Case Report

Aceclofenac-Induced Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome

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Abstract

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a rare but severe and potentially life-threatening systemic clinical condition. We report a case of a 44-year-old female, who developed DRESS syndrome after taking two doses of aceclofenac, paracetamol, and thiocolchicoside fixed-dose combination. The patient presented with maculopapular rashes, itching, fever, pedal edema, swelling of the face and lips, difficulty in swallowing, loose stools, and vomiting for 4 days following drug intake. Laboratory and histopathological investigations supported the diagnosis following RegiSCAR criteria. The DRESS syndrome in this patient was definite as per Naranjo's adverse drug reaction probability scale. The patient was adequately managed using systemic corticosteroids, antibiotics, and intravenous fluids. Aceclofenac is the most likely causative agent of DRESS syndrome in this patient. Early detection and withdrawal of the suspected drug along with adequate supportive treatment are the mainstay of management.

Keywords: Aceclofenac, eosinophilia, systemic symptoms syndrome, paracetamol, RegiSCAR criteria

Introduction

The prevalence of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome varies from 1/1000 to 1/10,000, with a mortality rate of 10%–20%.[1] The clinical manifestations include rashes, cough, eosinophilia, lymphadenopathy, and involvement of multiple internal organs. It has a long latency period, symptoms arising 2–6 weeks after the ingestion of the offending drug. DRESS syndrome is mostly caused by antibiotics, antigout agents, and anticonvulsants.[2] There is no published literature on aceclofenac causing DRESS syndrome. We report a case of DRESS syndrome induced by aceclofenac.

Case Report

A 44-year-old female patient was presented with the complaints of rashes and itching all over the body, fever, difficulty in swallowing, 5–8 episodes of loose stools, and 2–3 episodes of vomiting for 4 days. One day before the onset of these clinical features, the patient had received two doses of a tablet containing aceclofenac (100 mg), paracetamol (325 mg), and thiocolchicoside (4 mg) fixed-dose combination for body ache. A detailed medication history interview revealed that the patient had suffered a similar reaction 6 months ago after taking one dose of a fixed-dose combination containing aceclofenac (100 mg) and paracetamol (500 mg) for shoulder pain. However, she never experienced any adverse effects while she was using paracetamol alone in the past.

At admission, the patient was febrile (39°C), had bilateral pedal edema, cervical lymphadenopathy, swollen face and lips [Figure 1a], and generalized maculopapular rashes all over the body [Figure 1b]. The hematological test showed

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elevated total leukocyte count (18920 × 10^9 cells/L), lymphocytes (1759.56 × 10^9 cells/L), eosinophils (9970.84 × 10^3 cells/μL), and erythrocytes sedimentation rate (80 mm/h). The biopsies of gastrointestinal tract (GIT) revealed eosinophil infiltration in the lining of stratified squamous epithelium and in gastric and duodenal lamina propria suggestive of eosinophilic esophagitis, eosinophilic gastritis, and eosinophilic duodenitis, respectively [Figure 2a-c]. The bone marrow aspiration smear showed hypercellularity with increased eosinophils and their precursors [Figure 2d], and fine-needle aspiration cytology of cervical lymph node showed reactive lymphadenitis. The liver function test showed hypoalbuminemia (2.86 g/dL) and elevated alkaline phosphatase (543 U/L). The ultrasonography of abdomen and pelvis revealed hepatomegaly with fatty changes, thickened and edematous gall bladder wall reactionary, right mild pleural effusion with minimal ascites. The total RegiSCAR score was five indicating it a probable case of DRESS syndrome. The Naranjo's causality assessment scale score was ten, indicating a definite relation between drug exposure and DRESS syndrome in this patient. The patient was symptomatically better [Figure 1c and d] after receiving systemic steroids, antibiotics, and supportive treatments for 2 weeks.

Discussion

The DRESS syndrome usually occurs 2–8 weeks after the initiation of the offending drug, with a mean onset time of 3 weeks. Upon re-challenge with the offending drug, the sign and symptoms may reoccur within a day. A patient may typically experience fever in the early cycle of drug reaction, later accompanied by the development of other systemic symptoms. Rashes may appear as very mild exanthema to severe blisters and skin loss may present with frequent pruritus. The development of autoimmune reactions can be a sequela to DRESS syndrome.[3]

However, in this patient, the reaction appeared within 24 h of taking the causative agent on both occasions. During the first episode (6 months back), the reaction was limited to slight fever, rashes, facial edema, and edema of lower limbs. However, it was not thoroughly evaluated for the involvement of other organs and/or drugs for causing the reaction. The patient was hospitalized and was symptomatically treated. During the current episode, the reaction was comparatively much severe, probably because of the development of an autoimmune cascade after the first event.

The case was evaluated following RegiSCAR diagnostic criteria for DRESS syndrome.[2] The presence of absolute eosinophilia (9970.84 cells/μL) (score 1), generalized maculopapular rashes all over the body (>50% of body surface area) (score 2), exfoliative dermatitis and facial edema (score 3), negative for antinuclear antibody test, negative serology for Hepatitis B and C and other infections such as human herpes virus, cytomegalovirus, Epstein–Barr virus, and human immunodeficiency virus (score 4), and involvement of GIT (biopsies suggestive of eosinophilic esophagitis, gastritis, and duodenitis) (score 5) in this patient, contributed for a total score of five suggesting probable case of DRESS syndrome.

