulation or release of

inflammatory mediators such as leukotrienes, which produce clinical syndromes. Drug reactions including acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and DRESS are severe cutaneous adverse reactions to drugs acknowledged to be dominantly T-cell mediated. Cases of severe cutaneous adverse drug reaction are limiting, ranging from 5 cases per million including acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia systemic symptoms (DRESS) to 1 case per million of toxic epidermal necrolysis.[1]

The adverse drug reaction monitoring center of CNMCH has actively participated in pharmacovigilance programme of India by reporting few adverse drug reactions including the following cases. It is iterated that pharmacovigilance programme extends beyond just mere detection and reporting of adverse drug reactions and also should involve in assessment and understanding the cases, thus facilitating control and prevention of these cases.[2] Particularly in times of COVID pandemic there has continuous amendment in the treatment guidelines both at central and state level. Incorporation of various antibiotics, anti-parasitic and antiviral drugs for treatment of COVID, has potentiated risk of development of drug allergies.[3] Admittedly, detailed understanding of drug allergy cases has been in general constrained with relative lack of access to standardized laboratory diagnostic tests. Focused research need of hr in order to understand drug allergies better.[4]

Objective

Primary objective of this study is to observe the number of cases of CADR out of treatment of Covid pneumonia

CASE SERIES

It is a cross sectional study done on covid patients attending in fever clinic at CNMCH within six months duration. Patients with RTPCR positive, admitted in COVID ward in CNMCH with features of adverse drug reaction were included in this study. Patients not willing to participate or having severe mental illness were excluded from the study.

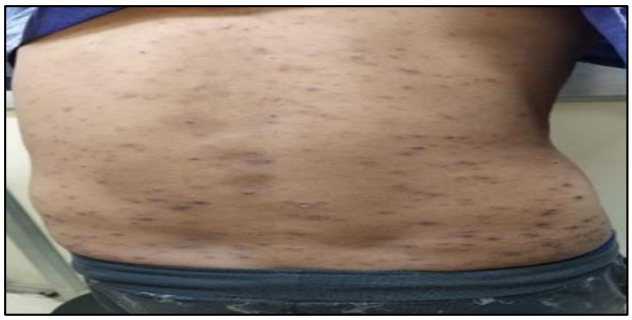

Figure 1: Provisional diagnosis-cotrimoxazole induced maculopapular rash in 44 years old male patient (Case 1).

In case 1, a 42 years old male patient with RT PCR for COVID-19 positive, was advised to take tablet cotrimoxazole for 7 days. He showed itching, non-tender maculopapular rashes over abdomen, after 4 days. After withdrawal of this drug, these were recovered with symptomatic management.

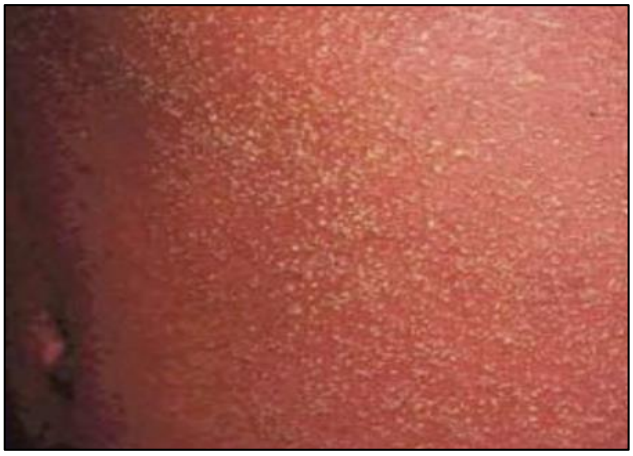

Figure 2: Provisional diagnosis-azithromycin induced AGEP in a 11 year old female patient (Case 2).

In case 2, a 11 year old girl with RTPCR for COVID-19 positive, was advised to take tablet Azithromycin 500 mg once daily for 7days. She complained of pustular rashes over abdomen and forearm and this was diagnosed as acute generalized exanthematous pustulosis (AGEP).

