Case Report

Ceftriaxone induced drug rash with eosinophilia and systemic symptoms

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ABSTRACT

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a drug reaction commonly occurring in association with aromatic anticonvulsants and allopurinol. It is characterized by triad of fever, skin eruption, and systemic involvement. DRESS is rare with beta-lactam antibiotics and even rarer with ceftriaxone. We describe a case of pneumonia who developed ceftriaxone-induced rash, bicytopenia, eosinophilia, transaminitis and was eventually diagnosed and managed successfully as a case of DRESS.

Keywords: Ceftriaxone; Drug rash with eosinophilia and systemic symptoms; Eosinophilia

INTRODUCTION

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is an acute, severe, unpredictable cutaneous reaction to drugs leading to skin eruptions and visceral involvement. The characteristic features include a diffuse maculopapular rash, facial edema, exfoliative dermatitis, fever, lymphadenopathy, visceral involvement (renal impairment, carditis, pneumonitis), hematological abnormalities (mainly eosinophilia, lymphocytosis and atypical lymphocytes). DRESS was first described by Chaiken et al. in 1950 with dilantin (phenytoin). It occurs with numerous drugs (e.g., anticonvulsants, sulphonamides, and allopurinol). DRESS with beta-lactam antibiotics has been also reported. Ceftriaxone, a cephalosporin is used for variety of infections. This drug is known to be associated with rare and mild side-effects such as urticaria, skin rash, diarrhea, vomiting, transient neutropenia, and hemolysis. However, ceftriaxone-induced DRESS is rare. To the best of our knowledge, there have been only two cases reported in the literature. We report herein one case of DRESS induced by ceftriaxone.

CASE REPORT

A 33-year-old male was admitted (10, November 2013) with fever and dry cough of 4 days duration in a peripheral hospital. The patient had no known comorbidities and didn’t give history of any drug allergy in the past. On examination, he was found to be febrile (100 F), had a pulse of 90/min, blood pressure of 126/80 mmHg, respiratory rate of 24/min and had crackles in right infrascapular region. Based on the clinical examination and chest X-ray, he was diagnosed to have pneumonia. His hematological and biochemical parameters were within the normal limit. He was started on injection of ceftriaxone (1 g, intravenous, every 24 h). On the 3rd day of admission, his fever dropped down and he was afebrile by day 6. Ceftriaxone was continued. On the 7th day, he developed transaminases elevation, alanine aminotransferase (ALT) = 219 IU/L; aspartate aminotransferase (AST) = 356 IU/L; alkaline phosphatase (ALP) = 246 IU/L. On the 11th day, he had recurrence of high grade fever with maculopapular rash over trunk, extremities and swelling of wrist and ankles [Figures 1-3]. He was transferred to our center on day 11, with the following laboratory findings: Hemoglobin = 11.4 g%; total leucocyte count (TLC) = 1900/cm³ with relative eosinophilia of 10%; platelets (Plt) count = 1,47,000/cm³
His peripheral blood smear showed leucopenia with relative eosinophilia, 6% atypical lymphocytes, Plt: 1,50,000/cm$^3$ and no evidence of hemolysis and hemoparasite. His liver enzymes were markedly raised as below: ALT = 766 IU/L; AST = 2424 IU/L; ALP = 162 IU/L, and lactate dehydrogenase = 3732 IU/L. His urea and creatinine were 46 and 1.7 mg/dL, respectively. Bone marrow aspiration/biopsy was done and presented to be normal. His hepatitis B surface antigen, antihepatitis C virus antibody, and human immunodeficiency virus antibody were all negative. Rapid diagnostic test for malaria and dengue serology were negative. A diagnosis of ceftriaxone-induced DRESS was made, based upon European Registry of severe cutaneous adverse reactions (RegiSCAR) criteria.$^5$ Ceftriaxone was stopped and patient was treated with injection of dexamethasone 4 mg, thrice a day for initial 2 days and later oral prednisolone 60 mg/day, which was gradually tapered over 6 weeks. Only after 48 h of steroid therapy, patient started improving symptomatically and became afebrile after 72 h. His rash cleared over 5 days and his hematological and biochemical parameters started improving after 72 h and became normal by day 8 of starting steroids [Table 1].

## DISCUSSION

Drug rash with eosinophilia and systemic symptoms syndrome is a life-threatening adverse reaction to a drug with associated mortality rate of about 10%. Proposed mechanism of pathogenesis of DRESS has been failure of drug detoxification pathways leading to accumulation of harmful metabolites which in turn activate CD4 + CD8 + T-cells. These cells release interleukin-5 which activates eosinophils and sets up an inflammatory cascade.$^6$ Earlier, there was no consistent name for this syndrome and it was named after the culprit drug as phenytoin syndrome, allopurinol hypersensitivity syndrome, dapsone syndrome, etc., Bocquet et al.$^7$ proposed the term drug rash with eosinophilia and systemic symptoms (DRESS) to simplify the nomenclature of drug-hypersensitivity syndromes. Since then, various criteria have been evolved to define DRESS [Table 2]. Among all the criteria being used to diagnose DRESS, RegiSCAR criteria$^5$ is the most widely used.

