CASE REPORT

Sudden Worsening of DRESS Syndrome on Tapering Steroid Dose with Dramatic Improvement on N-acetylcysteine and Steroid Dose Escalation

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Abstract
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a serious and life-threatening drug reaction characterized by fever, skin rash, peripheral eosinophilia, presence of atypical lymphocytes in peripheral blood smear, generalized lymphadenopathy and involvement of other body organs. The only agreed-upon therapy for DRESS in literature is withholding the culprit drug. There are no controlled trials on the use of steroids in this condition. Reports on the use of N-acetylcysteine in DRESS are very few. We report here a case of 36 year old female with severe DRESS that deteriorated rapidly upon tapering steroid therapy and dramatically improved on combination of pulse steroid therapy and N-acetylcysteine. This paper suggests that higher doses and gradual tapering of corticosteroid is a wise approach in treating patients with DRESS. It further emphasizes the possible beneficial role of N-acetylcysteine in this condition.

Key Words: DRESS, Eosinophilia, Drug Reaction, N-acetylcysteine, Steroid Therapy.

Introduction

DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) is a serious and life-threatening drug reaction characterized by fever, skin rash, peripheral eosinophilia, presence of atypical lymphocytes in peripheral blood smear, generalized lymphadenopathy and involvement of other body organs, commonly the liver. Over 44 drugs have been implicated in the literature as the cause of DRESS, with Carbamazepine being the most common culprit (1). The exact pathogenesis underlying this serious drug reaction is still unknown. Proposed theories include defective metabolism and detoxification of the drugs by CYP450 and reactivation of human herpes virus 6 (HHV-6) (2,3). The only agreed upon therapy for DRESS is withdrawal of the offending drug. In spite of their use in many case reports, there are no controlled trials on the

use of corticosteroids in this condition. Furthermore, the optimal dose of corticosteroids, the duration of therapy and their effect on mortality is unknown. Reports on the use of N-acetylcysteine in DRESS can be counted on the fingers of one hand (4-6). We report here a case of severe DRESS that deteriorated rapidly upon tapering steroid therapy and dramatically improved on combination of pulse steroid therapy and N-acetylcysteine. In our case, other possible diagnoses have been excluded by extensive work-up.

Case Report

Clinical presentation

A 36 year-old Egyptian woman was admitted to the medical ward because of four week history of high grade fever and three week history of skin rash. Four weeks prior to this admission, she was prescribed Sulphasalazine 500 mg tid for non-specific colitis that manifested as abdominal pain and bloody diarrhea. Colonoscopy with colonic biopsy at that time revealed non-specific chronic colonic inflammation. One month from starting Sulphasalazine, she developed fever and skin rash. The rash began over her back and extended to her abdomen and limbs. She also reported nausea with repeated vomiting, generalized body aches and arthralagia. She visited the emergency room twice for her symptoms, and was diagnosed as "possible viral illness". She denied any extra-marital sexual contact and never smoked or drank alcohol. Family history was unremarkable and there was no sick contact. Physical examination revealed a sick-looking woman with temperature of 39.9 °C, shivering with tachycardia at 122 beats per minute. A diffuse erythematous macular rash that blanches on pressure extended over all her body (Figure 1). Her sclera was icteric and her conjunctiva was pale. She had bilateral axillary lymph node enlargement and a hepatomegaly of 4 cm below the costal margin.

Initial investigations

Her complete blood count on admission revealed leukocytosis of 38.5 $X10^3$/ul with lymohocytosis (63%), and eosinophilia (23%). Hb was 11.1 g/dl, Hct 35.6 %, MCV 69.8 fl and platelet count was 278 X 10^3/ul. Erythrocyte sedimentation rate (ESR) was 13 mm/hr and C-reactive protein (CRP) was 19 mg/l (Normal < 5). A blood smear showed mild hypochromic-microcytic anemia with anisopoikilocytosis, lymphocytosis with many pleomorphic atypical lymphocytes, left shift and prominent eosinophils. Derangement of liver function tests on admission was noted. Alkaline phosphatase (ALP) was 444 U/L, alanine aminotransferase (ALT) was 153 U/L, aspartate aminotransferase (AST) was 138 U/L, total protein was 57 g/L, plasma albumin was 29 g/L, total bilirubin was 58 umol/L, prothrombin time (PT) 12.9 seconds and INR 1.2. Serum creatinine and blood urea nitrogen were within normal range. Chest radiography was unremarkable. Abdominal ultrasound on admission showed hepatomegaly (19.1 cm) with normal echotexture. Repeated blood and urine cultures did not grow any organism and procalcitonin level was 0.77ng/ml. Blood testing for enterovirus, parvovirus B19, measles, cytomegalovirus (CMV), Epstein Bar Virus (EBV), adenovirus, herpes viruses (HSV) including HSV1, HSV2, HHV6 and HHV7 using polymerase chain reaction (PCR) were all negative. In addition, testing for rubella, measles and hepatitis A, B and C viruses and human immunodeficiency virus (HIV) were all unremarkable.

