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CASE REPORT

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome following Ticagrelor administration leading to serious complications.

Dr. Chandrama Das[1*], Dr. Deepika Ramrao Dharmkare[2], Dr. Siddhartha Mani[3], Dr. Ranabrata Sen[4]

[1]Resident, Dept. of Cardiology, NH-R. N. Tagore Hospital, Kolkata, India)
[2]Resident, Dept. of Cardiology, NH-R. N. Tagore Hospital, Kolkata, India)
[3]Consultant, Dept. of Cardiology, NH-R. N. Tagore Hospital, Kolkata, India)
[4]Resident, Dept. of Cardiology, NH-R. N. Tagore Hospital, Kolkata, India)

*chandramadas14@gmail.com

ABSTRACT

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is rarely reported with administration of Ticagrelor. We report a case, where such complication developed after 7 days of Ticagrelor administration, leading to acute severe complications requiring hospitalization. There was airway and renal involvement with elevated inflammatory markers. On withdrawing Ticagrelor, there was rapid resolution of symptoms.

Introduction

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, first described in 1936 during treatment with anticonvulsant drugs is an idiosyncratic drug reaction presenting with rash, fever, lymphadenopathy and single or multiple organ involvement

Rapid identification is essential because the key to treatment is stopping the offending medication as soon as possible. However, there is ongoing debate regarding the possible therapeutic role of corticosteroids.

Ticagrelor administration leading to DRES Syndrome as seen in our case necessitating hospitalization and Critical care is not very common.

Case Report

A 69 years male, hypertensive and diabetic gentleman presented on 24/8/2023 with complaints of facial puffiness, reddish discolouration of face and trunk, perineal swelling, acute onset dyspnea which was progressively increasing since last 2 days and required local hospitalization with Oxygen support, following which patient was shifted to our hospital for better management.

The patient had Inferior Wall Myocardial Infarction, coronary angiogram showing Triple Vessel Disease with left ventricular systolic dysfunction (Left Ventricular Ejection Fraction – 40%) and hence underwent Percutaneous Coronary Intervention(PCI) with stenting to Right Coronary Artery on 15/8/2023 and PCI with stenting to Obtuse Marginal 1, Obtuse Marginal 2 and Left Anterior Descending Artery on 18/8/2023. He was put on treatment with Dual Antiplatelet Therapy (aspirin and ticagrelor), Atorvastatin, Trimetazidine, Ranolazine, Bisoprolol, Torsemide/ Spironolactone combination, Dapagliflozin/ Metformin combination and pantoprazole.

The patient reported that after taking ticagrelor he experienced generalized itching for last few days, although he couldn't specify about the incriminatory drug as he was on multiple medications.

Patient was dyspneic on presentation with SaO2 of 88% at room air. Physical examination revealed temperature 38° C, swelling of entire face along with the eyelids to such an extent that the patient was unable to open eyes, swelling of lips was also noted, maculo-papular itchy rash was present over face and trunk (Fig. 1, 2). There was no evidence of lymphadenopathy or organomegaly. Chest auscultation revealed diffuse rhonchi and coarse occasional crackles. Cardiovascular examination revealed tachycardia with S3 gallop and short ejection flow murmer at aortic area. No other remarkable findings were noted in systemic examination.

