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Case Report

Severe drug reaction with eosinophilia and systemic symptoms with acute liver failure managed with therapeutic plasma exchange: case report

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a drug reaction which is associated with systemic symptoms. The exact pathogenesis is not known but may be related to drug specific immune response. The severity of disease varies from mild skin eruptions with transaminasemia to life threatening organ failure. Liver is the most common organ involved. However, acute liver failure is less common. Once liver failure develops patients need liver transplant. Transplant is not always feasible. We present a case report of a middle-aged male who presented with phenytoin induced DRESS and acute liver failure. He was salvaged with low volume plasma exchange; 1.5 to 2 times of patient's plasma volumes was replaced with fresh frozen plasma. This new and novel technique has no major side effects can be life-saving in situations where the patient cannot undergo a transplant.

Keywords: DRESS, Acute liver failure, Therapeutic plasma exchange

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) occurs in approximately 0.9 to 2 per 100,000 patients per year.[1] The most commonly implicated drugs include aromatic anticonvulsants (phenytoin, carbamazepine), allopurinol, antibiotics (sulphonamides, minocycline, vancomycin, anti-tuberculosis drugs), nevirapine and mexiletine. Clinically the patients present with fever, rash, lymphadenopathy, eosinophilia, atypical lymphocytosis and variable organ involvement. Liver is the most common organ involved and it manifests as elevated liver enzymes. Kidney and lung involvement can also occur. In severe case acute liver failure and cardiac involvement may occur. In some patients there is reactivation of human herpes virus and cytomegalovirus and this is associated with poor outcome. Management involves prompt identification and removal of offending drug and avoidance of unnecessary drugs that may cross react and cause clinical deterioration.[2,3] Mild disease (skin eruption and modest elevation of liver enzymes [<3 * ULN]) can be managed with topical steroids. For severe disease with pulmonary and renal involvement systemic steroid is needed. For acute liver failure a liver transplant is needed. In the absence of transplant, the prognosis is poor. We report probably the first case of a 45-year-old male who presented with severe DRESS with acute liver failure who could not undergo a transplant because of poor financial condition and was successfully managed with therapeutic plasma exchange (TPE). TPE can be life-saving, especially in resource constrained settings.

CASE REPORT

A 45-year-old male had a road traffic accident and CT scan showed contusion in fronto-temporal area. He was recovering at home and was started on prophylactic phenytoin. After 20 days patient developed itchy maculopapular rash involving face and extremities (Figure 1 and 2).

Figure 1: Facial puffiness and desquamation.

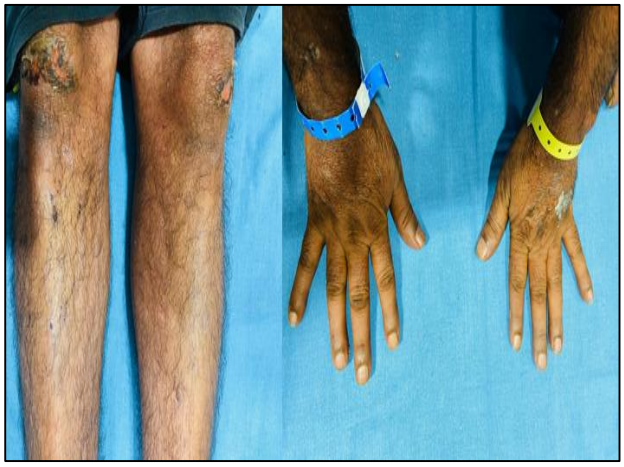

Figure 2: Rash over legs and hands.

Later on, they became erythematous and there was desquamation. Patient developed jaundice five days after rash and ten days later he was disoriented with irrelevant talking and inability to recognize attendants. Examination revealed a male with altered sensorium, fever, maculopapular rash, desquamation of skin, facial edema, cervical lymphadenopathy, icterus, flapping tremors and a liver span of ten cm. There was no ascites and pulmonary examination was also normal. Blood investigation on admission showed leukocytosis with the eosinophilia, direct hyperbilirubinemia with elevated transaminases as well as alkaline phosphatase, coagulopathy, normal platelet count, no ascites on ultrasound abdomen and no extrahepatic biliary obstruction on magnetic resonance cholangiopancreatography (Table 1).

