

The development of mucous membrane epidermolysis bullosa acquisita in a pediatric patient



Kathryn Rentfro, BS,^a and Megan Arthur, MD^b
Omaha, Nebraska

Key words: DRESS; drug rash with eosinophilia and systemic symptoms; mucous membrane epidermolysis bullosa acquisita.

INTRODUCTION

Autoimmune diseases have been reported to develop months to years following drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. However, the development of autoimmune bullous diseases in a patient with a history of DRESS syndrome is extremely rare. We here report the unusual case of mucous membrane epidermolysis bullosa acquisita (MM-EBA) presenting 2 years after lamotrigine-induced DRESS syndrome in a pediatric patient. The patient also developed nonpathogenic autoantibodies directed against BP 180 and BP 230.

CASE REPORT

A 14-year-old girl was referred for fluid-filled blisters on periocular skin, recurrent bleeding of the gums, and erosions in her mouth and nose. Two years previously, she had been diagnosed with lamotrigine-induced DRESS, which resolved with prednisone and cyclosporine treatment. She was also recently diagnosed with Graves disease and was on treatment with methimazole. A punch biopsy of a vesicle on her eyelid performed by an outside dermatologist showed a subepidermal vesicle with a perivascular inflammatory infiltrate consisting of lymphocytes, histiocytes, and eosinophils. The initial indirect immunofluorescence (IIF) used serum that was serially diluted and applied to monkey esophagus substrate, and the result was negative. Direct immunofluorescence of the perilesional skin biopsy showed linear deposition of IgG, IgA, and C3 along the basement membrane. Initial salt-split skin studies from the perilesional skin revealed IgG and C3 on

Abbreviations used:

DRESS:	drug rash with eosinophilia and systemic symptoms
EBA:	epidermolysis bullosa acquisita
IIF:	indirect immunofluorescence
IVIG:	intravenous immunoglobulin
MM-EBA:	mucous membrane epidermolysis bullosa acquisita

both the roof and the floor of the vesicle. The patient had been unsuccessfully treated with doxycycline and niacinamide, prednisone, and dapsone.

Physical examination revealed desquamative gingivitis and intact vesicles and erosions on the posterior pharynx and mucosal part of the lip (Figs 1 and 2). Ophthalmologic evaluation was notable for trichiasis with no symblepharon. She was found to have increased IgG antibodies against BP 180 (43 units, negative ≤ 9 units), BP 230 (32 units, negative ≤ 9 units), and type VII collagen (44 units, negative ≤ 6 units) by enzyme-linked immunosorbent assay testing. A repeat IIF with salt-split skin with serial dilutions applied to both monkey esophagus and human substrate showed IgG positivity in a dermal pattern to the human substrate. Based on these results, she was diagnosed with MM-EBA. As she did not have epidermal immunofluorescence on IIF with salt split skin, her antibodies toward BP 180 and BP 230 were believed to be non-pathogenic.

She was treated with 100 mg dapsone daily, mycophenolate mofetil 1500 mg daily, and topical steroids for her oral and mucosal lesions. She continued to develop new lesions in her mouth

From the University of Nebraska Medical Center, College of Medicine^a; and University of Nebraska Medical Center, Department of Dermatology.^b

Funding sources: None.

Correspondence to: Dr. Megan Arthur, UNMC Department of Dermatology, Lauritzen Outpatient Center, 4th Floor, 4014 Leavenworth St, Omaha NE 68198-5645. E-mail: megan.arthur@unmc.edu.

JAAD Case Reports 2021;11:3-5.

2352-5126

© 2021 by the American Academy of Dermatology, Inc. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.jdc.2021.02.027>



Fig 1. Posterior aspect of the pharynx with erosions.

and nose on this treatment regimen; thus, intravenous immunoglobulin (IVIg) at a dose of 2 g/kg given over 2 consecutive days was added with a subsequent reduction in symptoms. She was evaluated by an ear, nose, and throat physician to check for laryngeal involvement due to the presence of chronic cough. The patient declined to undergo laryngoscopy, and her cough resolved with the addition of IVIg. Oral involvement relapsed after 6 months of IVIg necessitating initiation of rituximab therapy.

