Apremilast-associated drug reaction with eosinophilia and systemic symptoms

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INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially life-threatening condition with a risk of mortality estimated between 2% and 10%. Skin findings are usually accompanied by fever, peripheral eosinophilia, and multiorgan involvement.[1] First described as an adverse reaction to anticonvulsants, many medications are implicated in DRESS.[2] We present a case of apremilast-induced DRESS in a patient treated for pityriasis rubra pilaris (PRP). To our knowledge, this is the first reported case of apremilast-associated DRESS.

Abbreviations used:

DRESS: drug reaction with eosinophilia and systemic symptoms
PRP: pityriasis rubra pilaris

CASE REPORT

A 38-year-old white woman with a history of PRP presented to the inpatient dermatology consult service with progressive redness and swelling of her face and worsening skin rash 6 weeks after initiation of apremilast. She had persistent cough and shortness of breath that started a few days after initiation of apremilast. Erythematous scaly plaques with islands of sparing appeared on the trunk, bilateral upper and lower extremities, and buttocks (Fig 1). There was significant facial edema, diffuse injection of the conjunctiva, and bilateral cervical lymphadenopathy (Fig 2). She was afebrile and tachycardic with a heart rate of 122 beats/minute. Laboratory results on admission included an eosinophil count of 0.9 K/μL (normal range, 0.00-0.50 K/μL). Tests for influenza A and B, thyroid-stimulating hormone, free thyroxine, urinalysis, and complete metabolic panel were all within normal limits, and her alanine aminotransferase and aspartate aminotransferase were 32 (normal range, <35 IU/L) and 18 (normal range, 8-30 IU/L), respectively. Three days later, she had transaminitis with alanine aminotransferase and aspartate aminotransferase of 77 and 42 IU/L, respectively. Epstein-Barr virus, cytomegalovirus, and human herpesvirus-6 titers were negative. Skin biopsy found psoriasiform hyperplasia, spongiotic dermatitis, dyskeratosis, and many eosinophils (Fig 3). Chest radiograph was negative. Hepatitis A, B, and C virus serologic testing was negative a week after discharge. Her RegiSCAR score was 4: afebrile (-1 point); bilateral cervical lymphadenopathy (0 points); circulating atypical lymphocytes, unknown (0 points); eosinophil count, 0.9 k/μL (1 point); cutaneous eruption, greater than 50% body surface area (1 point), suggestive of DRESS (1 point); biopsy suggestive of DRESS (0 points); involvement of the lungs and liver (2 points); resolved in greater than 15 days (0 points); negative hepatitis serology, antinuclear antibody, blood cultures, and *Chlamydia* and *Mycoplasma* serology, unknown (0 points).

Triamcinolone 0.1% ointment wet wraps twice daily under occlusion were initiated along with a 6-week prednisone taper starting at 60 mg/d with clinical improvement and normalization of laboratory values. At a 4-week follow-up visit, she had flaring on 20 mg of prednisone, so her taper was extended, and she was started on ustekinumab for PRP. Systemic retinoids were avoided given her

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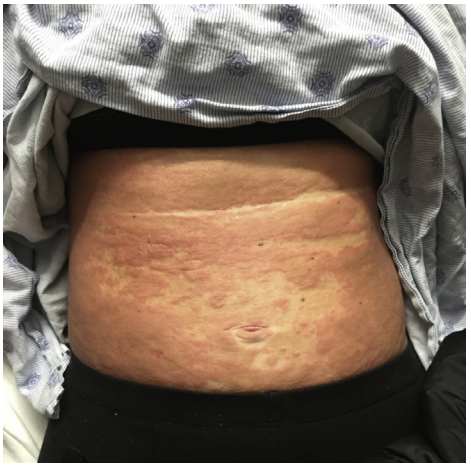

Fig 1. DRESS. Confluent erythematous plaques with islands of sparing on the abdomen.

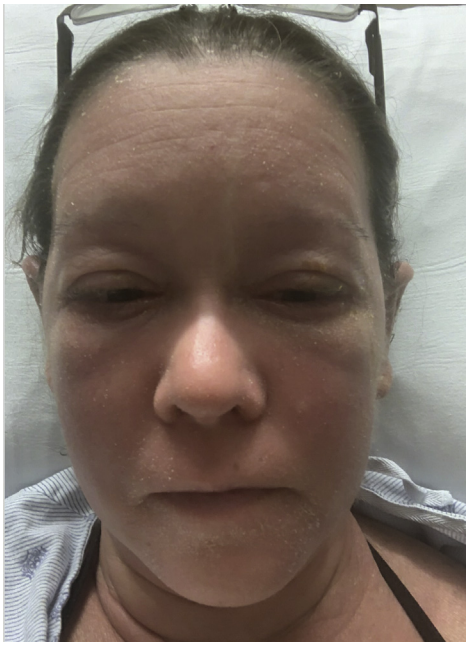

Fig 2. DRESS. Significant facial edema with erythema and scale.