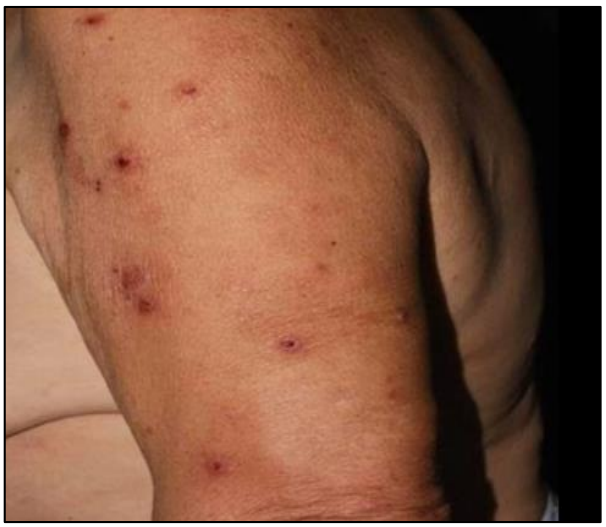

Figure 3: Provisional diagnosis remdesivir induced maculopapular rash in a 82 year old male patient (Case 3).

In case 3, 82 years old male, with RT PCR for COVID-19 positive, was advised to take tablet Remdesivir once daily for 7 days. After 6 days, he complained of appearance of itching, non-tender maculopapular rashes over arms and forearms. After withdrawal of this drug, these were recovered with symptomatic management.

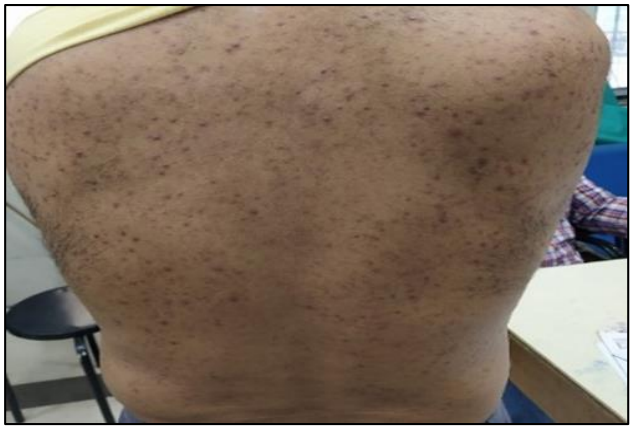

Figure 4: Provisional diagnosis-HCQ induced maculopapular rash in 42-year-old male patient (Case 4).

In case 4, 40 years old male patient with RT PCR for COVID-19 positive, was advised to take tablet Hydroxychloroquine 400 mg once daily for 7days. After 6 days, he complained of appearance of non-itching, non-tender purple maculopapular rashes over trunk and back. After withdrawal of this drug, these were recovered with symptomatic management within 7 days.

In case 5, 15 years old male patient with RT PCR for COVID-19 positive, complained of non-tender and non-itching purple eruptions over lips and forearms 5 days after taking tablet doxycycline 100 mg once daily. These were diagnosed as fixed drug eruptions (FDE). After withdrawal of this drug, these were recovered with symptomatic management within 10 days.

In case 6, 50 years old male patient with RT PCR for COVID-19 positive, was advised to take tablet Azithromycin 500 mg once daily for 7 days. After 6 days, he complained of appearance of non-itching, non-tender purple maculopapular rashes over trunk. After withdrawal of this drug, these were recovered with symptomatic management within 13 days.

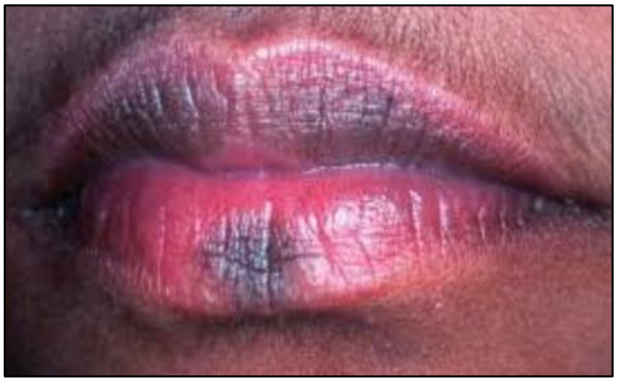

Figure 5: Provisional diagnosis doxycycline induced FDE in a 15-year-old male patient (Case 5).

