Phenytoin-Associated Hypersensitivity Syndrome With Features of DRESS and TEN/SJS

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Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, toxic epidermal necrolysis (TEN), and Stevens-Johnson syndrome (SJS) are rare and life-threatening conditions that may be precipitated by anticonvulsive agents. We describe a patient with overlapping features of these hypersensitivity syndromes.

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Hypersensitivity reactions are caused by idiosyncratic cutaneous reactions to drugs that may lead to long-lasting skin eruptions combined with visceral involvement and lymphadenopathy. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) may represent ends of a single spectrum of disease, but drug rash with eosinophilia and systemic symptoms (DRESS) syndrome typically is a distinct presentation.[1]

Drug rash with eosinophilia and systemic symptoms syndrome typically presents with diffuse exfoliative dermatitis, a morbilliform rash, facial edema, lymphadenopathy, fever, multivisceral involvement, eosinophilia, and lymphocytosis.[2] This hypersensitivity reaction usually appears acutely in the first 3 weeks to 3 months after the initiation of the responsible drug, persists in some cases for months, and is potentially life-threatening with a mortality rate of 10%.[3] Hypothyroidism is a common sequela. Drug rash with eosinophilia and systemic symptoms syndrome has been attributed to numerous drugs such as sulfonamides, nevirapine, phenobarbital, sulfasalazine, carbamazepine, and phenytoin, among others (Table 1).[2,4] The incidence of DRESS syndrome in response to phenytoin, carbamazepine, or phenobarbital treatment is approximately 1 in 5000 exposures.[14] Currently, an association of drug reactions with human herpesvirus 6 infections also has been hypothesized, though the exact pathophysiological pathway is unidentified.[15] In 9 reported cases, systemic corticosteroid therapy in combination with the rapid withdrawal of the responsible drug comprises the basic therapeutic approach; however, a beneficial outcome is not always reported, and randomized placebo-controlled clinical trials have not examined the benefit of systemic corticosteroid use in the treatment of DRESS syndrome.[16] Toxic epidermal necrolysis and SJS represent a spectrum of disease characterized by cell-mediated necrosis of keratinocytes with resulting slough. The use of corticosteroids in TEN/SJS is controversial and it has been suggested that there is an increased risk for septic death if corticosteroids are used. We describe a patient with clinical features of DRESS syndrome and histologic features resembling early TEN/SJS. The patient responded to corticosteroid therapy.

Case Report

A 49-year-old woman with a history of type 2 diabetes mellitus, stroke, and seizure disorder presented with a fever (maximum axillary temperature, 39.5°C), malaise, nausea, vomiting, mild facial and bilateral hand edema (Figure 1), and a diffuse morbilliform rash that started on the trunk and spread to the bilateral upper extremities of 10 days' duration (Figure 2). The patient was started on oral phenytoin 100 mg twice daily 3 weeks prior to the onset of these symptoms. At the time of initial presentation to the emergency

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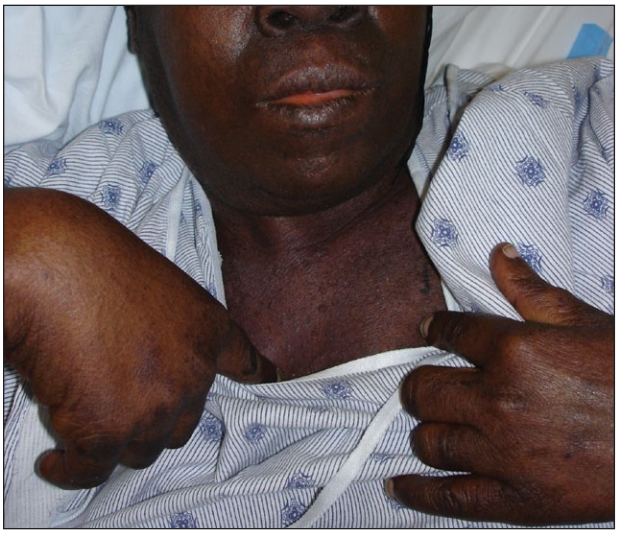

Figure 1. Facial edema.

department, the patient also was on metformin hydrochloride, glyburide, ferrous sulfate, and subcutaneous insulin.

