

Title of the manuscript: Trimetazidine a hitherto unreported cause of Drug reaction with eosinophilia and systemic symptoms

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CASE REPORT

A 64-year-old female presented to the dermatology unit with a 2-week history of generalized redness, scaling and pruritus, associated with fever. She suffered from dilated cardiomyopathy and was on treatment with aspirin, carvedilol and torsemide for 10 years. In addition, she had been started on trimetazidine 6 weeks prior in view of her deteriorating angina.

On examination, the patient was febrile and had exfoliative dermatitis involving more than 90% of body surface area, facial edema, hemorrhagic crusting over lips and edema of the distal extremities. (Figure 1) There was significant lymphadenopathy in bilateral cervical and axillary regions but no palpable hepatosplenomegaly. On investigation, she had eosinophilia (serum eosinophils $700/\text{mm}^3$) and impaired renal function (blood urea 177 mg/dL, serum creatinine 5.5mg/dL). Serology for hepatitis B and C viruses was negative while HHV6/7 testing was not available. Her total leucocyte count was $5600/\text{mm}^3$, lymphocytes were $1800/\text{mm}^3$ with no atypical lymphocytes on peripheral smear. Complement levels and liver functions were normal, ANA negative, urine examination was essentially normal and chest-X ray showed no abnormality. There was no history of a pre-existing dermatoses and the patient's previous renal function tests, performed routinely every six months, showed no abnormality.

Accepted Article

A diagnosis of Drug reaction with eosinophilia and systemic symptoms (DRESS) with renal involvement, possibly induced by trimetazidine was considered. Naranjo probability score was 5 signifying a probable association, while RegiSCAR score was 7, consistent with a definite diagnosis of DRESS syndrome (Table1). In view of the extensive involvement, the patient was started on prednisolone 1mg/kg/day along with supportive care in terms of fluid and electrolyte management, high protein diet, condy's compresses and paraffin gauze dressings and topical antibiotics over eroded surfaces. In view of poor renal function, dialysis was done on the day of admission and again on days 1 and 4 of admission. As renal function deterioration had been acute, with normal documented renal function beforehand, and the patient was old and had multiple co-morbidities, a renal biopsy was not attempted. The patient's skin condition started improving with discontinuation of presumed culprit drug trimetazidine while aspirin, carvedilol and torsemide was continued. Prednisolone was gradually tapered off over 6 weeks of hospital stay. (Figure 2) The renal condition also gradually improved over this time and her renal functions were back to normal at the time of discharge.

Discussion

DRESS is an idiosyncratic life-threatening multi-organ hypersensitivity reaction that usually appears 2-6 weeks after drug exposure.[1] Most common culprit drugs are anticonvulsants (carbamazepine, lamotrigine, phenobarbital, phenytoin, valproate), antimicrobials (dapsone, rifampicin, isoniazid, cotrimoxazole, vancomycin), allopurinol, diuretics, Non-steroidal anti-Inflammatory drugs, antihypertensives(amlodipine and captopril), and antidepressants (fluoxetine,

bupropion).The prognosis depends entirely on the visceral involvement, with a fatal outcome in about 10% of cases.[2] The most commonly internal organ involved is liver(75-94%) followed by kidney (12-40%), lung, heart and central nervous system.[3] Severe DRESS syndrome, with significant systemic involvement necessitates addition of prednisone, 1 mg/kg/d, or an equivalent.[2]

A lymphocyte transformation test was unavailable at our center, and the patient refused a drug patch test post recovery. Hence, the diagnosis could not be confirmed by further allergological work-up, which is a limitation. Still, the chronology of events with simultaneous cutaneous manifestations and renal dysfunction and the complete recovery with treatment strongly suggested a drug induced etiology for both events and the RegiSCAR score confirmed a diagnosis of DRESS.

Trimetazidine is a cytoprotective anti-ischemic drug commonly prescribed by cardiologists. It is generally well tolerated with only a few reported adverse effects like gastrointestinal disturbances, thrombocytopenia, agranulocytosis and liver dysfunction. However, no serious cutaneous adverse reactions have been reported with the drug as yet.[4]

In view of the severity of DRESS that developed in our patient, with trimetazidine as the most likely cause, and especially with an association with severe renal dysfunction requiring short term hemodialysis, it is important for clinicians to be aware of this potentially serious adverse effect of the drug. Further, it is essential to know the variable outcomes of DRESS induced renal impairment in order to prognosticate the patients appropriately.

References

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Figure Legends

Figure 1: Upper chest showing erythema and scaling

Figure 2: Face showing (A) exfoliative dermatitis at the time of admission (B) resolution after 6 weeks

Table 1: RegiSCAR DRESS scoring system

RegiSCAR criteria fulfilled	Patient's Score
Extent of rash >50% body surface area	1 point
Rash suggestive of DRESS	1 point

Systemic involvement: a) Lymphadenopathy b) Eosinophilia c) Atypicallymphocytosis d) Organ involvement	4 (Lymphadenopathy, Eosinophilia and organ involvement)
Relevant negative serological tests	1 point
Total score	7 points



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COD_13715_Figure 2A and 2B.jpg