

Corticosteroid-induced drug reaction with eosinophilia and systematic symptoms successfully treated with a tumor necrosis factor alpha inhibitor

Sangchul Kim,¹ Eun-Jeong Joo,¹ U Jin Kim,¹ Ji Hye Kim,¹ Bomi Kim,¹ Heun Joo Lee,²
Seoung Wan Chae,³ Han-Na Kim,⁴ Hae Suk Cheong¹

Abstract

Background: Despite recent advances in the treatment of drug reaction with eosinophilia and systemic symptoms (DRESS), the mainstay of treatment involves discontinuing the culprit drugs and administering topical or systemic corticosteroid.

Objective: The clinical use of a tumor necrosis factor (TNF)-alpha inhibitor was rarely explored in treatment of DRESS.

Methods: We present a case of corticosteroid-induced DRESS that was successfully treated with a TNF-alpha inhibitor without sequelae.

Results: This is the first case report that showed the clinical use of a TNF alpha inhibitor in treating corticosteroids-induced DRESS and immediate hypersensitivity reactions. The HLA-B*5801 was identified as a possible genetic factor associated with a corticosteroid-induced DRESS.

Conclusion: A TNF-alpha inhibitor could be a primary option in treating DRESS, especially in patients with hypersensitivity reaction to corticosteroids.

Key words: Drug Hypersensitivity Syndrome; Drug Eruption; Steroids; Etanercept; Tumor Necrosis Factor-alpha

From:

¹ Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea;

² Department of Dermatology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea;

³ Department of Pathology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

⁴ Medical Research Institute, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul, Republic of Korea

Corresponding author:

Eun-Jeong Joo
Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine
29 Saemun-ro, Jongno-gu, Seoul 03181, Republic of Korea
E-mail: iamjoo@hanmail.net or iamjoo@skku.ac.kr

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, but potentially life-threatening adverse drug reaction, which is characterized by skin rash with fever, hematologic abnormalities such as leukocytosis with eosinophilia, lymphadenopathy, and internal organ involvement.¹ Despite recent advances in treatment of DRESS,² the mainstay of therapy involves discontinuing culprit drugs and administering systemic corticosteroid. Therefore, treatment options are limited

if the causative agent of DRESS is a corticosteroid. Recently, a tumor necrosis factor (TNF)-alpha inhibitor, such as infliximab and etanercept, has been successfully used to treat toxic epidermal necrosis (TEN) and Steven Johnson syndrome (SJS).³ Previously, in treatment of DRESS, however, the clinical use of a TNF-alpha inhibitor was limited as described in a case report.⁴ In this report, we present a case of corticosteroid-induced DRESS that was successfully treated with a TNF-alpha inhibitor.

Report of Case

A 26-year-old Asian woman presented to our emergency department (ED) with persistent fever over a period of six days. She had been previously healthy until being admitted to another tertiary care hospital for headache and nausea two months prior to her presentation, when she was presumptively diagnosed with tuberculous meningitis and received anti-tuberculosis medication. Six days prior to her visit to our ED, she complained of fever and visited the same hospital where she had been prescribed anti-tuberculosis medication and was advised to discontinue it with the suspicion of drug fever. Despite termination of the anti-tuberculous agents, the fever persisted, and she was admitted to the hospital for evaluation. Computed tomography (CT) scans and laboratory tests were performed, but test results did not show an evident infection focus. She was transferred to our ED on the second day of admission. During the flight to our hospital, a generalized skin rash developed rapidly from the trunk to the four extremities. At the time of presentation to ED, generalized skin rash and enlarged cervical lymph nodes were observed. Her initial vital signs on arrival were systolic/diastolic blood pressure, 105/72 mmHg; heart rate, 100 beats per min; respiratory rate, 20 breaths per min; and body temperature, 40.2°C. Initial serum lab findings showed mild leukocytosis (11,200/mm³) and elevated liver function tests; aspartate transaminase (AST), 184 IU/L; alanine transaminase (ALT), 181 IU/L.