At admission, her temperature was 38.9°C with a blood pressure of 116/57 mm Hg and heart and respiratory rates of 114 beats and 20 breaths per minute, respectively. On physical examination, a generalized, diffuse, morbilliform, erythematous, pruritic rash was noted over the trunk and upper extremities (Figure 2), and no conjuntival, scalp, or nail involvement was noted. There was a superficial, white, cheeselike exudate on the buccal mucosa with perioral edema as well as evidence of bilateral cervical and inguinal lymphadenopathy. The patient had questionable hepatomegaly by palpation. The neurological examination and the remainder of the physical examination were unremarkable. Initial laboratory blood studies revealed a white blood cell count of $3.8\times10^9/\mu L$ with 14.0% lymphocytes and 8.0% eosinophils. The hemoglobin and hematocrit values were 11.8 g/dL (reference range, 14.0–17.5 g/dL) and 37.3% (reference range, 41%–50%), respectively. The platelet count and coagulation profile were within reference range. The blood creatinine level was within reference range, and the blood urea nitrogen level was low at 6 mg/dL (reference range, 8–23 mg/dL). The erythrocyte sedimentation rate was 23 mm/h (reference range, 0–20 mm/h) in the first hour. Liver function tests initially were abnormal: aspartate aminotransferase, 132 U/L; alanine aminotransferase, 188 U/L; alkaline phosphatase, 240 U/L. The serum bilirubin level was low at 0.2 mg/dL (reference range, 0.3–1.2 mg/dL). Additional reference ranges are provided in Table 2. Antinuclear antibody and rheumatoid factor serology and hepatitis B and C

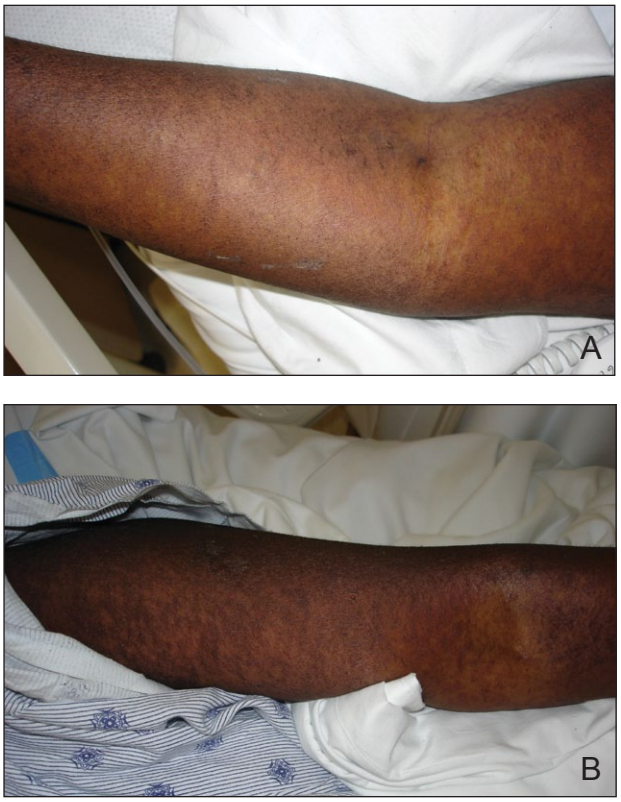

Figure 2. Diffuse maculopapular rash on the upper extremities (A and B).

panels were negative. Blood cultures obtained at admission remained negative throughout her hospitalization. Liver scan showed a 2.3×2.0-cm liver nodule of unclear characteristics. A 2-mm skin biopsy of the right abdominal area demonstrated histopathologic evidence of interface vacuolar changes with numerous necrotic keratinocytes and a normal stratum corneum. Perivascular lymphocytic and neutrophilic infiltrates also were present. These histopathologic findings were consistent with TEN/SJS (Figure 3).

A diagnosis of DRESS syndrome was proposed on the basis of the patient's de novo phenytoin exposure and clinical features. Given the elevation in liver enzymes, corticosteroid therapy was considered prudent. Phenytoin anticonvulsant therapy was immediately discontinued and replaced with valproic acid therapy. The fever was treated with acetaminophen. Intravenous methylprednisolone sodium succinate therapy was started at 60 mg every 8 hours, continued during the next 10 days of hospitalization, and subsequently tapered off to oral administration as her clinical status improved. The patient subsequently was switched to oral prednisone. Alendronate sodium therapy also was instituted at 70 mg per week.

Table 1.