Work up for liver dysfunction including viral infection [HBsAg, IgM HBc antibody, anti-hepatitis C virus (HCV) antibody, IgM-anti-hepatitis A virus (HAV) antibody, IgM anti-hepatitis E virus (HEV) antibody], autoimmune hepatitis [anti-nuclear antibody (ANA), anti-smooth muscle antibody (SMA), anti LKM1 antibody], Wilson disease (normal ceruloplasmin and no Kayser-Fleischer ring) were negative. RegiSCAR score was 6 confirming a diagnosis of definite DRESS. Patient was advised liver transplantation in view of deteriorating sensorium however family refused it as they could not afford the treatment. Then they were offered TPE. The patient underwent 3 sessions of low volume plasma exchange. After three sessions the lab parameters improved and patient was out of encephalopathy. Patient also received steroid which was tapered over 3 months. On follow up after 6 months patient was symptom free with normal liver function tests.

Table 1: Blood investigations at admission and discharge.

Investigation	Value at admission	Value at discharge
Hemoglobin (g/dl)	12.2	13.1
Total leucocyte count (per microliter)	14,000	6200
Absolute eosinophil count (per microliter)	5040 (36%)	62 (1%)
Platelets (per microliter)	2,09,000	2,93,000
Peripheral smear	No atypical cells, eosinophilia	
Creatinine (mg/dl)	0.82	0.40
Sodium (meq/L)	125	132
Potassium (meq/L)	4.3	5.4
International normalized ratio	5.16	0.98
Total bilirubin/ direct bilirubin (mg/dl)	15.6/8.8	5.9/3.2
Aspartate aminotransferase/ alanine aminotransferase (IU/L)	186/182	46/44
Alkaline phosphatase (IU/L)	768	200
Gamma glutamyl transpeptidase (U/L)	1670	180
Protein (g/dl)	3.9	4.5
Albumin (g/dl)	2.7	3

DISCUSSION

We report a case of severe DRESS syndrome with acute liver failure due to phenytoin in a male patient who was successfully managed with low volume plasma exchange in the absence liver transplantation. Acute liver failure is a life-threatening disorder with mortality rate of approx., 75 % in the absence of transplant. In the INDILI registry 10% patients with drug induced liver injury (DILI) develop acute liver failure. Most common drugs implicated for DILI are anti-tubercular drugs (46.4%), complementary and alternative medicines (13.9%) and antiepileptic drugs (8.1%).[4] Phenytoin is a common drug implicated in DRESS syndrome and overall the incidence of DRESS with anticonvulsants varies from 1 in 1000 to 1 in 100000 exposures.[5] Higuchi et al described a 53 year old patient with DRESS due to diaphenylsulphone treated with plasma exchange where patient had relapse of disease despite withdrawal of offending agents. However, patient did not have ALF.[6] DRESS complicated by acute renal failure, pancreatitis, thyroiditis and hepatitis (No ALF) and resistant to systemic steroid was successfully managed by plasma exchange.[7] Phenytoin toxicity due to suicidal intention treated with plasma exchange is also reported but the patient did not have DRESS or ALF.[8] Similarly toxic epidermal necrosis has been managed with plasma exchange.[9] Relapses are common after resolution of acute disease and can occur in up to 25% of patients with a median symptom free period of about 4.5 months.[10] This is probably the first case report where patient with severe DRESS and ALF was successfully managed with low volume TPE . There was no relapse of the disease till 12 months of follow up.

In low volume plasma exchange 1.5 to 2 times the patient's plasma (70* weight of the patient*[1-Hematocrit]/100) is removed and is replaced by fresh frozen plasma (as in our patient) or albumin. The exact mechanism by which plasma exchange helps in DRESS is not known but may be related to decreased levels of pro-inflammatory cytokines. In ALF plasma exchange may help by providing the liver time to regenerate and it also improves liver microcirculation by decreasing levels of vWF and increasing levels of ADAMTS 13.

Patients who recover from DRESS must avoid offending and cross-reacting drugs. DRESS survivors should be monitored for development of autoimmune diseases like autoimmune thyroiditis, alopecia, vitiligo, autoimmune hemolytic anemia, lupus erythematosus and type I diabetes in the long term.

CONCLUSION

To conclude, DRESS is managed with stopping the offending agent and local or systemic steroids (if severe organ involvement is present). However, with ALF liver transplantation is the only hope. In resource constraint settings TPE can be successfully used to treat severe DRESS with ALF.

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