Drug Reaction with Eosinophilia and Systemic Symptoms Secondary to Naproxen: A Case Report and Literature Review

Sreethish Sasi\textsuperscript{a}  Heba Altarawneh\textsuperscript{b}  Mahir A. Petkar\textsuperscript{c}  Arun P. Nair\textsuperscript{d}

\textsuperscript{a}Department of Internal Medicine, Hamad Medical Corporation, Doha, Qatar; \textsuperscript{b}Weil Cornell Medical College, Doha, Qatar; \textsuperscript{c}Department of Laboratory Medicine and Pathology, Hamad Medical Corporation, Doha, Qatar; \textsuperscript{d}Department of Infectious Diseases, Hamad Medical Corporation, Doha, Qatar

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Drug hypersensitivity · Drug rash · Eosinophilia

Abstract
Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe adverse drug reaction presenting with rash, fever, lymphadenopathy, and single or multiple organ involvement. It is most commonly associated with antiepileptics, NSAIDs, and sulfa drugs. We report a 40-year-old man who presented with a 1-week history of fever, sore throat, and a diffuse pruritic macular rash that started on the face and trunk before spreading to all extremities 4 weeks after the use of naproxen. He had lymphadenopathy, hepatosplenomegaly, transaminitis, and peripheral eosinophilia. A Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) score of 8 gave a diagnosis of definite DRESS syndrome. Significant resolution of symptoms and laboratory abnormalities were seen after 2 weeks of corticosteroid therapy. DRESS syndrome is a life-threatening condition, and the clinical status of patients can worsen rapidly. Given the high variability in clinical presentation, the diagnosis of DRESS syndrome
requires a high degree of suspicion and clinical judgment. Case reports on this entity will equip physicians in acute medicine to recognize and treat the condition early. This report reinforces the importance of using the RegiSCAR score in the diagnosis of DRESS syndrome.

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is an idiosyncratic, drug-induced hypersensitivity reaction that presents with skin rash, involvement of internal organs like liver, lung, or kidney, lymphadenopathy, and hematological manifestations such as eosinophilia and atypical lymphocytes. It is a rare condition with an annual incidence of 0.9/100,000 [1]. There is a latency of 2–8 weeks between drug exposure and the onset of skin rash in DRESS syndrome, which is more than in most other drug reactions. The most common culprits are antiepileptics like carbamazepine, lamotrigine, or phenytoin in 35%, NSAIDs in 13%, sulfonamides like sulfasalazine, dapsone, trimethoprim-sulfamethoxazole, or sulfadiazine in 12%, antibiotics such as vancomycin, minocycline, or penicillin in 11%, and allopurinol in 6% of cases [2]. The pathogenesis is complex and multifactorial. We present the case of a young man with no comorbidities who presented with fever, rash, lymphadenopathy, elevated liver enzymes, eosinophilia, and atypical lymphocytes 4 weeks after the use of naproxen.

Case Presentation

A 40-year-old South Asian man presented to the emergency department with a 1-week history of fever, sore throat, and a diffuse pruritic macular rash that started on the face and trunk before spreading to all extremities. One month before this presentation, the patient had been treated with naproxen 500 mg twice a day for 3 days by a local health center for back pain. On admission he had a low-grade fever, with otherwise stable vitals. Physical examination showed a diffuse maculopapular rash with centrifugal distribution on the head, nape of the neck, and extremities, including palms and soles. The lips were involved, but the oral cavity, conjunctiva, and mucous membranes were spared. There was mild facial edema but no peripheral edema. Nonblanching purpura was noted on the lower limbs with negative Nikolsky sign. The patient’s skin lesions on admission are shown in Figure 1. Initial laboratory studies revealed a white blood cell count of 12.4 × 10^3/µL, with 60% neutrophils, 30% lymphocytes, and 4% eosinophils (Table 1). A blood smear showed many pleomorphic atypical reactive lymphocytes. Renal function and electrolytes were normal, and polymerase chain reaction tests for common viral infections were negative. Serological tests for hepatitis and human immunodeficiency viruses were negative. Blood cultures were positive for Staphylococcus epidermidis, which is a common skin contaminant. Malarial smear and echinococcus serology were negative. Autoimmune serology was negative for antimitochondrial, antiliver kidney microsomes, and antinuclear antibodies. Complement levels (C3 and C4) were within normal range. On imaging, the patient had a normal chest X-ray. An abdominal ultrasound showed
mild hepatomegaly with fatty changes, gallbladder wall thickening, mild splenomegaly, and minimal free fluid in the abdomen. Computed tomography of the abdomen with contrast revealed a bulky spleen with two hypodense lesions. Proximal and mid ascending colon showed mucosal thickening. Echocardiography was normal.