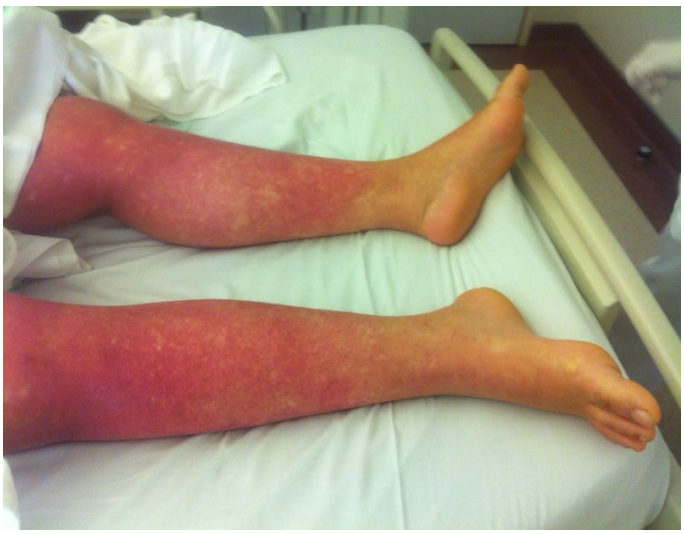

Figure 1. The skin rash appearance at presentation

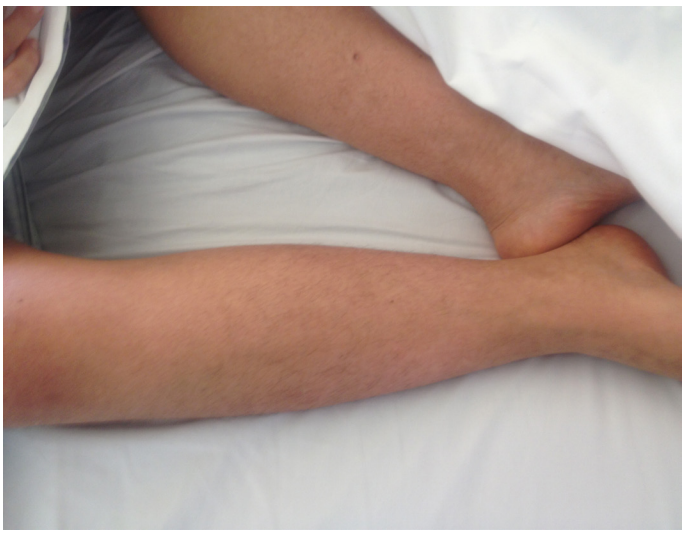

Figure 2. Skin rash disappeared two days after the use of steroids and N-acetylcysteine

Table 1. The diagnostic criteria for Hypersensitivity Syndrome / Drug Reaction with Eosinophilia and Systemic symptoms (HSS/DRESS) (HSS/DRESS) proposed by the RegisSCAR and for drug-induced hypersensitivity syndrome (DIHS) established by a Japanese Consensus Group.

The RegiSCAR Inclusion Criteria[1] (9-11)	The Japanese Consensus Group[3] (12,13)
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: -Lymphocytes above or below the laboratory limits -Eosinophils above the laboratory limits[2] -Platelets below the laboratory limits	1. Macropapular rash developing > 3 weeks after starting with a limited number of drugs 2. Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug 3. Fever (>38°C) 4. Liver abnormalities (alanine aminotransferase > 100 UL-1)[4] 5. Leucocyte abnormalities (at least one present) -Leucocytosis (> 11 x 10 9 L-1) -Atypical lymphocytosis (>5%) -Eosinophilia (> 1.5 x 109 L-1) 6. Lymphademopathy 7. Human herpesvirus 6 reactivation
1. Three or more required to confirm the diagnosis. 2. In either percentage or absolute count	3. The diagnosis is confirmed by the presence of the seven criteria above (*typical DIHS*) or of the five (1-5) (*atypical DIHS*). 4. This can be replaced by other organ involvement. such as renal involvement.

Auto-immune workup including antinuclear antibodies (ANA), extractable nuclear antigens (ENA), rheumatoid factor and serum complement levels were all normal. Serum ferritin and cryoglobulin levels were within normal range. Direct Coomb's test was positive. Abdominal and chest CT scans with contrast showed widespread intra-abdominal and axillary lymph node enlargement. Excisional biopsy from enlarged left axillary lymph node revealed reactive changes only with no evidence of malignancy. Flow cytometry results showed no evidence of clonality. A skin biopsy of the rash was also performed and the microscopic evaluation revealed interface cytotoxic dermatitis and positive immunofluorescence at the basement membrane in a granular fashion with IgA, IgM, and C3. Mild acanthosis, vacuolization of the basal cell layer, and mild spongiosis were also seen.

