

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome successfully treated with mepolizumab

Nikhita Ange, MBBS^a, Sonia Alley, MBBS^{a,b},
Suran L. Fernando, MBBS, PhD^{a,c,d}, Luke Coyle, MBBS^{b,d,e},
and James Yun, MBBS, PhD^{a,d}



Clinical Implications

- The anti-IL-5 mAb mepolizumab shows promise as a novel therapy in the treatment of relapsing/refractory drug reaction with eosinophilia and systemic symptoms syndrome.

TO THE EDITOR:

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a potentially life-threatening, idiosyncratic adverse drug reaction. It typically manifests as a morbilliform rash with fever, lymphadenopathy, hematological abnormalities (including eosinophilia and atypical lymphocytes), and multiorgan involvement.¹ A number of drugs can cause DRESS syndrome, including antiepileptic drugs (eg, carbamazepine, phenobarbital, and phenytoin), allopurinol, and sulfonamides.² The exact incidence is unknown, but the estimated overall population risk is 1 in 1,000 to 10,000 drug exposures.³ Although uncommon, it has a 10% mortality rate mainly from fulminant hepatitis.⁴

In addition to stopping the culprit drug, treatment comprises systemic corticosteroids, initially starting at prednisone 1 mg/kg. Patients usually improve within days of steroids initiation, but rapid reduction in steroid dose often results in flares or relapses. These can be severe, fatal even. Therefore, prednisone is gradually tapered over 3 to 6 months.⁵

DRESS syndrome is likely driven by drug-specific T-cell responses. Elevated IL-5 levels have been observed in early DRESS syndrome patients; this study suggests that IL-5 production is mainly derived from activated lymphocytes, probably drug-specific T cells.⁶ Biopsies from affected organs contain eosinophils, strongly suggesting that they are the final mediators of tissue damage.⁵ In this context, mepolizumab, the anti-IL-5 mAb, may be a useful adjunct to steroids in the treatment of DRESS syndrome. Clinical utility of mepolizumab has already been shown for other eosinophilic disorders such as hypereosinophilic syndrome, severe eosinophilic asthma, and, recently, eosinophilic granulomatosis with polyangiitis.⁷ Because IL-5 secreted by drug-specific T cells plays an important role in eosinophil recruitment and the subsequent tissue damage, blocking the IL-5 pathway with mepolizumab is likely to result in disease control. We present for the first time a patient with relapsing DRESS syndrome successfully treated with mepolizumab.

A 56-year-old white woman who had undergone a busulphan-cyclophosphamide-conditioned autologous stem cell transplant (SCT) 1 month earlier for FLT3-positive acute myeloid leukemia presented to a regional hospital with fever, cough, and

rhinorrhea. Allogeneic SCT was not performed because she had broadly reactive anti-HLA antibodies that would have resulted in graft rejection. She was empirically treated with piperacillin-tazobactam and gentamicin. Antibiotics were ceased after 3 days when *picornavirus* was isolated on a viral swab. Her eosinophil count and liver function test results were normal on presentation. She had been on trimethoprim-sulfamethoxazole 400 mg/80 mg, fluconazole 200 mg, and valaciclovir 500 mg, all daily for a month, for posttransplant prophylaxis. On day 6 of the admission, she developed a generalized morbilliform rash and eosinophilia ($1.1 \times 10^9/L$) but was discharged. Two days later, she represented with worsening eosinophilia ($2.4 \times 10^9/L$), fever ($39.5^\circ C$), and hypoxia. She was transferred to a tertiary hospital for further management.

Her morbilliform rash had worsened and she developed small pustules but there was no mucosal involvement. She had marked facial edema but lymphadenopathy was not noted. Her skin biopsy showed a spongiotic reaction pattern with spongiotic vesicles, small pustules with lymphocyte, and eosinophil predominance. She had thrombocytopenia ($49 \times 10^9/L$), lymphopenia ($0.9 \times 10^9/L$), and atypical lymphocytes on the peripheral blood film. She had normal renal function, but had abnormal liver function test results with alanine aminotransferase 899 unit/L (normal <55 unit/L), aspartate aminotransferase 432 unit/L (12-36 unit/L), gamma glutamyl transaminase 111 unit/L (12-64 unit/L), alkaline phosphatase 80 unit/L (30-110 unit/L), and total bilirubin 11 $\mu mol/L$ (3-20 $\mu mol/L$). IgG was 5.12 g/L and HHV-6 PCR was positive. The eosinophil count peaked at $6.4 \times 10^9/L$ the next day. Bone marrow biopsy showed a reactive, hypercellular marrow with marked eosinophilia accounting for 37% of all nucleated cells with all stages of maturation seen.