During the emergency department’s initial evaluation, the patient received antihistamine, hydrocortisone, and levocetirizine, as drug reaction was suspected. However, he showed no signs of improvement. The fever persisted, reaching as high as 40°C, and he developed hypoxemia in room air (93%) with tachypnea. The lactic acid level was 4.2 mmol/L. Sepsis was suspected, and he was started empirically on broad-spectrum coverage with intravenous piperacillin-tazobactam 4.5 g 8-hourly. On the third day of admission, vancomycin was added as the Gram stain of peripheral blood showed gram-positive cocci in clusters. His clinical condition continued to worsen, and he was admitted to the intensive care unit as the requirement of oxygen went up to 12 L via a nonrebreather mask. Initial blood cultures were positive for *S. epidermidis* in one out of four bottles. However, repeated blood cultures were negative, and the labs showed progressive leukocytosis (38 × 10^3/µL) with eosinophilia (8.9 × 10^3/µL) as well as increasing bilirubin (68.0 µmol/L), aspartate aminotransferase (449 U/L), alanine aminotransferase (1,564 U/L), and alkaline phosphatase (436 U/L). Antibiotics were stopped after 4 days as clinical history and the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) score of 8 were suggestive of DRESS syndrome.

A 3-mm skin punch biopsy from the thigh revealed spongiotic epidermis with prominent lymphocytic exocytosis with occasional eosinophils (Fig. 2). The patient was then started on a 2-day course of 40 mg intravenous methylprednisolone followed by a 12-day tapering course of 80 mg oral prednisolone. He showed immediate response to the steroids (Fig. 3) and was discharged on day 14 after normalization of white blood cell count, eosinophil count (0.3 × 10^3/µL), coagulation profile, and improvement of the rash. Elevated liver functions were back to normal during follow-up after 1 month. There was complete resolution of his symptoms by the end of the third week.

**Discussion and Conclusion**

Some studies have revealed the genetic association in DRESS syndrome; notably, HLA-B*58:01 is associated with allopurinol hypersensitivity, and HLA-B*13:01 is associated with dapsone hypersensitivity [3, 4]. DRESS syndrome occurs as a result of the activation of T cells specific to each drug, making the reaction drug-specific. It often results in reactivation of viruses, especially human herpesviruses, a phenomenon thought to be due to the expansion of regulatory T cells [5, 6]. Patients usually present with high-grade fever, malaise, and lymphadenopathy, followed by a morbilliform eruption. The eruption spreads rapidly to involve >50% of the body surface area and the lesions become confluent, erythematous, and scaled. Facial edema is another classic feature. Most characteristic laboratory abnormalities described in DRESS syndrome are leukocytosis with eosinophilia >700 µL, presence of atypical lymphocytes, and elevated alanine aminotransferase [7]. Other clinical and laboratory features depend on the organs involved. The liver is the most commonly involved organ (in up to 86% of patients) and usually presents as hepatitis, jaundice, or asymptomatic transaminitis. Twenty to thirty percent of patients may have renal involvement presenting in the form of
acute interstitial nephritis. This is most commonly associated with allopurinol. Other organs which might be involved are the lungs (interstitial pneumonitis), heart (eosinophilic myocarditis/pericarditis), gastrointestinal tract (diarrhea and mucosal erosions), pancreas (pancreatitis), thyroid (autoimmune thyroiditis), brain (encephalitis, meningitis), muscle (myositis, increase in creatine kinase), peripheral nerves (polyneuritis), and eyes (uveitis) [8, 9]. The histological features of DRESS syndrome are usually nonspecific. The most common patterns observed in skin biopsies of patients with DRESS syndrome include interface dermatitis, spongiosis, vascular damage, and superficial perivascular inflammation. The coexistence of some of these patterns may offer a clue to the diagnosis of DRESS syndrome, albeit with good clinical history and clinicopathological correlation [10].

The European RegiSCAR devised a scoring system based on clinical features, the extent of skin involvement, organ involvement, and clinical course to help clinicians confirm or exclude the diagnosis of DRESS syndrome [11]. Our patient had a RegiSCAR score of 8, which makes him a case of definite DRESS syndrome (Table 2). Identification and prompt withdrawal of the offending drug is the mainstay of treatment. Those with exfoliative dermatitis require fluid, electrolyte, and nutritional support. In a case series, complete recovery was reported in patients without severe organ involvement treated with only supportive care, including topical corticosteroids. In such patients, it is unclear whether systemic corticosteroids shorten the clinical course [12]. Systemic corticosteroids are of unproven benefit for most forms of drug hepatotoxicity, and there is no consensus on their use [13]. However, in our case, the patient showed excellent clinical response with the initiation of systemic corticosteroids. Given the high variability in the clinical presentation, the diagnosis of DRESS syndrome in many cases requires a high degree of suspicion and clinical judgment.

There are reports of relapses induced by the introduction of new drugs, particularly beta-lactam antibiotics. However, it is not clear whether these were relapses or evolution of the natural course of DRESS syndrome. In our case, the clinical course initially worsened when he was treated with beta-lactams. Hence, we would recommend avoiding treatment with beta-lactam antibiotics during the course of DRESS syndrome.

