



Letter

Skeletal myositis as the sole feature of relapsing drug reaction with eosinophilia and systemic symptoms syndrome

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome represents a potentially life-threatening systemic immune response to medication. It is characterized by rash, fever, lymphadenopathy, eosinophilia, and internal organ involvement, most commonly hepatitis. We report a case of DRESS syndrome caused by sulfasalazine with acute morbilliform rash, fever, eosinophilia, and hepatitis with subsequent skeletal muscle involvement. To date, literature reports of skeletal muscle involvement with DRESS syndrome have been limited to 2 cases, only one of which involved histopathologic evidence of eosinophilic infiltration on skeletal muscle biopsy.¹ Both cases have featured skeletal muscle involvement in association with the systemic disease. This is the first case described involving eosinophilic myositis as a feature in relapsed disease, which developed in isolation of preceding, remitting clinical manifestations.

A 19-year-old man with no prior medical history was prescribed sulfasalazine for a diagnosis of Crohn disease in March 2016. He responded well initially but was admitted to the hospital in late May 2016 with facial edema and a rash on his trunk and limbs with associated pustular eruptions. On admission, his temperature was 38.6°C, blood pressure was 89/56 mm Hg, and heart rate was 112/min. On examination, he had cervical and axillary lymphadenopathy. No organomegaly was detected, and he denied any inflammatory bowel symptoms. Initial blood cell counts revealed an eosinophil count of $0.7 \times 10^9/L$ with an otherwise normal complete blood cell count. His C-reactive protein level was 132 mg/L (reference range, <20 mg/L). Liver function test results were abnormal, with a bilirubin level of 26 $\mu\text{mol/L}$ (reference range, <20 $\mu\text{mol/L}$), γ -glutamyltransferase (GGT) level of 275 U/L (reference range, <36 U/L), alanine aminotransferase (ALT) level of 181 U/L (reference range, <55 U/L), and aspartate aminotransferase (AST) level of 205 U/L (reference range, <36 U/L).

The patient was given anti-infective empirical treatment because of the severity of presentation; however, all culture results were negative. He was found to be experiencing a drug reaction, and sulfasalazine therapy was ceased within 48 hours of symptom onset. Two days later, inflammatory bowel symptoms flared, and the patient was prescribed oral prednisolone, 10 mg/d, with good response. Prednisolone therapy was stopped abruptly after a week, and a few days later he was readmitted with a recurrence of fevers, rash, and lymphadenopathy. His complete blood cell count revealed a leukocyte count of $18.5 \times 10^9/L$ (reference range, <11 $\times 10^9/L$) and an eosinophil count of $4.0 \times 10^9/L$ (reference range, <0.5 $\times 10^9/L$). This represented a greater than 4-fold increase during 3 weeks. Blood film revealed neutrophilia with left shift and reactive lymphocytes

consistent with inflammation. Liver function tests again revealed a hepatic picture: GGT, 324 U/L; ALT, 1091 U/L; and AST, 446 U/L. His C-reactive protein level remained between 80 and 120 mg/L. Serologic test and nucleic acid detection results for bacterial, viral, and parasitic infections were negative. Drug hypersensitivity reaction was again suspected, and the presence of recurrent fever, rash, lymphadenopathy, hepatitis, and peripheral blood eosinophilia resulted in a diagnosis of DRESS syndrome. Human herpesvirus 6 (HHV-6) IgM serologic test results were negative, and IgG serologic test results were positive. HHV-6 polymerase chain reaction was not performed. High-dose oral prednisone, 60 mg (1 mg/kg) daily, was instituted as treatment for DRESS syndrome and to prevent a further flare of inflammatory bowel disease. Fever and rash resolved, and the patient was discharged. Through the subsequent weeks, eosinophil count fluctuated, reaching a second peak of $2.38 \times 10^9/L$ without recurrence of rash. Within 2 months, the patient was readmitted with a preceding 3-day history of significant muscle weakness. He was unable to walk up stairs and had fallen twice while walking on flat ground. He was unable to raise his arms above his head or flex his neck against gravity. Importantly, he denied any respiratory or bulbar dysfunction. He had an eosinophil count of $1.2 \times 10^9/L$ despite taking prednisolone, 60 mg/d, adherent since diagnosis, with an absence of recurrence of rash, lymphadenopathy, or hepatitis. Creatine kinase (CK) level was elevated at 9,536 U/L. Liver enzymes remained abnormal but improved from previous levels.