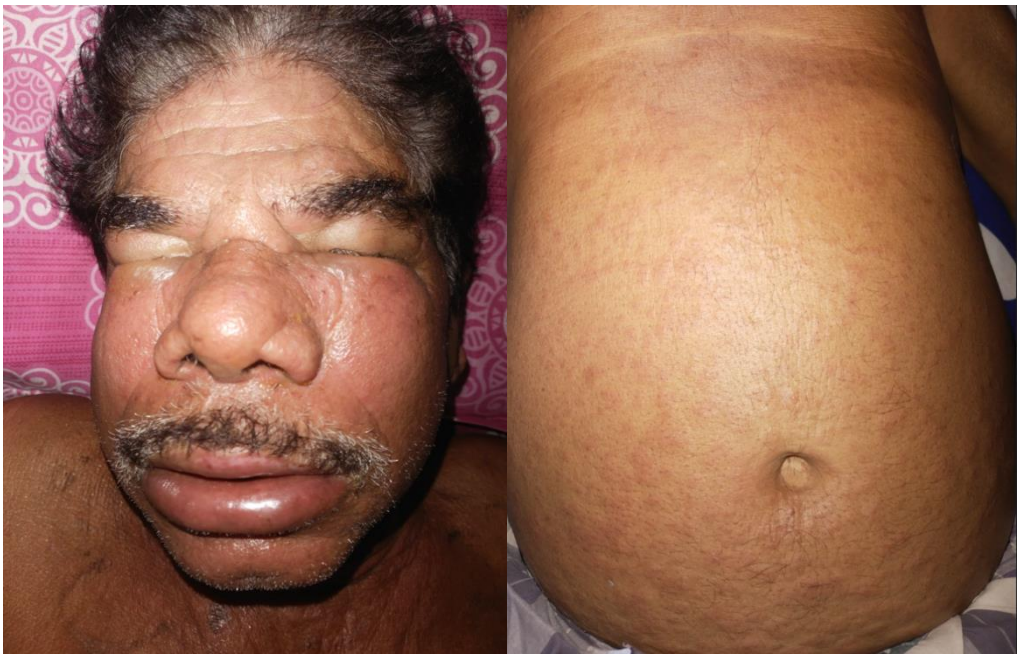

Fig. 1, 2: Swelling of face and lips with redness. Diffuse reddish maculo-papular rashes over face and trunk.

Initial investigations revealed the following:

24/8/23
TLC - 21700/microl
Absolute counts: Neutrophil-19530/microl Lymphocyte-610/microl Eosinophil – 960/microl
ESR – 15mm/1 hr
CRP – 65.4 mg/l
Serum IgE – 3372.02KIU/L
S creat – 1.54 mg/dl
Ast – 75 u/l, alt – 61 u/l, alp – 191 u/l

Urine routine examination showed glycosuria with 4-6 pus cells, urine c/s showed no growth of organism, malarial antigen was negative for Plasmodium vivax and Plasmodium falciparum. Serological evaluation was done for Salmonella typhi, Leptospira, Dengue, Scrub typhus and all were negative. Viral panel from throat swab revealed commensals and no definite growth. Thyroid antibody(IgM) was negative.

Based on the clinical and biochemical parameters Dress syndrome was suspected after consultation with dermatologist. Ticagrelor was stopped on suspicion and clopidogrel was started with reloading with 300 mg in its place along with initiation of steroid therapy, inj. Hydrocortisone 100mg thrice, cream betamethasone+fusidic acid local application twice, and antibiotic Injection Cefuroxime to prevent secondary bacterial infection to which the patient responded well, facial lesions started fading away along with improvement of biochemical parameters in the next 72 hours. USG whole abdomen revealed mild splenomegaly, fatty liver and mesenteric lymph nodes.

Blood parameters during further course in the hospital are as follows:

26/8/23	28/8/23
TLC – 18700/microl	TLC – 17500/microl
Absolute counts: Neutrophil – 13920/microl Eosinophil - 1010/microl	Absolute counts: Neutrophil - 8750 Eosinophil – 4200
S creat – 1.04 mg/dl	S creat – 0.93 mg/dl

The patient was discharged with tab aspirin, tab clopidogrel, tab atorvastatin, tab torsemide, tab bisoprolol, tab allegra, tab teczine, betamethasone+fusidic acid after 5 days since this hospitalization.