The most seriously damaged internal organ in this patient was the gastro intestinal tract. Other significant clinical features include cervical lymphadenopathy, liver enlargement with associated hypoalbuminemia, elevated alkaline phosphatase, edematous gall bladder wall, and right mild pleural effusion with minimal ascites. In addition, the bone marrow aspiration analysis revealed hypercellularity with increased eosinophils and their precursors. Despite these clinical features being

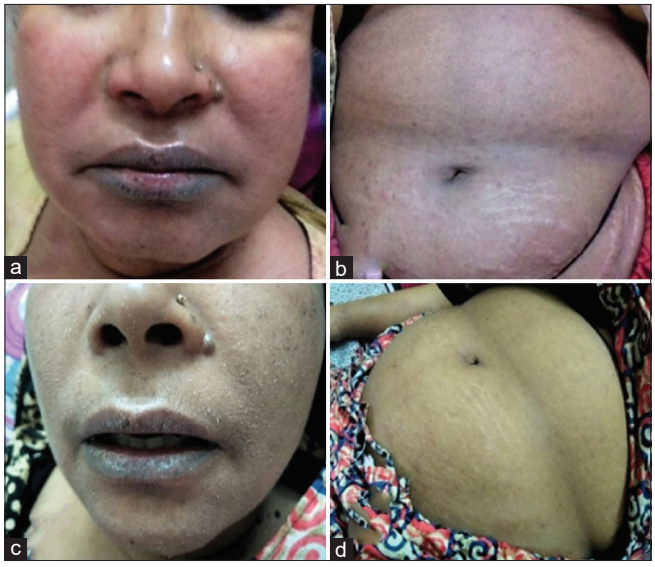

Figure 1: (a) Pigmented-edematous face and lips (b) Maculopapular rashes over trunk (c) Resolved pigmented-edematous face and lips after treatment (d) Resolved normal appearance of skin on trunk after treatment

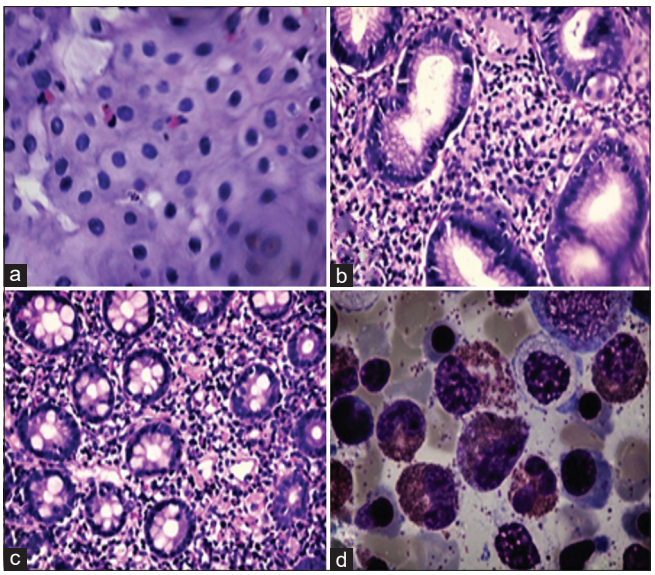

Figure 2: Biopsy slides showing eosinophilia (a) esophagus (b) Gastric section (c) Duodenum section (d) Bone marrow aspiration smear

significant, as the RegiSCAR criteria do not encompass these clinical features, they were not considered for diagnosing DRESS syndrome in this patient. The causality assessment following Naranjo's algorithm revealed a definite relation between drug exposure and DRESS syndrome.[4] The severity of DRESS syndrome in this patient was severe (level 5) requiring intensive medical care as per Modified Hartwig and Siegel scale.[5]

Anticonvulsants, antibacterials, antitubercular drugs, antivirals, sulfonamides, antipyretics, and analgesics are reported to cause DRESS syndrome. Among antipyretics and analgesics, paracetamol, diclofenac, celecoxib, and ibuprofen are the most common drugs reported.[2] Paracetamol can cause DRESS syndrome but it is very rare.[6] There are no reports of aceclofenac causing DRESS syndrome. Aceclofenac and diclofenac both belong to the same phenylacetic group of analgesics that share the same aromatic ring. Moreover, aceclofenac is partially metabolized into diclofenac, and there could be possibilities of cross-sensitivity existing between them in inducing hypersensitivity reactions.[7] Theoretically, there are possibilities that the reaction in this patient was aggravated due to the use of two potentially causative agents that are aceclofenac and paracetamol. However, it is important to note that, this patient had a safe history for the use of paracetamol alone, in the past. Therefore, the reaction in this patient is most likely because of aceclofenac.

There could be more than one possible mechanism for the development of DRESS syndrome. Accumulation of drug metabolites in individuals with genetic deficiency of metabolizing enzymes can trigger the eosinophilic activation and inflammatory cascade following the release of interleukin-5 from drug-specific T-cells. Second, a drug hypersensitivity may occur as a result of genetic associations between human leukocyte antigen (HLA). Polymorphism in genes encoding HLA molecules is another possibility. Finally, a virus-drug interaction associated with viral reactivation may induce a reaction.[2] As all the viral causes were ruled out in this patient, the pathogenesis of DRESS syndrome could be closer to the first two mechanisms.

The management of DRESS syndrome includes early detection and withdrawal of the causative agents, followed by supportive treatment. The use of systemic corticosteroids helps in significant improvement in clinical symptoms and laboratory results in DRESS syndrome.[2] In this patient, systemic corticosteroid therapy was used for 14 days to halt the accumulation of eosinophils, along with antibiotics to prevent sepsis and intravenous fluids to correct the electrolyte disturbances. Preventing similar adverse drug reactions for the same or similar drug/s in the future is also a part of patient management. The clinical pharmacist counseled patient and patient caretakers and an adverse drug reaction alert card had been provided. The patient was advised to carry and produce the alert card to the prescribers and the pharmacist as and when required, to alert them and prevent the use of the same or similar drugs in future.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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