Drug reaction with eosinophilia and systemic symptoms without skin rash

Sarita Sasidharanpillai, Manikoth P. Binitha, Neeraj Manikath, Anisha K. Janardhanan

Departments of Dermatology and Venereology and General Medicine, Government Medical College, Kozhikode, Kerala, India

Received: 13-04-2015
Revised: 30-04-2015
Accepted: 25-08-2015

Correspondence to:
Dr. Sarita Sasidharanpillai, E-mail: saritasclt@gmail.com

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a milder form of drug-induced hypersensitivity syndrome.[1] It can present in various or unusual clinical patterns[1,2] which may confuse the clinician since diagnosis is based mainly on the exclusion of other possible diseases. We report a case of DRESS induced by salazopyrin where the absence of a rash led to diagnostic difficulty.

Case Report

A 31-year-old man presented with high-grade fever, cough, jaundice, and vomiting of 5 days duration. His drug history included prednisolone 10 mg daily and salazopyrin 500 mg twice daily by mouth for the past 2 weeks, and hydroxychloroquin 200 mg twice daily by mouth for the past 1-year for pain in the right knee joint, which had been diagnosed as reactive arthritis.

On clinical examination, the patient was febrile, with a temperature of 42°C. There were multiple enlarged, firm, tender, mobile, anterior cervical and axillary lymph nodes ranging in size from 2 cm × 2 cm to 1 cm × 1 cm, as well as hepatosplenomegaly. There were no cutaneous lesions.

A complete blood count revealed a leukocytosis of 21,000 cells/mm³, comprising of 82% neutrophils, and an elevated absolute eosinophil count of 1822 cells/µl (normal: 450/µl). His liver function tests were deranged, with levels of total bilirubin 5.8 mg/dL (normal: 0.2–1.2 mg/dL), conjugated bilirubin 5.2 mg/dL (normal: 0.2–1.2 mg/dL), and alkaline phosphatase 512 IU/L (normal: 0–115 IU/L).

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Cite this article as: Sasidharanpillai S, Binitha MP, Manikath N, Janardhanan AK. Drug reaction with eosinophilia and systemic symptoms without skin rash. Indian J Pharmacol 2015;47:687-9.
bilirubin 4 mg/dL (normal: 0.1–0.4 mg/dL) aspartate transaminase 221 IU/ml (normal: 10–40 IU/ml), and alanine transaminase 247 IU/ml (normal: 7–56 IU/ml).

Urine microscopy, renal function tests, blood sugar and serum pancreatic enzyme levels, chest X-ray and electrocardiogram were all within normal limits. Bacterial cultures of urine and blood were sterile. Serology for antinuclear antibody and antibodies to human immune deficiency virus, hepatitis A, B, and C viruses, Epstein–Barr virus, dengue virus, chikungunya virus, typhoid, leptospira, and rickettsiae were all negative. An ultrasonogram of the abdomen confirmed the hepatosplenomegaly.

A peripheral blood smear revealed atypical lymphocytes accounting for 30% of the peripheral lymphocytes and an eosinophilia of 10% (normal <7% of the circulating leukocytes) [Figure 1a and b]. A cervical lymph node biopsy showed reactive hyperplasia. Bone marrow aspiration and trephine biopsy from the iliac crest showed respectively normocellular marrow and an increase in eosinophil precursors [Figure 2]. He was started on oral cefixime in a dose of 500 mg twice daily as an antibiotic cover. Since infective and autoimmune causes for the fever were not evident, the patient was suspected to have a drug allergy. As prednisolone and salazopyrine were the recently introduced drugs, they were stopped. Though cough and vomiting subsided, the fever persisted and repeated liver function tests on the 5th day of admission showed no improvement. A definite diagnosis of DRESS due to salazopyrin was made as per the registry of severe cutaneous adverse reactions (RegiSCAR) DRESS validation score.[12,13] The causality was “probable” as per the Naranjo’s adverse drug reaction probability scale.[14]

Treatment with oral prednisolone was initiated in a dose of 1 mg/kg body weight/day. Within 24 h, the fever had subsided, and the abnormal liver function tests steadily improved and normalized over the subsequent 4 weeks. The prednisolone was tapered slowly over 7 weeks so as to avoid the flare up of DRESS associated with rapid tapering of corticosteroids. A repeat abdominal ultrasonogram 2 months later revealed a normal study.