childbearing potential. Her disease flared again after completing the prednisone taper at week 10, and a repeat skin biopsy was suggestive of drug eruption, so she was started on cyclosporine, 100 mg twice daily, and ustekinumab was discontinued. Mycophenolate mofetil, 1500 mg twice daily, was started with improvement seen. At the time of this writing, she was maintained on mycophenolate mofetil without flares of PRP or recurrence of DRESS.

DISCUSSION

DRESS develops 2 to 6 weeks after drug initiation. Commonly implicated medications include carbamazepine, phenobarbital, phenytoin, dapsone, sulfasalazine, minocycline, trimethoprim-sulfamethoxazole, vancomycin, abacavir, nevirapine, bupropion, amlodipine, and allopurinol.[3]

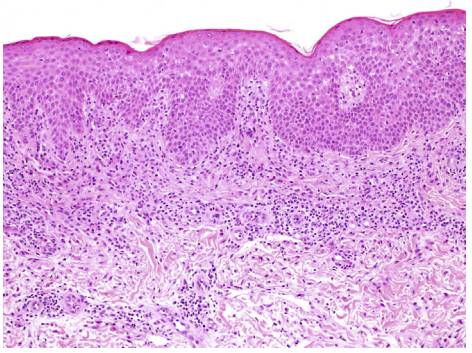

Fig 3. DRESS. Mild irregular epidermal hyperplasia with an underlying patchy lichenoid infiltrate comprised of lymphocytes and eosinophils.

DRESS usually begins as a morbilliform rash. Facial edema is the hallmark of DRESS, and peripheral blood eosinophilia, atypical lymphocytes, mild mucosal involvement, and fever constitute the main findings. Patients may have lymphadenopathy, hepatitis, nephritis, myositis, pneumonitis, and myocarditis, with the liver being the most frequently involved internal organ.[4] A systematic review found the most common pulmonary manifestations included dyspnea and cough, which may precede the other findings as was seen in our case.[5]

The RegiSCAR scoring system for DRESS is a helpful diagnostic tool, and patients with a score of 4 to 5 represent a probable case.[6] The J-SCAR scoring system takes into account the time course of development of the rash, time to resolution, and the presence or absence of fever, liver and leukocyte abnormalities, lymphadenopathy, and human-herpesvirus 6 reactivation. No scoring system is entirely specific for DRESS, and there are limitations to consider including the fact patients can have hematologic abnormalities that are not accounted for in the RegisSCAR scoring system.[6] Additionally, the morphology of DRESS can vary, making it challenging to assess whether the cutaneous eruption is suggestive of DRESS. In this case, it was challenging to differentiate between a severe flare of PRP and DRESS. The timing of the eruption after starting apremilast and the development of lymphadenopathy, facial edema, peripheral eosinophilia, and systemic organ involvement all supported a diagnosis of DRESS.

Skin biopsy of DRESS typically finds a superficial perivascular lymphocytic infiltrate with eosinophils.[3,4] Although there may be occasional

eosinophils and plasma cells in the dermal infiltrate of PRP, the degree of tissue eosinophilia and spongiosis in this case was most consistent with DRESS.[7]

Patients with DRESS should undergo routine laboratory monitoring including complete blood count with differential and liver function tests until normalized. Patients are at increased risk for type 1 diabetes mellitus and thyroiditis, and thyroid-stimulating hormone and free thyroxine testing should be repeated at 3 months, 1 year, and 2 years.[8,9] Our patient had unremarkable laboratory findings during her follow-up period.

The pathogenesis of DRESS is not fully elucidated, but reactivation of human herpes viruses, genetic polymorphisms in drug metabolism, and immune mechanisms including human leukocyte antigen susceptibility and interleukin-5–driven drug-specific T cells may all play a role.[3]

Prompt discontinuation of the offending medication is crucial, and therapy with oral corticosteroids is often initiated for patients with significant symptoms or systemic involvement. A slow corticosteroid taper over weeks to months is recommended to avoid relapse. Our patient had flare up during her 6-week prednisone taper, requiring a repeat skin biopsy to determine if her skin findings were consistent with relapse of DRESS or uncontrolled PRP, and a more prolonged prednisone taper was required. Other potential therapies include cyclosporine, cyclophosphamide, mycophenolate mofetil, and rituximab.[10]

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