Drugs Associated With DRESS Syndrome

Class	Drug	Skin Lesions	Systemic Symptoms Noted
Anticonvulsants	Phenytoin,[5] carbamazepine,[2,5] phenobarbital,[6] oxcarbazepine,[7] primidone[6]	Maculopapular pruritic rash,[2,5,8] delayed skin eruption[9]	Fever, lymph node enlargement, hepatic abnormalities (increased liver enzymes), leukocytosis, eosinophilia, neutrophilia,[6,8] hypogammaglobulinemia[9]
Antibiotics	Amoxicillin, amoxicillin–clavulanate potassium, monifloxacin, minocycline	Maculopapular rash, facial angioedema[9]	
Antidepressants	Amitriptiline	Generalized maculopapular rash[9]	Leukocytosis, eosinophilia[9]
Immunomodulators	Imatinib mesylate[10]	Macular and pruritic eruption[10]	Fever, diffuse lymphadenopathy, hypereosinophilia[10]
Antiretroviral drugs	Nevirapine[4]	Generalized macular and pruritic eruption[4]	DRESS syndrome complicated by meningoencephalitis[4]
Sulfa drugs	Sulfasalazine,[11] sulfonamides	Pruriginous maculopapular erythema and cutaneous rash[8]	Cytolytic hepatic damage,[11] eosinophilia (lymphocytosis), hyperbasophilic cells[8]
Quinines	Quinine sulfate, thiamine mononitrate	Maculopapular erythema and cutaneous rash[12]	Hypereosinophilia and/or atypical lymphocytes, hypogammaglobulinemia, asthenia, fever, erythroderma, facial edema and painful cervical lymph nodes[13]

Abbreviation: DRESS, drug rash with eosinophilia and systemic symptoms.

Table 2.

Evolution of Laboratory Tests

	Admission[a] (Day 1)	Peak (Day 5)	Discharge (Day 10)	Reference Range
White blood cell count, $\times 10^9/\mu L$	3.8	6.8	9.8	4.3–11.0
Leukocytes, %				
Neutrophils	56.0	70.0	58.4	39–77
Lymphocytes	14.0	22.0	35.5	16–47
Monocytes	22.0	4.5	4.7	5–12
Eosinophils	8.0	0.5	0.6	0–8
Serum albumin, g/dL	3.1	3.1	3.2	3.9–5.0
Aspartate aminotransferase, U/L	132	692	29	10–30
Alanine aminotransferase, U/L	188	451	104	10–40
Alkaline phosphatase, U/L	240	267	206	38–126

[a]Started intravenous systemic steroid therapy.

Table 3.

Disorders Associated With Eosinophilia

Category	Disorders
N (neoplasm)	Hodgkin disease, myeloproliferative disorders, acute myelocytic leukemia[5,18-20]
A (allergy)	Hypersensitivity reaction[5]
A (atopic)	Atopic eczema, atopic rhinitis, atopic asthma[5,21]
A (autoimmune)	Addison disease[5,22]
C (collagen vascular disease)	Churg-Strauss syndrome[5,23]
S (systemic disease)	Cholesterol emboli[5]
S (skin disorder)	Wells syndrome, hypereosinophilic syndrome, eosinophilic fascitis[5]
I (infectious)(parasites, eosinophilic gastroenteritis[5])	Other conditions/disorders associated with eosinophilia