We initiated intravenous 55 mg of methylprednisolone at a dose of 1 mg/kg per day with the impression of drug hypersensitivity reaction to anti-tuberculous agents. On hospital day 3, after the administration of systematic corticosteroids and intravenous antipyretics, the systolic blood pressure had dropped to 70 mmHg, respiratory rate had increased up to 44 breaths per min, and a drowsy mental status was noted. She was promptly transferred to the intensive care unit for endotracheal intubation. In addition to fluid resuscitation, vasopressors were administered to maintain an appropriate blood pressure. Echocardiogram showed features of stress-induced cardiomyopathy with severe left ventricular dysfunction. Serum lab findings showed severe leukocytosis (34,400/mm³) with eosinophilia (2,064/mm³) and atypical lymphocytes (2,408/mm³). Elevated liver function tests were also noted (AST/ALT, 601/542 IU/L).

With the impression of immediate hypersensitivity reaction to corticosteroids, a TNF-alpha inhibitor (50 mg weekly subcutaneous injection of etanercept) was administered to the patient on hospital day 4. Three days after an initial etanercept injection, her vital signs were stabilized and the skin rash improved dramatically. On hospital day 10, she was transferred back to the general ward. A total of four weekly etanercept 50 mg subcutaneous injections were done.

Skin biopsy was performed of her left inner thigh on day 3 of hospitalization. At 100× magnification, tissue section showed superficial perivascular lymphocyte infiltration with focal and mild basal vacuolar degeneration. Mild interstitial lymphocytes and few eosinophils were observed (**Figure**). At 400× magnification, tissue section showed mild and focal basal vacuolar degeneration with lymphocytic exocytosis, and non-specific mild perivascular lymphoid infiltration. There were a few eosinophils in the upper dermis. These pathologic findings

were compatible with DRESS. Based on a scoring system for classifying DRESS,⁵ the patient had a final score of eight, indicating a definite case of DRESS.

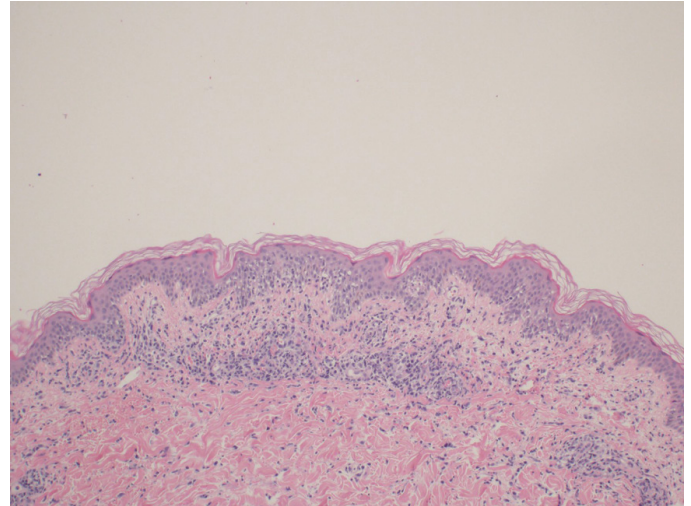


Figure. Skin, thigh, inner, left, punch biopsy, ×100

The medical chart review of her past medication showed that she had been taking dexamethasone (daily dose of 1 mg), isoniazid, rifampicin, and ethambutol for two months; these were stopped after the fever developed. It was also found that 50 mg of hydrocortisone was given to her just before her transfer to our ED. In a few hours after the injection of hydrocortisone, her skin rash had spread to the whole body as she flew back on the plane. On hospital day 24, 0.5 mg of dexamethasone was tested on the patient. Shortly after the administration of dexamethasone, skin rash and tachycardia were noted, suggesting that corticosteroids were the cause of the immediate hypersensitivity reaction and DRESS. Since the diagnosis of tuberculous meningitis was not definite, anti-tuberculous medication was not resumed.

