

Case Report

Successful Treatment of Imatinib-Induced DRESS Syndrome Using Reslizumab without Cessation of Imatinib: A Case Report

Hyerin Park^a Gil-Soon Choi^b Eun Mi Lee^b

^aKosin University College of Medicine, Busan, South Korea; ^bDepartment of Internal Medicine, Kosin University College of Medicine, Busan, South Korea

Keywords

Drug reaction with eosinophilia and systemic symptoms · Imatinib mesylate · Gastrointestinal stromal tumor · Reslizumab

Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe cutaneous adverse drug reaction; reported cases are sometimes imatinib mesylate induced. The main treatment is the withdrawal of the causative drug, and most cases with imatinib-induced DRESS syndrome required withdrawal of imatinib. However, in such cases involving anti-cancer drugs, this may compromise cancer treatment. Herein, we report a patient with imatinib-induced DRESS syndrome that was successfully treated with reslizumab while continuing imatinib treatment. A 65-year-old female presented with facial edema and generalized skin rash after being given 400 mg imatinib 2 weeks ago for metastatic gastrointestinal stromal tumor. After stopping imatinib, the clinical symptoms improved. Imatinib desensitization was performed, and it was administered again. However, the clinical symptoms reappeared more severely 2 months after restart of imatinib, and the peripheral absolute eosinophil count increased to 1,690/ μL . A diagnosis of imatinib-induced DRESS syndrome was made, based on the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) criteria. Imatinib desensitization was repeated, but the clinical symptoms reappeared, and the peripheral eosinophilia persisted. We administered reslizumab, an interleukin-5 monoclonal antibody, without cessation of imatinib. The absolute eosinophil count decreased immediately, and the clinical symptoms improved gradually. After 2 weeks, the clinical symptoms reappeared mildly, but after administering reslizumab again, these disappeared completely.

Reslizumab can be considered in the management of DRESS syndrome in cases wherein the causative medication needs to be continued.

© 2021 The Author(s).
Published by S. Karger AG, Basel

Introduction

Imatinib mesylate, a selective inhibitor of KIT protein tyrosine kinase, is the primary treatment for patients with advanced, unresectable, or metastatic gastrointestinal stromal tumor (GIST) and for those at intermediate or high risk of recurrence after surgical resection [1–3]. The toxicity of imatinib may decrease with prolonged therapy and is managed with supportive care [4].

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe adverse drug reaction characterized by an extensive skin rash in association with visceral organ involvement, lymphadenopathy, eosinophilia, and atypical lymphocytosis. The risk of DRESS syndrome varies from drug to drug, and DRESS syndrome associated with imatinib has been occasionally reported. Although systemic glucocorticoids can be used in patients with moderate to severe symptoms, withdrawal of the causative drugs is the main treatment for all patients with DRESS syndrome [5]. However, it is not easy to stop the causative drugs in cases due to anticancer drugs.

Reslizumab is a humanized immunoglobulin G (IgG)4 kappa monoclonal antibody that binds to human interleukin (IL)-5, thereby reducing the production and survival of eosinophils. It has been approved for treatment of severe eosinophilic asthma [6]. Some case reports have also indicated its efficacy for the treatment of hypereosinophilic syndrome [7–9]. Herein, we successfully treated imatinib-induced DRESS syndrome with reslizumab in a patient with metastatic GIST while continuing imatinib treatment.

Case Presentation

A 62-year-old female was referred to our department to treat multiple peritoneal masses on abdominal CT. The patient had a history of small bowel resection for GIST approximately 2 years ago. A recurrence of GIST was diagnosed, and she was started on 400 mg imatinib daily. Two weeks later, she complained of facial edema and skin rash over her entire body. Laboratory tests were normal. Imatinib was stopped, and 15 mg oral prednisolone once daily was started. Two weeks later, the symptoms slightly resolved, and the patient was hospitalized for imatinib desensitization. At that time, a slight elevation of absolute eosinophil count of 600/ μ L (15%, range: 0%–5%) was observed in the complete blood count. Imatinib desensitization was performed as follows: imatinib 25 mg, 25 mg, 50 mg, and 100 mg was orally administered sequentially at 30-min intervals on day 1, and then imatinib was increased to 200 mg on day 2 and 400 mg on day 4. After desensitization, imatinib 400 mg with antihistaminergic drugs was administered, and the patient took the medication relatively well. However, facial edema (shown in Fig. 1) and skin rash on the whole body reappeared more severely after 2 months, requiring hospitalization. Complete blood count revealed an increased absolute eosinophil count of 1,690/ μ L (27%, range: 0%–5%) and a slightly decreased lymphocyte count of $1,320 \times 10^3$ / μ L (21%, range: 24%–50%) (shown in Fig. 2). Liver function testing revealed a slightly elevated gamma-glutamyl transpeptidase (γ -GTP) level of 61 U/L (range: 0–50 U/L). The serologies for viral infections (hepatitis B virus, hepatitis C virus, and