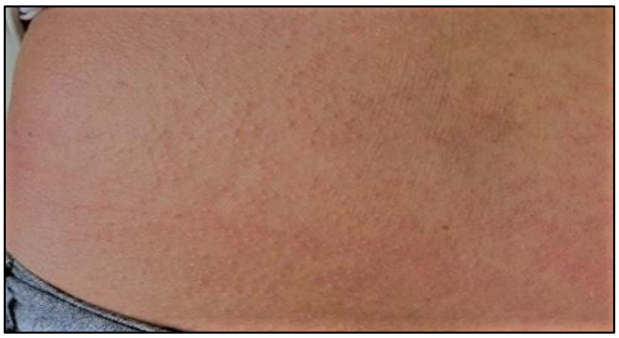

Figure 6: Provisional diagnosis azithromycin induced maculopapular rash in a 25-year-old male patient (Case 6).

Table 1: Description of case series of different cutaneous adverse drug reactions during COVID-19 pandemic.

Patient's age (years)	Sex	Diagnosis	Culprit drug	Date of onset	Date of recovery	Naranjo score	WHO UMC score
42	M	Maculopapular rash	Co-trimoxazole	4 days after intake	13 days after withdrawal	5	Probable
11	F	AGEP	Azithromycin	5 days after intake	12 days after withdrawal	4	Possible
82	M	Maculopapular rash	Remdesivir	6 days after intake	13 days after withdrawal	6	Probable
40	M	Maculopapular rash	HCQ	6 days after intake	7 days after withdrawal	6	Probable
15	M	FDE	Doxycycline	5 days after intake	10 days after withdrawal	7	Probable
50	M	Maculopapular rash	Azithromycin	6 days after intake	13 days after withdrawal	5	Probable

DISCUSSION

COVID-19-associated cutaneous manifestations had been increasingly reported, their pathophysiological mechanisms need to be extensively explored.[5] Cutaneous adverse reactions during Covid 19 pandemic were classified into pustules (pseudo-chilblain) (19%), other vesicular eruptions (9%), urticarial lesions (19%),

maculopapular eruptions (47%) and livedo or necrosis (6%).[6] There were 6 cases of cutaneous adverse drug reactions taken. Among them 5 patients were male and one is female patient. Four cases were diagnosed as maculopapular drug rash (about 67%) due to administration of co trimoxazole, remdesivir, hydroxychloroquine and azithromycin. One case of doxycycline induced fixed drug eruption (16.5%) and azithromycin induced acute generalized exanthematous pustulosis (16.5%) were reported. Most patients who presented with an erythematous rash had mild itch. There was no correlation between the presence of rash and fever. Involved sites were primarily the trunk and upper limbs, but the head and face were largely spared. In other studies, other investigations like prothrombin time, d dimer level, fibrinogen etc. were measured to correlate the type rashes with purpura.[7] In this study, no other investigations were made. Patients were not advised for any antigen antibody test to exclude herpes or varicella infection.[8] The adverse drug reactions were rated between 4 to 7 in Naranjo's scale and probable in WHO-UMC scale. Diagnosis of drug allergy is based on clinical examination and through history taking as confirmatory laboratory tests are very limited. After withdrawing the drugs, all the adverse drug reactions were reduced simultaneously. All of them were discharged with favorable condition. All the cases were reported under PVPI.

CONCLUSION

All the drugs causing those effects are commonly used drugs in COVID-19 pandemic situation. The patients should be gone through for antibiotic sensitivity tests. Patients' compliance and adherence should be priority before administration of antibiotics. The role of pharmacovigilance programme should not be only restricted to mere reporting but also emphasis should be given to proper follow up.

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