**Figure 1:** (a) Atypical and normal lymphocytes in the peripheral smear (Leishman, ×1000) (b) Increased number of eosinophils with normal lymphocytes (Leishman, ×1000)

**Figure 2:** Increased eosinophil precursors in the bone marrow biopsy (H and E, ×400)

**Discussion**

DRESS is considered a severe drug reaction with a case fatality rate of 10–20%. The unique features of this condition include a long latent interval between the onset of drug intake and the appearance of symptoms (1-week to 3 months), persistence or even worsening of the symptoms in spite of the withdrawal of the culprit drug as noted in our case, and waxing and waning of the disease often necessitating prolonged treatment with systemic steroids.[15] It is described as a reaction pattern characterized by the triad of rash, systemic involvement and eosinophilia.[16] However, on rare occasions, it can present as a purely systemic disease without any cutaneous involvement.[16,17] It can closely mimic viral exanthema or neoplastic or autoimmune diseases. In the absence of confirmatory diagnostic criteria, it remains a diagnostic challenge, especially in cases lacking a skin rash.

Currently, the RegiSCAR DRESS validation score is used to diagnose DRESS. One point each is assigned for: (1) Skin rash with two of the four features - facial edema, rash resolving with psoriasiform desquamation, purpuric lesions on areas other than the legs, and infiltrated skin lesions (2) rash involving >50% of the body surface (3) lymphadenopathy of size more than 1 cm, affecting two or more anatomic locations (4) the presence of atypical cells in the peripheral smear (5) eosinophilia in the range of 750–1499 cells/µl (6) involvement of one internal organ due to DRESS. If two or more internal organs are affected or eosinophilia is equal to or more than 1500 cells/µl, two points are added. If serology for antinuclear antibody, hepatitis A, B, and C infections are negative and the blood culture is sterile, one more point is added. One point each is reduced in the case of rash not suggestive of DRESS, skin biopsy conclusive of another diagnosis, symptoms resolving within 15 days, and the absence of fever. As per this score, our patient had a RegiSCAR score of 6, sufficient to categorize him as a case of definite DRESS.[12,13]

Patients with DRESS with mild or no skin involvement have been found to be immunocompromised - they were either receiving immunosuppressant drugs including prednisolone equal to or more than 10 mg/day or they were suffering from human immunodeficiency virus infection.[17] The concomitant administration of prednisolone 10 mg/day and hydroxychloroquin (which is an
immune modulator drug) with salazopyrin might be the reason for the absence of rash in our case.

The possibility of hydroxychloroquin precipitating DRESS was unlikely in our case since the patient was on this drug for a year without any untoward effects, and his symptoms resolved in spite of continuing the drug. The rare possibility of prednisolone inducing the reaction was ruled out by the lack of symptoms on its reintroduction.

We report this case to highlight the significance of a detailed drug history whenever a patient presents with pyrexia of unknown origin and systemic complications, with or without a rash. Once diagnosed, DRESS can be managed by withdrawing the drug and administering steroids, but mere withdrawal of the drug will not arrest the disease process and a delay in starting steroid treatment may prove fatal.

Financial Support and Sponsorship
Nil.

Conflicts of Interest
There are no conflicts of interest.

References
1. Criado PR, Avancini J, Santí CG, Medrado AT, Rodrigues CE, de Carvalho JF. Drug reaction with eosinophilia and systemic symptoms (DRESS): A complex interaction of drugs, viruses and the immune system. Isr Med Assoc J 2012;14:577-82.
2. Kardaun SH, Sidoroff A, Valeyr-ie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: Does a DRESS syndrome really exist? Br J Dermatol 2007;156:609-11.
3. Chen YC, Chang CY, Cho YT, Chiu HC, Chu CY. Reply to: Using a diagnostic score when reporting the long-term sequelae of the drug reaction with eosinophilia and systemic symptoms. J Am Acad Dermatol 2013;69:1060-2.
4. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
5. Kumari R, Timshina DK, Thappa DM. Drug hypersensitivity syndrome. Indian J Dermatol Venereol Leprol 2011;77:7-15.
6. Sasidharanpillai S, Riyaz N, Rajan U, Binita MP, Khader A, Mariyath OK, et al. Drug reaction with eosinophilia and systemic symptoms: Observations from a tertiary care institution. Indian J Dermatol Venereol Leprol 2014;80:221-8.
7. Ben M'trad M, Leclerc-Mercier S, Blanche P, Franck N, Rozenberg F, Filla Y, et al. Drug-induced hypersensitivity syndrome: Clinical and biologic disease patterns in 24 patients. Medicine (Baltimore) 2009;88:131-40.