DISCUSSION

DRESS is a drug-induced hypersensitivity reaction with diagnostic criteria that include internal organ involvement, blood count abnormalities, skin rash, and an inciting drug.¹ Antiepileptic drugs are common causes of DRESS in both the adult and pediatric population.¹ The pathogenesis of DRESS is not fully understood but is thought to reflect a strong T-cell response to the inciting drug along with potential reactivation of a human herpes virus.¹

Autoimmune diseases have been reported to occur several months to years after DRESS syndrome in adults.² Graves disease, Hashimoto thyroiditis, type 1 diabetes mellitus, autoimmune hemolytic anemia, alopecia areata, sclerodermoid lesions, and systemic lupus erythematosus have all been reported in adult patients.^{2,3} Autoimmune thyroiditis and type 1 diabetes mellitus have also been described in a pediatric patient.⁴ Impaired regulatory T cells and viral reactivation are also thought to contribute to the development of autoantibody formation and autoimmune disease following DRESS.⁵ Ushigome et al. reported that autoantibodies are detected at higher rates in patients who were not treated with corticosteroids for their DRESS syndromes.⁵

Autoimmune bullous diseases have rarely been reported following DRESS. Kijima et al described an



Fig 2. Desquamative gingivitis and vesicles on the lower mucosal part of the lip.

adult patient who developed bullae on her trunk and extremities 77 days after treatment with steroids for DRESS.⁶ She was diagnosed with bullous pemphigoid after observation of IgG autoantibodies at the basement membrane, and BP 180 antibodies were detected.⁶ Auto-antibodies against a 190-kDa protein, seen in pemphigus foliaceus and paraneoplastic pemphigus, have also been detected in an adult patient with acute DRESS and were thought to contribute to the development of the disease.⁷

Epidermolysis bullosa acquisita (EBA) is a sub-epidermal blistering disease with a median age of onset of 50 years.⁸ In a study by Hashimoto et al⁹ of 103 EBA patients, BP180 IgG antibodies were detected in 4.7% of the patients, and BP 230 IgG antibodies were found in 2.9% of the patients. We report the case of a pediatric patient who developed MM-EBA 2 years after she was diagnosed with DRESS. Our patient's pemphigoid panel showed Type VII collagen IgG antibodies, and salt-split skin IIF showed linear IgG antibody deposition in a dermal pattern, consistent with EBA. As our patient only experienced mucosal involvement, these serology results are compatible with MM-EBA. She also displayed increased levels of IgG BP 180 and

IgG BP 230 antibodies, which are probably not pathogenic.

The development of MM-EBA following DRESS syndrome in a pediatric patient is very rare. The co-occurrence of IgG BP180 and IgG BP230 antibodies with anti-type VII collagen antibodies is uncommon and may be best explained by epitope spread. Our patient is currently treated with dapsone, mycophenolate mofetil, monthly IVIG infusions, and she recently started rituximab infusions.

Conflicts of interest

None declared.

REFERENCES

1. Kim GY, Anderson KR, Davis DMR, Hand JL, Tollefson MM. Drug reaction with eosinophilia and systemic symptoms (DRESS) in the pediatric population: A systematic review of the literature. *J Am Acad Dermatol.* 2020;83(5):1323-1330.
2. Kano Y, Ishida T, Hirahara K, Shiohara T. Visceral involvements and long-term sequelae in drug-induced hypersensitivity syndrome. *Med Clin North Am.* 2010;94(4):743-759.
3. Chen YC, Chang CY, Cho YT, Chiu HC, Chu CY. Long-term sequelae of drug reaction with eosinophilia and systemic symptoms: a retrospective cohort study from Taiwan. *J Am Acad Dermatol.* 2013;68(3):459-465.
4. Brown RJ, Rother KI, Artman H, et al. Minocycline-induced drug hypersensitivity syndrome followed by multiple autoimmune sequelae. *Arch Dermatol.* 2009;145(1):63-66.
5. Ushigome Y, Kano Y, Ishida T, Hirahara K, Shiohara T. Short- and long-term outcomes of 34 patients with drug-induced hypersensitivity syndrome in a single institution. *J Am Acad Dermatol.* 2013;68(5):721-728.
6. Kijima A, Inui S, Nakamura T, Itami S, Katayama I. Does drug-induced hypersensitivity syndrome elicit bullous pemphigoid? *Allergol Int.* 2008;57(2):181-182.
7. Yun SJ, Lee JB, Kim EJ, et al. Drug rash with eosinophilia and systemic symptoms induced by valproate and carbamazepine: formation of circulating auto-antibody against 190-kDa antigen. *Acta Derm Venereol.* 2006;86(3):241-244.
8. Kridin K, Kneiber D, Kowalski EH, Valdebran M, Amber KT. Epidermolysis bullosa acquisita: a comprehensive review. *Autoimmun Rev.* 2019;18(8):786-795.
9. Hashimoto T, Jin Z, Ishii N. Clinical and immunological studies for 105 Japanese seropositive patients of epidermolysis bullosa acquisita examined at Kurume University. *Expert Rev Clin Immunol.* 2016;12(8):895-902.