Case Report

DRESS syndrome: Tricky to diagnose but easy to treat

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ABSTRACT

A 27-year-old female presented to us with a short history of fever, jaundice, rash, and worsening hepatic dysfunction subsequent to treatment with intravenous antibiotics and alternative medicine for a urinary tract infection. The eosinophilia, lymphadenopathy, and transaminitis prompted us to consider a diagnosis of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) which can be fatal if not treated. The patient showed improvement in clinical and laboratory parameters after a course of steroids. This case is presented as DRESS syndrome that can prove rapidly fatal if not diagnosed and treated immediately.

Key words: Drug Reaction with Eosinophilia and Systemic Symptoms, Eosinophilia, Transaminitis, Rashes

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is an idiosyncratic drug reaction characterized by fever, skin rashes, and hepatic dysfunction. Various medications have been implicated in DRESS, primarily anticonvulsants, sulfonamides, antitubercular agents, penicillins, hydroxychloroquine, and proton-pump inhibitors. The incidence of DRESS is 1 per 1000–10,000 exposures [1]. Untreated, the mortality rate can be as high as 10% [2].

We report this case as mortality is high in untreated DRESS, and hence, a high index of clinical suspicion and early recognition is critical for appropriate management. In addition, this is one of the few reported cases linking DRESS to native medicine intake.

CASE REPORT

A 27-year-old female with no prior comorbidities had undergone inpatient treatment with piperacillin-tazobactam for a urinary infection 2 weeks before admission at our center. Following discharge, she received a course of native medicine (Ayurveda) for malaise and fatigue. She presented to us with a 3-day history of fever, jaundice, and abdominal pain. On arrival at the emergency department, her vitals were as follows: Blood pressure – 90/60 mmHg, heart rate – 120 beats per minute, and respiratory rate – 20 breaths/min. She had a diffuse maculopapular rash, predominantly on the forearms and legs. Cervical lymphadenopathy and right hypochondriac tenderness were noted.

Investigations done on admission revealed anemia and leukocytosis (15,200 cells/cumm) with significant eosinophilia (24% – absolute eosinophil count: 3648). Procalcitonin was elevated at 16 ng/ml (>10 ng indicative of sepsis). She also had hepatic dysfunction in the form of transaminitis**,** hyperbilirubinemia, and elevated international normalized ratio (INR) (PT-control: 11.5, test: 25.6, and INR: 2.17). Serial investigations are summarized in Table 1. Considering the patient's occupation (farming), the fact that she lived in a leptospirosis endemic area, and the elevated bilirubin, we considered an initial diagnosis of leptospirosis/sepsis with multiple organ dysfunction syndrome. However, this diagnosis did not explain the eosinophilia, and a day later, her lepto IgM was reported negative. The sensitivity of lepto IgM is reported to be 86% [3]. Considering her age group, the eosinophilia and the lymphadenopathy, a remote possibility of Hodgkin's lymphoma, were considered. However, node biopsy revealed only reactive lymphadenopathy. The worsening transaminitis, persistent eosinophilia, history of prior antibiotics, and alternative medicine use prompted us to consider DRESS as a diagnosis.

With the diagnosis of DRESS, the patient was initiated on pulsed methylprednisolone (1 g/day × 5) therapy. Improvement was noted on the 2nd day of steroids in the form of reducing eosinophilia and transaminitis. By the 4th day, her fever, transaminitis, and eosinophilia had resolved completely. The patient was discharged on tapering steroids. On follow-up, clearing of the rash was noted. Steroids were tapered and stopped and the patient was completely well on further follow-up visits.

DISCUSSION

DRESS syndrome is also known as drug induced pseudolymphoma, multisystem hypersensitivity reaction, febrile mucocutaneous

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Table 1: Laboratory investigations of the patient