Given the above findings, DRESS syndrome was diagnosed. Trimethoprim-sulfamethoxazole, the presumed culprit medication, was ceased. She was given intravenous dexamethasone 10 mg 4 times a day and intravenous immunoglobulin (IVIg) 70 g (1 g/kg) for 2 days. Meropenem and oseltamivir were also initiated because she had respiratory compromise with positive parainfluenza A PCR on nasopharyngeal aspirate. After clinical improvement, she was started on prednisone 70 mg daily and then was weaned by 10 mg fortnightly. *Pneumocystis jirovecii* prophylaxis was changed to pentamidine. Despite clinical improvement in DRESS syndrome, she had persistent pancytopenia (hemoglobin 104 g/L; white cell count $3.9 \times 10^9/L$; platelets $15 \times 10^9/L$). She required multiple platelet transfusions.

Two and a half weeks later, she developed a new morbilliform rash on her trunk with pulmonary infiltrates and eosinophilia ($1.0 \times 10^9/L$) when prednisone was reduced to 60 mg daily. She was diagnosed with a DRESS syndrome flare, and prednisone dose was increased to 110 mg per day for 2 days with good response. She was given another infusion of IVIg, and prednisone weaning was attempted again. This resulted in recurrence of the rash, facial swelling, and mild eosinophilia ($0.8 \times 10^9/L$). The prednisone dose could not be reduced below 80 mg daily. Her liver function and renal function were unaffected. The decision was made to trial mepolizumab 100 mg subcutaneously because the risk of giving prolonged high dose of prednisone was considered too high in view of her recent autologous SCT and neutropenia. This dose is

currently approved and available for eosinophilic asthma. The eosinophil count dropped to $0.0 \times 10^9/L$ within 3 days of the first dose. Within 1 week, the rash was much improved. The prednisone dose was then weaned by 10 mg weekly until 20 mg over the next 6 weeks and thereafter; it was tapered at a slower rate until it was ceased completely in 3 months. She developed a milder DRESS syndrome flare up in the context of starting cefepime for a respiratory infection with morbilliform rash when she was on prednisone 20 mg daily, but eosinophils remained $0.0 \times 10^9/L$ and it settled promptly after changing cefepime to meropenem. Higher prednisone doses were not required. Mepolizumab was continued monthly for 3 months until prednisone was ceased completely. At 6 months post-DRESS syndrome, she had no further recurrences and her acute myeloid leukemia remains in remission with normal blood cell counts.

In summary, the complete resolution of previously relapsing DRESS syndrome with mepolizumab suggests a promising new, safe therapy for DRESS syndrome. In steroid refractory cases, IVIg had been used but this was ineffective in our patient. Single case reports of cyclophosphamide, cyclosporine, and rituximab are also published as steroid-sparing agents but given the high risk of severe infection in the context of a recent SCT, these were contraindicated in our case.⁴ Further studies are required to determine whether mepolizumab is suitable for all patient groups affected by this disease and to clarify what the ideal dose should be.

^aDepartment of Clinical Allergy and Immunology, Royal North Shore Hospital, Sydney, Australia

^bDepartment of Haematology and Transfusion Medicine, Royal North Shore Hospital, Sydney, Australia

^cImmunorheumatology Laboratory, Pathology North, Royal North Shore Hospital, Sydney, Australia

^dThe University of Sydney, Sydney, Australia

^eHaematology, Pathology North, Royal North Shore Hospital, Sydney, Australia

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Corresponding author: James Yun, MBBS, PhD, Department of Clinical Immunology and Allergy, The Royal North Shore Hospital, Reserve Rd, St Leonards, Sydney, NSW 2065, Australia. E-mail: james.yun@sydney.edu.au.

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