In order to identify the genetic factor that causes a predisposition to corticosteroid-induced DRESS, HLA genotyping was performed. The patient tested positive for the HLA-B*58:01 allele.

Discussion

SCARs to drugs include SJS, TEN, and DRESS, which are rare but can be life-threatening with high mortality rate and are responsible for severe, potentially chronic sequelae.⁶ In our case, a corticosteroid-induced DRESS and immediate hypersensitivity reaction was successfully treated with a TNF-alpha inhibitor without sequelae. The patient had been sensitized to dexamethasone for two months and was re-exposed to another type of corticosteroid, hydrocortisone, prior to the visit to our ED; this administration resulted in the development of generalized skin rash as a typical presentation of IgE-mediated type I hypersensitivity. As an additional high dose of a systemic corticosteroid was administered in our hospital, both immediate and delayed types of hypersensitivity reactions were noted in the patient, leading to anaphylactic shock with multiple organ dysfunction. In this case, treatment with a TNF-alpha

inhibitor was successfully attempted in the situation when a corticosteroid was suspected to be a culprit drug for the hypersensitivity reaction. This is the first case report that showed the clinical use of a TNF alpha inhibitor in treating corticosteroids-induced DRESS and immediate hypersensitivity reactions.

The use of a TNF-alpha inhibitor, especially etanercept, has been approved to treat autoimmune diseases including rheumatoid arthritis, ankylosing spondylitis, juvenile rheumatoid arthritis, and psoriasis. Its use in treating cytotoxic T cell-mediated SCAR has therefore been rarely explored. In a recent randomized, controlled trial, compared to the conventional systematic corticosteroid therapy, etanercept treatment resulted in reduced mortality rate and skin-healing time in SJS/TEN patients.³ The successful use of a TNF-alpha inhibitor in treating DRESS was only reported in one case of lithium-induced DRESS.⁴ In addition to a prior report, our experience provides further evidence for the clinically effective and safe use of a TNF-alpha inhibitor in treating DRESS, even though it requires further evaluation.

Immune mechanisms of SCARs are related to the activation of drug-specific cytotoxic T cells, inflammatory cells, or regulatory T cells and the differential secretion of inflammatory cytokines.⁶ The underlying mechanism for how T cells recognize drugs and promote an immune response is partially explained by direct or indirect drug-binding to specific HLA molecules; this may result in cytotoxic T cell activation. Several genetic factors that cause a predisposition to SCARs have been previously reported in the HLA-A, B, or C alleles.⁶ The HLA-B*5801 allele has been strongly associated with the allopurinol hypersensitivity syndrome and has been found in higher frequency in Asian.^{7,8} In the Korean population, the frequency of HLA-B*5801 is relatively high (12.2%),⁹ and 92.3% of patients with allopurinol-induced SCARs were positive for the HLA-B*5801 allele.¹⁰ In accordance with previous pharmacogenetic research, HLA-B*5801 was detected in this patient but further research is needed to link HLA-A*5801 to a corticosteroid-induced DRESS.

Hypersensitivity reactions to corticosteroids are rare in the general population but not uncommon in high-risk groups such as patients who have received repeated doses of corticosteroids.¹¹ The literature review during the period between 2004 and 2014 identified 120 cases of immediate hypersensitivity reactions to corticosteroids; of these, 60.8% were anaphylaxis cases.¹² A delayed hypersensitivity reaction to corticosteroids was limited to contact dermatitis.¹³ To our knowledge, this is the first case that reported not only an immediate hypersensitivity reaction to corticosteroids but also a delayed hypersensitivity reaction, DRESS. For this patient who had received several drugs simultaneously, however, it is unclear whether anti-tuberculous agents played any role in progression of DRESS. *In vitro* tests including lymphocyte transformation test and interferon-gamma enzyme-linked immunospot assay are potentially promising in demonstrating the causative agent for delayed hypersensitivity reactions.¹⁴ Validation of these tests remains difficult for clinical use and their use was not available in our institution.

