



Letter

A severe case of minocycline-induced DRESS resulting in liver transplantation and autoimmune sequelae

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a drug-induced hypersensitivity reaction that includes rash, hematologic abnormalities, lymphadenopathy, and internal organ involvement. The initial signs of fever, rash, and increased transaminase levels usually resolve once the acute episode subsides. However, physicians need to be aware that there are autoimmune sequelae that can develop long after the initial insult, such as thyroid dysfunction, lupus, and type 1 diabetes mellitus (T1DM).¹ T1DM has been noted to occur after DRESS, but this has been fulminant T1DM, a subtype characterized by extreme non-autoimmune rapid β -cell destruction. The present case highlights a severe presentation of DRESS that resulted in autoimmune T1DM, which rarely occurs after DRESS, and is only the third case reported to our knowledge.^{2,3}

A 13-year-old girl presented to the emergency department with rash and fever 3 weeks after starting minocycline for acne. The patient was diagnosed with DRESS based on eosinophilia (1,992/ μ L), leukocytosis (24,000/ μ L), fever (41.0°C), increased transaminase levels (aspartate aminotransferase 566 U/L, alanine aminotransferase 655 U/L), increased bilirubin level (1.4 mg/dL), increased creatinine level (1.50 mg/dL, serum urea nitrogen 14 mg/dL), and activated human herpes virus-6 (HHV6; 57,571 copies/mL) and started on high-dose steroids. Blood pressure (109/74 mm Hg) and glucose level (85 mg/dL) were normal. Within 48 hours, the patient developed liver failure and received a donor liver transplant the following day. Since transplantation, the patient has been immunosuppressed with tacrolimus, mycophenolate mofetil, and prednisone. She has been followed by the gastroenterology and allergy and immunology services since discharge from the hospital.

During routine evaluation 5 months after presentation, the patient was found to be hyperglycemic with a blood glucose level of 529 mg/dL. Routine laboratory tests performed 1 month previously did not show hyperglycemia. The patient had been on 1 mg/kg of prednisone daily at discharge and had been slowly weaned to 0.5 mg/kg daily for 2 months before diabetes diagnosis. The patient denied any polyuria or polydipsia, but further workup showed a hemoglobin A_{1c} of 9.4%, indicating chronic hyperglycemia. However, hemoglobin A_{1c} was more affected by the recent blood glucose level and the patient seemed to develop hyperglycemia within 1 month. Furthermore, glutamic acid decarboxylase antibodies were detected (2 U/mL, negative level <0.5 U/mL), indicating an autoimmune pathogenesis (specificity 99%).⁴ Islet cell antibody was negative. She developed hyperglycemia within 1 month while on a weaning dose of prednisone that was likely partly responsible for her hyperglycemia. In

addition, she was positive for antithyroid peroxidase (18 IU/mL, negative level <9 IU/mL) and antithyroglobulin antibodies (6.7 IU/mL, negative level <1 IU/mL), indicating thyroid involvement. The patient's thyroid-stimulating hormone and free thyroxine levels were normal. Since then, the patient has been on insulin and has been followed by the endocrinology service. Approximately 10 months after presentation, the patient also developed rapid-onset alopecia of unclear etiology, but an autoimmune pathogenesis is suspected.

Although the exact pathogenesis of post-DRESS autoimmunity is still elusive, it is believed that T-regulatory (T-reg) cells play a significant role. Studies have shown that T-reg cells are significantly increased during the acute stage of DRESS. With this increase and therefore increased immune suppression, viruses such as HHV6 can reactivate in an uncontrolled fashion.⁵ After DRESS, T-reg cells were found to have lost their ability to inhibit cytokine production and proliferate effector T cells. T-reg cells might have become overloaded initially and in turn become refractory after DRESS, leading toward an immune imbalance.^{5,6} This decrease in functional T-reg cells might, at least in part, have contributed to the autoimmunity.

In addition to deregulated T-reg cells, viral reactivation could play a role in post-DRESS autoimmunity. Viral reactivation has long been known to play a large role in DRESS pathogenesis so much so that HHV6 reactivation is often used as a criterion to diagnose DRESS.⁵ Other viruses associated with DRESS include Epstein-Barr virus and cytomegalovirus.⁶ Viral reactivation can be asymptomatic, cause reoccurrence of DRESS, or just cause organ-specific disease.⁶ The combination of nonfunctional T-reg cells after DRESS and viral reactivation could work synergistically in promoting autoimmunity (organ specific or systemic).^{5,6} Some studies have found that HHV6 in the thyroid is significantly higher in Hashimoto thyroiditis.⁷ Patients with lupus have higher titers of antibodies against Epstein-Barr virus and increased viral copy numbers than in the general population.⁶ The exact pathomechanism of how viruses contribute to post-DRESS autoimmunity needs further investigation.