Our patient was diagnosed as DRESS syndrome as he was fulfilling all Bocquet et al.$^7$ proposed criteria and criteria 1, 2, 3, 4, 6, 7 of RegiSCAR.$^5$ However, except for fever, no other Japanese consensus group criteria$^8$ was being fulfilled, as the symptoms and signs had appeared early (11 days of ceftriaxone administration), there was leucopenia (TLC = 1900) rather than leukocytosis, and absolute eosinophil count was only 190/cm$^3$ though there was relative increase in eosinophils (10% of TLC). Patient was treated as having ceftriaxone induced DRESS syndrome and he showed a uneventful recovery with steroids and cessation of the offending drug.
Table 1: Hematological and biochemical laboratory findings of the patient

| Laboratory test | On admission | Day 7 | Day 11 | Day 13 | Day 19 |
|-----------------|--------------|-------|--------|--------|--------|
| Hgb (g %)       | 13.0         | 12.8  | 11.4   | 12.6   | 12.2   |
| TLC (cm²)       | 7400         | 5600  | 1900   | 2800   | 6600   |
| DLC (P/L/E/M/B) | 62/33/4/1/0  | 66/27/1/0 | 30/58/10/2/0 | 48/41/8/2/1 | 78/16/3/2/1 |
| Platelets (cm³) | 2.0 L        | 1.80 L | 1.47 L | 1.68 L | 2.10 L |
| AST/ALT (IU/L)  | 27/22        | 356/219 | 2424/766 | 1098/438 | 34/28 |
| Serum bilirubin (mg/dL) | 0.8 | 1 | Total: 2.3 | Direct: 1.6 |
| LDH (IU/L)      | -            | 506   | 3732   | 1088   | 346    |
| Urea/creatinine (mg/dL) | 19/0.6 | - | 46/1.7 | 34/1.2 | 22/0.8 |

Hgb=Hemoglobin, TLC=Total leucocyte count, DLC=Differential leucocyte count, P=Polymorphs, L=Lymphocytes, E=Eosinophils, M=Monocytes, B=Basophils, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, LDH=Lactate dehydrogenase

Table 2: Scoring systems for diagnosis of DRESS

| Bocquet et al. | RegiSCAR study group | Japanese consensus group |
|----------------|----------------------|--------------------------|
| DRESS is confirmed by presence of 1 and 2 and 3 | More than 3 of the criteria are required for the diagnosis of DRESS | Typical DRESS (presence of all 7 criteria); atypical DIHS (all criteria present except lymphadenopathy and HHV-6 reactivation) |
| 1. Cutaneous drug eruption | 1. Hospitalization | 1. HHV-6 reactivation |
| 2. Adenopathies >2 cm in diameter or hepatitis (liver transaminases >2 times upper limit of normal) (or) interstitial nephritis (or) interstitial pneumonitis (or) cardiitis | 2. Reaction suspected to be drug related | 2. Prolonged clinical symptoms 2 weeks after discontinuation of causative drug |
| 3. Hematologic abnormalities | 3. Acute rash | 3. Maculopapular rash developing>3 weeks after starting drug |
| Eosinophilia>1.5x10⁹/L (or) atypical lymphocytes | 4. Fever above 38°C | 4. Fever above 38°C |
| 5. Lymphocyte abnormalities | 5. Involvement of at least one internal organ | 5. Lymphadenopathy |
| Eosinophils above or below laboratory limits | 6. Involvement of at least one internal organ | 6. ALT>100 U/L or other organ involvement |
| 6. Leukocyte abnormalities (at least one) | 7. Blood count abnormalities | 7. Leukocyte abnormalities (at least one) |
| Platelets below laboratory limits | Eosinophils above laboratory limits in percentage or absolute count | Leucocytosis (>11x10⁹/L) |
| | Platelets below laboratory limits | Atypical lymphocytosis (>5%) |
| | | Eosinophilia (1.5x10⁹/L) |

DRESS=Drug rash with eosinophilia and systemic symptoms, RegiSCAR=European Registry of severe cutaneous adverse reactions, DIHS=Drug-induced hypersensitivity syndrome, HHV-6=Human herpesvirus 6, ALT=Alanine aminotransferase

The culprit drugs most commonly associated with DRESS are anticonvulsants, allopurinol, minocycline, sulfasalazine, dapsone, nevirapine, and abacavir.[3] Ceftriaxone-induced DRESS is rare. To our knowledge, there have been only two cases of ceftriaxone-induced DRESS reported in the literature.[4] Until date, ceftriaxone has not been included in the list of drugs causing DRESS. DRESS is generally treated with moderate-or high-dose corticosteroids, but response may be suboptimal and prolonged treatment with systemic glucocorticoid may be required. Other immunosuppressive agents, such as cyclosporine, have also been used.[9]

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How to cite this article: Guleria VS, Dhillon M, Gill S, Naithani N. Ceftriaxone induced drug rash with eosinophilia and systemic symptoms. J Res Pharm Pract 2014;3:72-4.
Source of Support: Nil, Conflict of Interest: None declared.