A systemic corticosteroid has been considered as one of few treatment options for treating hypersensitivity reactions to

drugs, but it can also be one of many possible causes of immediate and delayed hypersensitivity reactions, including DRESS. The HLA allele, especially HLA-B*5801, was identified as a possible genetic factor associated with a corticosteroid-induced DRESS. A TNF-alpha inhibitor can be a primary treatment option in DRESS, especially in patients with hypersensitivity reactions to corticosteroids.

Conflict of interest

The authors declare no conflict of interest.

Source of funding

None declared.

Author contributions

- Sangchul Kim: drafting of the manuscript
- Eun-Jeong Joo: drafting of the manuscript and critical revision of the manuscript
- U Jin Kim, Ji Hye Kim, Bomi Kim, Heun Joo Lee: material support and acquisition of data
- Seoung Wan Chae: material support
- Han-Na Kim: analysis and interpretation of data
- Hae Suk Cheong: technical, or material support; and acquisition of data

References

1. Garon SL, Pavlos RK, White KD, Brown NJ, Stone CA Jr, Phillips EJ. Pharmacogenomics of off-target adverse drug reactions. *Br J Clin Pharmacol.* 2017;83:1896-911.
2. Watanabe H. Recent advances in drug-induced hypersensitivity syndrome/ drug reaction with eosinophilia and systemic symptoms. *J Immunol Res.* 2018;2018:5163129.
3. Wang CW, Yang LY, Chen CB, Ho HC, Hung SI, Yang CH, et al. Randomized, controlled trial of TNF-alpha antagonist in CTL-mediated severe cutaneous adverse reactions. *J Clin Invest.* 2018;128:985-96.
4. Leman RE, Chen L, Shi X, Rolimpandoei SP, Ling X, Su Y. Drug reaction with eosinophilia and systemic symptoms (DRESS) successfully treated with tumor necrosis factor-alpha inhibitor. *JAAD Case Rep.* 2017;3:332-5.
5. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol.* 2007;156:609-11.
6. Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. *Lancet.* 2017;390:1996-2011.
7. Cao ZH, Wei ZY, Zhu QY, Zhang JY, Yang L, Qin SY, et al. HLA-B*58:01 allele is associated with augmented risk for both mild and severe cutaneous adverse reactions induced by allopurinol in Han Chinese. *Pharmacogenomics.* 2012;13:1193-201.
8. Tassaneeyakul W, Jantararoungtong T, Chen P, Lin PY, Tiamkao S, Khunarkornsiri U, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. *Pharmacogenet Genomics.* 2009;19:704-9.
9. Lee KW, Oh DH, Lee C, Yang SY. Allelic and haplotypic diversity of HLA-A, -B, -C, -DRB1, and -DQB1 genes in the Korean population. *Tissue Antigens.* 2005;65:437-47.
10. Kang HR, Jee YK, Kim YS, Lee CH, Jung JW, Kim SH, et al. Positive and negative associations of HLA class I alleles with allopurinol-induced SCARs in Koreans. *Pharmacogenet Genomics.* 2011;21:303-7.
11. Vatti RR, Ali F, Teuber S, Chang C, Gershwin ME. Hypersensitivity reactions to corticosteroids. *Clin Rev Allergy Immunol.* 2014;47:26-37.
12. Patel A, Bahna SL. Immediate hypersensitivity reactions to corticosteroids. *Ann Allergy Asthma Immunol.* 2015;115:178-82 e3.
13. Otani IM, Banerji A. Immediate and delayed hypersensitivity reactions to corticosteroids: evaluation and management. *Curr Allergy Asthma Rep.* 2016;16:18.
14. Baeck M, Marot L, Nicolas JF, Pilette C, Tennstedt D, Goossens A. Allergic hypersensitivity to topical and systemic corticosteroids: a review. *Allergy.* 2009;64:978-94.