Discussion

Drug induced hypersensitivity reaction dates back to the introduction of hydantoin in the 1940s, reporting lymphadenopathy[1]. Different terminologies have been coined in last few decades to explain such reaction with different diagnostic criterias. *drug-induced pseudolymphoma* by Satlztein, *anticonvulsant hypersensitivity syndrome* (AHS), *drug-induced hypersensitivity* (DIHS), etc. were coined at different times. The term DRESS was introduced by Bocquet et al[2] and was based on a series of 24 patients by Callot et al[3] in 1996, The "R" in DRESS was changed from *rash* to *reaction* due to its diverse cutaneous presentations.

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is an idiosyncratic drug reaction presenting with rash, fever, lymphadenopathy and single or multiple organ involvement. In our case it was seen that patient presented with maculopapular facial rash along with acute kidney injury however there was no H/O fever.

Common agents which can lead to dress are phenytoin, phenobarbital, carbamazepine, sulphonamides, dapsone, allopurinol, captopril, calcium channel blockers, ranitidine, thalidomide, minocycline, sulfasalazine, non-steroidal anti-inflammatory drugs, tuberculostatics, α-methyldopa, antiretroviral drugs (zalcitabine, neviparine), etc.

This DRESS syndrome has a long latency period with onset usually ranging from 2 to 6 weeks after the initiation of the therapy[5], however in this case patient presented within 9 days of initiation of the inciting agent. The first symptoms are usually fever and rash. Almost 75% of the cases present with lymphadenopathy. Most commonly affected organ in DRESS syndrome is the liver however kidney, lung and heart are other sites that can also be affected, in this case patient landed in acute kidney injury. The diagnosis of DRESS syndrome is mainly clinical taking into account the latency period, diversity of symptoms, and exclusion of similar non-drug-induced conditions.

In order to systematise the diagnosis and management of DRESS multiple diagnostic criteria have been developed, albeit with limited success.

Bocquet *et al*, was the first to publish the diagnostic criteria for DRESS in 1996[6]. It includes the presence of three symptoms simultaneously

- Drug-induced skin eruption
- Eosinophilia ≥ 1500/mm^3

  And

  At least one of the following systemic abnormalities:
- Lymphadenopathy
- Hepatitis (transaminases >2 ULN)
- Interstitial nephropathy
- Interstitial lung disease
- Myocardial involvement

In this case we can see that the patient is fulfilling the above criteria i.e. drug induced skin eruption, eosinophilia along with acute kidney injury.

Skin biopsy may be an useful diagnostic tool but is usually non-specific. It shows a lymphocytic infiltration of the papillary dermis, with eosinophils and is generally

denser than in other drug reactions[7]. The most common differential diagnoses include Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hypereosinophilic syndrome and Kawasaki disease[8].

Ticagrelor is generally tolerated in most patients with acute coronary syndrome and is not a very common agent leading to DRES Syndrome. According to the drug description, hypersensitive reaction with ticagreloris relatively rare (≥1/1,000, <1/100). According to the Drug Information Portal (U.S. National Library of Medicine), a side effect of rash from ticagrelor was reported in 34 cases by the U.S. Food and Drug Administration. Quinn and Connelly[9] reported the first case of hypersensitive reaction to ticagrelor.

In another case, patient developed exanthematous itchy rashes after ticagrelor intake for 2 days. The rash improved after discontinuation, with a recurrence upon resumption of ticagrelor[10].

Structures of ticagrelor and clopidogrel differ. Patients with ticagrelor hypersensitivity, might be less likely susceptible to cross-reactive hypersensitivity to thienopyridines antiplatelet drugs (clopidogrel, prasugrel, and ticlopidine). Similar was the case in our patient with rapid resolution of symptoms on withdrawal of Ticagrelor and no further recurrence with clopidogrel initiation. Role of steroids need to be evaluated further.

Conclusion:

Many drugs have been incriminated as causative of DRES Syndrome, however, Ticagrelor is relatively rare in that list. Here we discussed a case of DRES Syndrome occurring after 7 days of Ticagrelor administration, leading to generalised rask with skin and mucosal involvement, organ involvement(kidney) and airway compromise landing into emergency crisis. Withdrawal of the drug led to rapid and sustained recovery.

Conflicts of Interest:

None

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None

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