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Statement of Ethics

The case report was approved by the Medical Research Center at Hamad Medical Corporation. Written informed consent was given by the patient to publish his case information, images, and details. The consent form is available from the corresponding author and can be produced on request from the editors.
Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S. Sasi: manuscript writing, manuscript editing, literature review, and patient management. He will act as a study guarantor. H. Altarawneh: manuscript writing and manuscript editing. M.A. Petkar: manuscript review and manuscript editing, histopathology inputs, and images. A.P. Nair: manuscript writing and literature review. All authors read and approved the manuscript.

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Fig. 1. Clinical images showing the skin lesions at presentation.
Fig. 2. Histopathological images from skin punch biopsy. a Orthokeratotic epidermis, spongiosis, and interface dermatitis. Note the prominent perivascular and periadnexal chronic inflammatory infiltrate in the dermis. H&E, ×4. b Higher-power view of the punch biopsy revealing red cell extravasation in the superficial dermis with marked perivascular inflammation. H&E, ×20. c Scattered eosinophils (blue arrow) were present among the dense inflammation as well as interstitially. H&E, ×40.
Fig. 3. Clinical images showing the resolution of skin lesions after systemic corticosteroid therapy.
Table 1. Results of relevant laboratory tests on admission, during hospital stay, and at discharge

|                               | Result admission | Result hospital stay | Result discharge | Normal range     |
|-------------------------------|------------------|----------------------|------------------|------------------|
| **Complete blood count**      |                  |                      |                  |                  |
| White blood cells, $\times 10^3/\mu L$ | 12.4             | 31.8                 | 7.3              | 4–10             |
| Red blood cells, $\times 10^6/\mu L$ | 5.3              | 4.4                  | 4                | 4.5–5.5          |
| Platelets, $\times 10^3/\mu L$   | 177              | 127                  | 251              | 150–400          |
| Hemoglobin, g/dL              | 14.1             | 11.7                 | 10.9             | 13.0–17.0        |
| Hematocrit, %                 | 41.4             | 34.6                 | 33.3             | 40.0–50.0        |
| Mean corpuscular volume, fl   | 98.4             | 78.1                 | 82.4             | 83.0–101.0       |
| Mean corpuscular hemoglobin, pg| 26.7             | 26.3                 | 27               | 27.0–32.0        |
| Mean corpuscular hemoglobin concentration, g/dL | 34.1             | 33.7                 | 32.7             | 31.5–34.4        |
| RDW, %                        | 14.1             | 15.6                 | 20.1             | 11.6–14.5        |
| Absolute neutrophil count, $\times 10^3/\mu L$ | 7.5              | 14.5                 | 10.2             | 2–7              |
| Lymphocytes, $\times 10^3/\mu L$ | 3.7              | 9.4                  | 3.6              | 1–3              |
| Monocytes, $\times 10^3/\mu L$ | 0.6              | 1.2                  | 2.8              | 0.2–1            |
| Eosinophils, $\times 10^3/\mu L$ | 0.5              | 6.1                  | 0.5              | 0–0.5            |
| Basophils, $\times 10^3/\mu L$ | 0.1              | 0.5                  | 0.3              | 0–0.2            |
| **Comprehensive metabolic panel** |                  |                      |                  |                  |
| Urea, mmol/L                  | 4.4              | 4.9                  | 3.6              | 2.8–8.1          |
| Creatinine, µmol/L            | 105              | 74                   | 68               | 62–106           |
| Total bilirubin, µmol/L       | 75               | 175                  | 32               | 3.4–20.5         |
| Alkaline phosphatase, U/L     | 332              | 463                  | 294              | 40–150           |
| Alanine aminotransferase, U/L  | 230              | 249                  | 265              | 0–55             |
| Aspartate aminotransferase, U/L | 93               | 255                  | 50               | 5–34             |
| C-reactive protein, mg/L      | 140              | 108                  | 33               | 0–5              |
### Table 2. Table showing the RegiSCAR score and its components

| Feature                                                                 | Value     | Points |
|-------------------------------------------------------------------------|-----------|--------|
| Fever (≥38.5°C)                                                         | yes       | 0      |
| Enlarged lymph nodes (≥2 sites, ≥1 cm)                                   | yes       | 1      |
| Atypical lymphocytes                                                    | yes       | 1      |
| Eosinophilia (700–1,499 or 10–19.9%)                                     | yes       | 1      |
| Skin rash                                                               |           |        |
| Extent >50%                                                             | yes       | 1      |
| At least two of: edema, infiltration, purpura, scaling                   | yes       | 1      |
| Biopsy suggesting DRESS syndrome                                         | yes       | 0      |
| Internal organ involved                                                 | two organs (liver and spleen) | 2      |
| Resolution delay                                                        | >15 days  | 0      |
| At least three biological investigations done and negative to exclude an alternative diagnosis | yes (antinuclear antibodies, blood cultures, serology for HAV/HBV/HCV) | 1 |

Total score: 8 (<2 no DRESS syndrome, 2–3 possible DRESS syndrome, 4–5 probable DRESS syndrome, ≥6 definite DRESS syndrome). DRESS, drug reaction with eosinophilia and systemic symptoms; RegiSCAR, Registry of Severe Cutaneous Adverse Reactions.