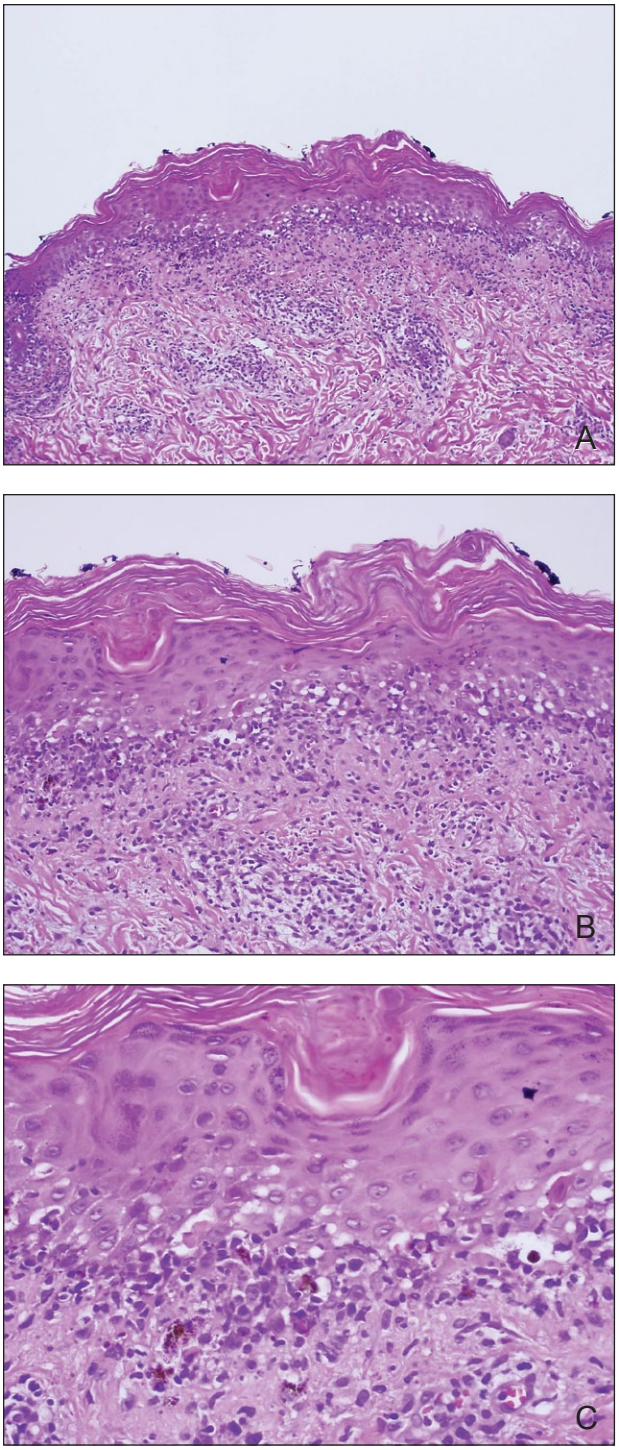

Figure 3. Histopathologic findings consistent with toxic epidermal necrolysis (A–C)(H&E; original magnifications ×100, ×200, and ×400, respectively).

Triamcinolone acetonide ointment 0.1% was applied twice daily to the involved areas and nystatin mouthwash was instituted 3 times daily to treat oral *Candida albicans* infection. The patient also was placed on sliding-scale insulin.

The patient had an evident improvement in her general condition 3 days after the initiation of intravenous and topical corticosteroid therapy. The fever also subsided by day 3 of hospitalization. However, liver enzyme levels remained elevated at this time: aspartate aminotransferase, 692 U/L; alanine aminotransferase, 451 U/L; alkaline phosphatase, 267 U/L. By day 10 after the institution of this therapeutic regimen, the skin eruption was resolved and all laboratory values were within reference range, except alanine aminostransferase and alkaline phosphatase. The patient was discharged to home in good condition on hospital day 10. At the time of discharge, only mild cutaneous desquamation was noted. Facial edema, cervical and inguinal lymphadenopathy, and oral C *albicans* infection were not present.

In summary, this patient had a clinical presentation that included a maximum temperature of 39.5°C; malaise; nausea; vomiting; and a generalized, diffuse, morbilliform rash over the trunk that spread to the upper extremities and was accompanied by facial and bilateral hand edema. The laboratory tests on the day of admission showed eosinophil levels of 8.0%. Eosinophil levels gradually decreased on day 5 of hospitalization to 0.5%. At the time of discharge, eosinophil levels were 0.6%. Although these features are consistent with DRESS syndrome, the histopathologic changes suggested TEN/SJS.

Comment

Drug rash with eosinophilia and systemic symptoms syndrome is a rare but life-threatening, drug-induced hypersensitivity reaction. This syndrome is characterized by a rash or severe cutaneous eruption; fever; hematologic dyscrasia, such as eosinophilia and lymphocytosis; and systemic symptoms, such as adenopathy and multiorgan involvement.[17] It falls into the category of disorder associated with eosinophilia, which is clinically differentiated from other hypersensitivity disorders (Table 3). The etiology of DRESS has been associated with exposure to a diversity of drugs. Although drugs such as phenobarbital, sulfasalazine, nevirapine, sulfonamides, and various antibiotics have been associated with the onset of DRESS syndrome, anticonvulsants have been most commonly associated, specifically phenytoin and carbamazepine. For DRESS syndrome, corticoids are used in cases of life-threatening systemic impairment, though case-controlled, randomized studies regarding the management of DRESS syndrome are lacking.[24,25] Our patient had overlapping features of DRESS and TEN/SJS and responded to corticosteroid therapy.

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