Because only a subset of patients with DRESS develops autoimmunity, genetically predisposing HLA genes might be a factor. Because of the limited number of cases of autoimmune T1DM associated with DRESS, no specific HLA association has been discussed. Some studies have linked DQA1*0303, DQB1*0401, and HLAB62 with fulminant T1DM after DRESS.^{8,9} In 1 of the other 2 case reports of autoimmune-induced T1DM, the HLA typing showed DQA1*0303, the reported HLA linked with those who developed fulminant T1DM.³ Why this patient developed autoimmune diabetes rather than fulminant diabetes is unclear.

In addition to these contributors, the culprit drug could play a role. There have been reports of minocycline-induced autoimmunity

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without DRESS.¹⁰ Minocycline can cause various symptoms including polyarthralgia, autoimmune hepatitis, lupus, and vasculitis.¹⁰ Studies on minocycline have shown that it has immunomodulatory effects, despite unclear pathogenesis. Some hypothesize that it might work similarly to other drug-induced autoimmunity, such as hapten formation, unmasking neoantigens, molecular mimicry, or cross-reactivity with self-antigens. It is hypothesized that all the following can contribute to minocycline-induced autoimmunity: inherent immunomodulatory effect of minocycline, HLA subtype, T-reg cell deregulation, and latent viral infection.¹⁰

This interesting case has important takeaway points. Physicians need to be constantly vigilant about detrimental complications so they can weigh the benefits against the risks of prescribing medications. Furthermore, it is important for physicians to be aware of potential complications of DRESS to perform appropriate screenings and provide timely treatment. In this case, the patient's diabetes was found incidentally. Hence, clinically relevant laboratory studies should be considered for a timely diagnosis to prevent severe complications.

Jennifer Lan, MD*
Amit Lahoti, MD†
D. Betty Lew, MD*

*Division of Allergy and Immunology
Department of Pediatrics
The University of Tennessee Health Science Center
Memphis, Tennessee

†Division of Endocrinology
Department of Pediatrics
The University of Tennessee Health Science Center
Memphis, Tennessee
dlew@uthsc.edu

References

- [1] Chen YC, Chang CY, Yung-Tsu C, et al. Long-term sequelae of drug reaction with eosinophilia and systemic symptoms: a retrospective cohort study from Taiwan. *J Am Acad Dermatol*. 2013;68:459–465.
- [2] Brown RJ, Rother KI, Artman H, et al. Minocycline-induced drug hypersensitivity syndrome followed by multiple autoimmune sequelae. *Arch Dermatol*. 2009;145:63–66.
- [3] Ozaki N, Miura Y, Oiso Y. A case of type 1 diabetes followed by methimazole-induced hypersensitivity syndrome. *Diabetes Care*. 2006;29:1179–1180.
- [4] Lernmark A. Type 1 diabetes. *Clin Chem*. 1999;45(8 Pt 2):1331–1338.
- [5] Aota N, Shiohara T. Viral connection between drug rashes and autoimmune diseases: how autoimmune responses are generated after resolution of drug rashes. *Autoimmun Rev*. 2009;8:488–494.
- [6] Pavlos R, Mallal S, Ostrov D, et al. Fever, rash, and systemic symptoms: understanding the role of virus and HLA in severe cutaneous drug allergy. *J Allergy Clin Immunol Pract*. 2014;2:21–33.
- [7] Descamps V. Drug reaction with eosinophilia and systemic symptoms and thyroiditis: human herpesvirus-6, the possible common link. *Br J Dermatol*. 2013;169:952.
- [8] Onuma H, Tohyama M, Imagawa A, et al. High frequency of HLA B62 in fulminant type 1 diabetes with the drug-induced hypersensitivity syndrome. *J Clin Endocrinol Metab*. 2012;97:E2277–E2281.
- [9] Tanaka S, Kobayashi T, Nakanishi K, et al. Association of HLA-DQ genotype in autoantibody-negative and rapid-onset type 1 diabetes. *Diabetes Care*. 2002;25:2302–2307.
- [10] El-Hallak M, Giani T, Yeniy BS, et al. Chronic minocycline-induced autoimmunity in children. *J Pediatr*. 2008;153:314–319.