Given the patient's history of rash and subsequent myopathy, investigations for autoimmune myositis was performed. His antinuclear antibody test result was negative. He had a transiently positive antineutrophil cytoplasmic antibody test result, with undetectable antimyeloperoxidase or anti-proteinase 3 antibodies. The results of a myositis antibody panel, including anti-Ro52, anti-Mi2, anti-aminoacyl-tRNA, anti-Jo1, anti-PL-7, anti-PL-12, anti-OJ, and anti-EJ antibodies, were negative. Electromyography of the upper and lower limbs, including deltoid, paraspinal, iliopsoas, vastus medialis tibialis anterior, and medial gastrocnemius muscles, was performed. Motor units revealed spontaneous activity with evidence of fibrillations, positive sharp waves, and fasciculations. On activation, there was evidence of short-duration polyphasic units with early recruitment with motor unit amplitude small between 1 and 2.5 mV, consistent with an inflammatory myopathic process. The findings of a muscle biopsy performed a week after symptom onset were consistent with a necrotizing myopathy, with foci of regenerating fibers. The presence of endomysial inflammatory infiltrate with large numbers of eosinophils was suggestive of a drug-related cause (Fig 1). Rimmed vacuoles were seen on immunohistochemical analysis, which, in the clinical context, were most likely degenerative in nature. Transthoracic

Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2017.03.007>

1081-1206/Crown Copyright © 2017. Published by Elsevier Inc on behalf of the American College of Allergy, Asthma & Immunology. All rights reserved.

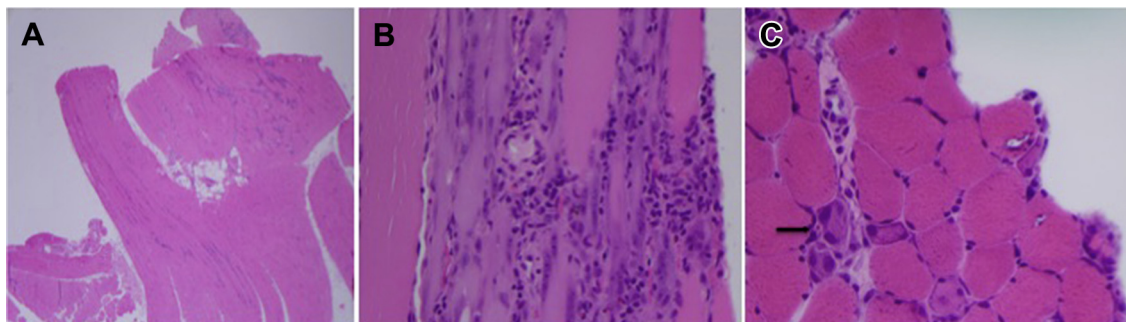


Figure 1. A and B, Necrotizing myopathy with foci of regenerating fibers and diffuse endomysial inflammatory infiltrate. C, Large numbers of eosinophils (arrow), suggestive of a drug-related cause.

echocardiography revealed normal cardiac chambers and ventricular function with a left ventricular ejection fraction of 60%.

The diagnosis of relapsing DRESS syndrome with polymyositis was made. Intravenous immunoglobulin (IVIG), 2 g/kg, was administered for 2 days. After IVIG, the patient recovered substantially and had return of full power on examination with the exception of distal finger extension weakness, which was graded at 4+/5 on the Medical Research Council scale for muscle strength. His CK level trended down and was 1,150 U/L on day 4 of admission and normalized within a week of discharge to less than 200 U/L. The patient was discharged home with a plan to gradually wean oral steroids from 60 mg/d by 5 mg/wk to 40 mg/d with a plan for a subsequent prolonged weaning regimen to avoid further relapse. Blood results at 6 weeks from IVIG treatment were all within the reference range, with an eosinophil count of $0.01 \times 10^9/L$, CK level of 73 U/L, GGT level of 33 U/L, ALT level of 24 U/L, and AST level of 20 U/L.