	Normal range	On admission	Day 03	Day 05 (Day 02 of steroids)	Day 08 (Day 05 of steroids)	Day 12
Hemoglobin	14–18 g/dl	10.1	9.8	10.3	10.8	11.1
Total cell count	4,000–11,000/cumm	15,200	12,100	13,100	10,700	9,800
Differential count	N, L, E, M, B	57,15,24,4,0	43,35,22,0,0	60,32,8,0,0	67,31,0,2,0	68,30,1,1,0
Absolute eosinophil count		3648	2662	1048	0	98
Platelet count	1.5–4 lakh/cumm	2.38	1.56	1.89	1.45	3.12
INR		2.17	2.22	1.99	1.34	1.11
Serum total bilirubin	0.3–1.2 mg/dl	2.27	3.52	3.06	1.18	0.8
Serum direct bilirubin	0–0.2 mg/dl	1.64	3.36	2.82	0.2	0.2
SGOT	up to 35 IU/L	92	1045	660	34	28
SGPT	up to 45 IU/L	114	540	328	43	35
Serum creatinine	0.7–1.3 mg/dl	1.04	0.65	0.70	0.68	0.78
Urea	10–50 mg/dl	32	11	12	10	12
Sodium	136–145 mEq/L	136	138	140	139	138

syndrome, and various other names [4]. It is a potentially life-threatening, severe adverse reaction with a mortality rate of 10% due to fulminant hepatitis with hepatic necrosis [2].

Initially, DRESS was reported after phenytoin use [5]. Subsequently, various other drugs including other anticonvulsants, sulfonamides, antitubercular agents, penicillins, proton-pump inhibitors, and hydroxychloroquine have been implicated [6-8]. In this case, it is difficult to pinpoint the causative agent. Piperacillin-tazobactam has been reported to cause DRESS [9]. However, the alternative medicines that the patient had received may have also played a role. A high percentage of Indians rely on complementary and alternative medicine systems including Ayurveda and Siddha [10]. While these may be useful in certain situations, the fact that the exact composition of these drugs is difficult to determine is a disadvantage; additionally, manufacturing processes are not completely standardized.

The exact pathogenesis of DRESS is still unclear; postulated mechanisms involve the reactivation of viruses and the activation of host immune responses against the virus [11]. Typically, DRESS manifests as a maculopapular eruption with fever and lymphadenopathy 2–6 weeks after the initiation of the incriminated agent. Further deterioration can result in the involvement of multiple systems producing hepatic, hematological, renal, pulmonary, and cardiac manifestations [12]. Our patient had cutaneous, hematological, and hepatic involvement. A study done by Ang *et al*., on 27 patients admitted with DRESS syndrome at a tertiary care center in Singapore showed morbilliform cutaneous eruption, hepatitis, eosinophilia, and fever in 81.5%, 96.3%, 81.5%, and 77.8% of the patients, respectively [13].

The diagnosis is usually clinical as there is no gold standard for confirmation. The skin patch test and lymphocyte transformation test can aid in supporting the diagnosis [14]. RegiSCAR inclusion criteria for a potential case of DRESS include the following; (three or more required) [15]: 1. Hospitalization 2. Reaction suspected to be drug related, 3. Acute skin rash 4.Fever above 38°C 5.Enlarged lymph nodes at least two sites 6. Involvement of at least one internal organ 7.Blood count abnormalities such as lymphocytes above or below the laboratory limits; eosinophils above the laboratory limits (in percentage or absolute count); and platelets below the laboratory limits. Our patient satisfied most of the above criteria (though she had lymphadenopathy only at one site).

The most important step in the management of DRESS is the immediate cessation of the suspected offending drug [16]. Supportive treatment includes antipyretics for fever, emollients, and topical steroids for cutaneous manifestations. We had administered meropenem to our patient with the initial diagnosis of severe sepsis (procalcitonin positive, tachycardia, and hypotension), however to be noted, empirical antibiotic therapy may result in exacerbation of the condition due to cross-reactivity between drugs [4]. Systemic corticosteroids are the mainstay in the treatment of DRESS. Rapid resolution of skin rash and fever occurs within days after initiation of corticosteroids. The recommended initial dose is 1.0 mg/kg/day (oral) of prednisolone which is tapered off gradually over 6–8 weeks based on clinical response [4,16]. In more severe illness, like in our patient, a course of pulsed methylprednisolone, 30 mg/kg intravenously for 3–5 days, can be administered, followed by oral corticosteroids with gradual tapering. Intravenous immunoglobulin), plasmapheresis and immunosuppressive agents (cyclophosphamide, mycophenolate mofetil, and rituximab) can also be used as alternative treatment modalities [4,16]. Most patients recover with the withdrawal of the offending drug and early initiation of corticosteroids.

CONCLUSION

DRESS syndrome is a potentially life-threatening adverse drug reaction. Diagnosis is clinical (presence of skin rash, fever, lymphadenopathy, hepatitis, and hypereosinophilia) as there are no gold standard tests for diagnosis. Most patients show complete resolution of symptoms within days after initiation of corticosteroids.

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