Management and progress

Upon admission, Sulphasalazine was discontinued and intravenous fluids were started along with antibiotic coverage with Meropenem and Teicoplanin whilst waiting for blood culture results. However, despite this treatment, she continued to spike high grade fever with worsening of skin rash and rise in ALT (207 U/L) and AST (138 U/L). Oral Prednisolone was started on the fourth day after admission at a dose of 60 mg daily resulting in improvement of her fever and liver enzymes. However, one day after reducing Prednisolone dose to 40 mg daily anticipating the possibility of lymphoma prior to lymph node biopsy, her fever relapsed at 41°C and liver enzymes peaked (AST 2165 U/L and ALT 1520 U/L). N-acetylcysteine was administered in a dose of 11700 mg over 60 minutes (150mg/kg) then 50 mg / kg over 4 hours then 100 mg/kg over 16 hours along with intravenous infusion of Methylprednisolone 500 mg for 3 days. On the second day following administration of N-acetylcysteine and Methylprednisolone, the liver enzymes improved and continued to decrease till it eventually normalized. The white cell count improved and the skin rash disappeared (Figure 2). Lymphnode size returned to normal. Six days later, she was discharged home in good condition on oral Prednisolone 60 mg per day that was tapered over 3 months when it was discontinued. Subsequent follow up visits up to one year after stopping Prednisolone revealed no recurrence of symptoms and normal liver enzymes.

Discussion

DRESS (also named drug induced hypersensitivity syndrome and drug induced pseudolymphoma) is a very rare type of drug reaction with an estimated incidence of 1 in 1000 to 1 in 10,000 drug exposures and a mortality rate of 10% (7-9). Prompt diagnosis and early recognition of this syndrome is therefore of paramount importance. There are over 44 drugs that have been implicated in this syndrome with anticonvulsants (particularly Carbamazepine) being the most common culprit (1). Two sets of diagnostic criteria for DRESS have been proposed by the European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) (9-11) and a Japanese consensus group (scoring system for the diagnosis of DRESS (12,13). For DRESS definition to be fulfilled, a patient must have three of the four main RegiSCAR criteria: an acute rash, fever above 38°C, lymphadenopathy at two sites, involvement of at least one internal organ, and abnormalities in lymphocyte and eosinophil counts (Table 1). Additional criteria include hospitalization and that the reaction being suspected to be drug-related. The Japanese consensus group requires meeting seven of the nine criteria in this system or all of the first mentioned five namely a maculopapular rash developing > 3 weeks after drug initiation, clinical symptoms continuing > 2 weeks after stopping therapy, fever > 38°C, liver abnormalities (ALT > 100 IU/L) or other organ involvement, leukocytosis, atypical lymphocytes, eosinophilia, lymphadenopathy, or HHV-6 reactivation (Table 1). Although the diagnosis of our case might seem a straight forward DRESS, the initial differential diagnosis was broad and included malignant, infectious, and autoimmune processes and other severe drug reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. By employing extensive laboratory investigations, lymph node biopsy, and skin biopsy, we could exclude with confidence other potential differential diagnoses. Withdrawal of the offending drug is the only agreed upon treatment of DRESS in the literature. Use of corticosteroid therapy in such a condition lacks controlled trials and is based mainly on isolated case reports (5). Furthermore, the optimal dose of corticosteroids, the duration of therapy and the effect on mortality remain unknown (5). To the best of our knowledge, our case is the fourth in the literature to improve after N-acetylcysteine administration. In 1993, Gabay and colleagues reported the first favorable response to N-acetylcysteine for what seemed to be Sulphasalazine-induced DRESS at that time (4). There was no use of steroids in that case. Two additional reports regarding the use of N-acetylcysteine were published more recently (5,6). Jose and Klein reported a case of 66 year-old woman with Sulphasalazine-induced DRESS whose condition deteriorated despite withholding Sulphasalzine and the use of intravenous methylprednisolone at a dose of 20 mg every 8 hours (5). Her condition improved dramatically upon escalating the dose of Methylprednisolone and administration of N-acetylcysteine. Moling et al in a more recent paper described a marked improvement of the liver function test in a patient with sulphasalazine-induced DRESS who was treated initially only with N-acetylcysteine in suspicion of Paracetamol toxicity (6). As discussed above, due to lack of controlled trials, there is no consensus in the literature on the optimal dose or duration of therapy of coricosteroids in treating DRESS. Aggressive high dose steroid therapy has been emphasized in a recent report of 10 cases of DRESS (14). Our case deteriorated rapidly (within one day) of tapering steroid therapy from 60 mg to 40 mg after initial improvement and recovered dramatically up on escalating steroid dose to Methylprednisole 500 mg daily for three days along with administration of N-acetylcysteine. This might suggest that higher doses of steroid are needed when treating patients with severe DRESS. Furthermore, longer courses of steroids with gradual tapering may be a wiser approach to treat such patients. Regular follow up visits of our patient up to one year after discontinuation of steroid therapy confirmed no recurrence of symptoms and maintenance of normal liver function. An important limitation of this case report is that we could not determine with confidence whether the marked improvement observed in our patient was a result of N-acetylcysteine administration, escalation of steroid dose or both. The role of N-actylcysteine in the treatment of severe DRESS syndrome is a fertile area for future multicenter research

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