Our patient was diagnosed with DRESS syndrome because he met the 4 clinical and laboratory criteria defined by the European Registry of Severe Cutaneous Adverse Reactions.² Initial clinical features were typical: fever, morbilliform rash, hypereosinophilia, and hepatitis, which began roughly 3 months after commencement of sulfasalazine therapy. Despite a reasonable systemic response to steroids, our patient developed myositis. Although myocardial involvement is not uncommon, skeletal muscle involvement with DRESS syndrome is rare. Lee et al¹ reported a case of DRESS in a 29-year-old woman undergoing celecoxib and tuberculosis treatment who presented with rash, eosinophilia, hepatitis, and myalgia with a CK level of 18,943 U/L. Electromyography revealed myopathic changes, and biopsy revealed perimysial infiltration of eosinophils with myonecrosis. The patient was treated with immunosuppressive agents and despite a protracted relapsing-remitting course made a complete clinical recovery.¹ Matsuda et al³ described a case of DRESS syndrome associated with carbamazepine. Ten days after symptom onset, the patient developed an increase in CK level and subsequent increases in levels of transaminases, with no evidence of cardiomyopathy on cardiac echography. Although no skeletal muscle biopsy was performed, the suggestion of skeletal muscle involvement was made in the context of systemic muscle weakness, dysphagia, and elevated CK level.³ to our knowledge, this is the first reported case of DRESS syndrome causing an eosinophilic polymyositis as the sole clinical manifestation of disease relapse. Differential diagnoses for eosinophilic polymyositis include parasitic infection, hematologic malignant tumor, drugs, muscular dystrophies, and systemic autoimmune disorders, specifically polyarteritis nodosa or eosinophilic granulomatosis with polyangiitis. The relapsing nature of the patient's clinical course, absence of other clinical or laboratory features suggestive of vasculitides or parasitic infection, the eosinophilic infiltration on muscle biopsy in the absence of vasculitis, and the rapid clinical improvement with the use of steroids and IVIG,

accompanied by the concomitant decrease in the eosinophil count and CK level, support the diagnosis of DRESS polymyositis.

The immunopathology of DRESS syndrome remains unclear but is thought to result from impaired pharmacokinetics, accumulation of drug metabolites, T-cell activation, and sequential reactivation of herpesviruses.⁴ Neurologic manifestations of DRESS are rare, although limbic encephalitis has been reported with the presence of HHV-6 polymerase chain reaction positivity in the cerebrospinal fluid.⁵ The mechanism of DRESS myositis presumably results from ongoing activation of eosinophils with release of cytotoxic granule proteins contributing to local muscle injury.⁶ Although no randomized trials have addressed treatment options in DRESS syndrome, the 2010 European guidelines recommend IVIG as first adjunct to prednisone in patients with life-threatening disease symptoms.⁷ This case represents a rare organ manifestation of DRESS syndrome as the sole clinical manifestation of disease relapse. Skeletal muscle involvement should be considered in any patient with a history of DRESS syndrome experiencing limb weakness, bulbar dysfunction, or respiratory symptoms.

Jennifer Massey, MBBS*
Kishore Kumar, MBBS, PhD*[†]

Karl Ng, MBBS, PhD*[‡]

James Yun, MBBS, PhD*[§]

Suran Fernando, MBBS, PhD*[§]

*Department of Neurology

Royal North Shore Hospital

Sydney, Australia

[†]Neurogenetics

Kolling Institute of Medical Research

Royal North Shore Hospital

Sydney, Australia

[‡]Sydney Medical School

University of Sydney

Sydney, Australia

[§]Department of Clinical Immunology and Allergy

Royal North Shore Hospital

Sydney, Australia

jennifer.massey@hotmail.com

References

- [1] Lee JP, Heo J, Kim TO, Kim GH. Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome induced by celecoxib and anti-tuberculosis drugs. *J Korean Med Sci*. 2008;23:521–525.
- [2] Mockenhaupt M. Epidemiology and causes of severe cutaneous adverse drug reactions. In: Pichler WJ, ed. *Drug Hypersensitivity*. Basel, Switzerland: Karger; 2007:18–31.
- [3] Matsuda SK, Takayanagi Y, Okazaki T, et al. Pustular-type drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms due to carbamazepine with systemic muscle involvement. *J Dermatol*. 2013;40:118–122.

- [4] Fernando S. Drug-reaction eosinophilia and systemic symptoms and drug-induced hypersensitivity syndrome. *Australasian J Dermatol.* 2014; 55:15–23.
- [5] Masaki T, Fukunaga A, Tohyama M, et al. Human herpesvirus 6 encephalitis in allopurinol-induced hypersensitivity syndrome. *Acta Derm Venereol.* 2003;83: 128–131.
- [6] Selva-O'Callaghan A, Trallero-Araguas E, Grau JM. Eosinophilic myositis: an updated review. *Autoimmun Rev.* 2014;13:375–378.
- [7] Descamps V, Ben Said B, Sassolas B, Trucheter F, Avenel-Audran M, Girardian P. Management of drug reaction with eosinophilia and systemic symptoms (DRESS). *Ann Dermatol Venereol.* 2010;137:703–708.