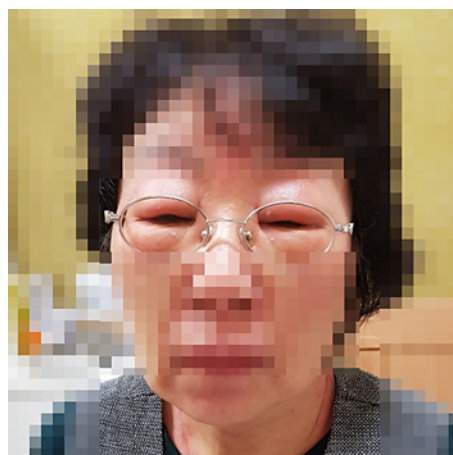


Fig. 1. Periorbital edema on the face at 2 weeks after treatment of imatinib.

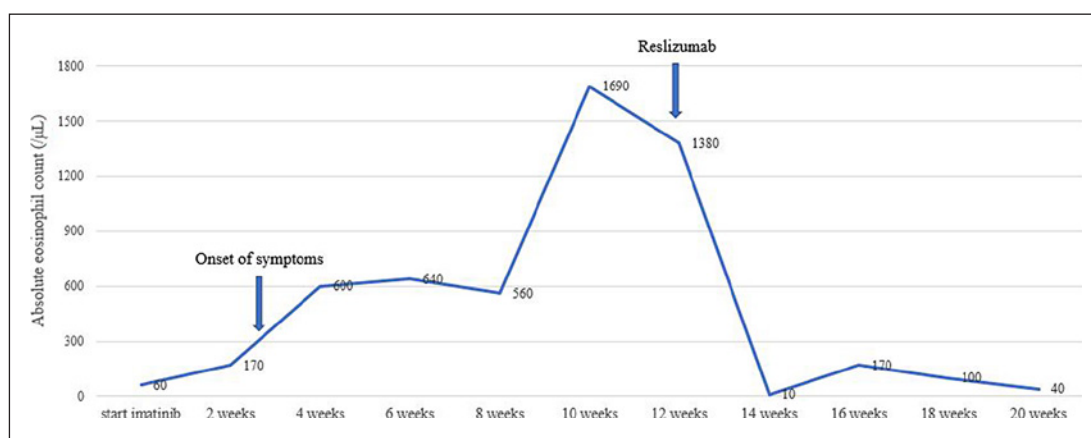


Fig. 2. Absolute eosinophil counts during treatment of imatinib.

human immunodeficiency virus) were negative, and the anti-nuclear antibody test showed a negative result. The tumor sizes on abdominal CT were remarkably decreased, and these showed partial response based on the Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (shown in Fig. 3).

The patient was diagnosed with imatinib-induced DRESS syndrome, based on the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) criteria [10]. Intravenous dexamethasone was temporarily administered with cessation of imatinib. Although desensitization treatment of imatinib was performed once again after the patient's clinical symptoms improved, the symptoms reappeared, and the eosinophilia on peripheral blood persisted. Good tumor response to imatinib treatment made it difficult to stop treatment, considering the clinical benefit of imatinib and the risk of disease progression if treatment is stopped. Thus, we administered reslizumab 100 mg intravenously, while the patient continued to take imatinib. After administration of reslizumab, the absolute eosinophil count immediately decreased to the normal range ($10/\mu\text{L}$, 0.1%, range: 0%–5%), and the clinical symptoms gradually improved without corticosteroids. However, a decreased lymphocyte count of $1,020/\mu\text{L}$ (14.6%, range: 24%–50%) and increased γ -GTP levels at 69 U/L (range: 0–50 U/L) were still noted. In 2 weeks, a mild generalized skin rash occurred again, but the absolute eosinophil count of $170/\mu\text{L}$ (2%, range: 0%–5%) did not increase. Without cessation of imatinib, reslizumab 200 mg was administered once more. After that, the symptoms completely resolved,

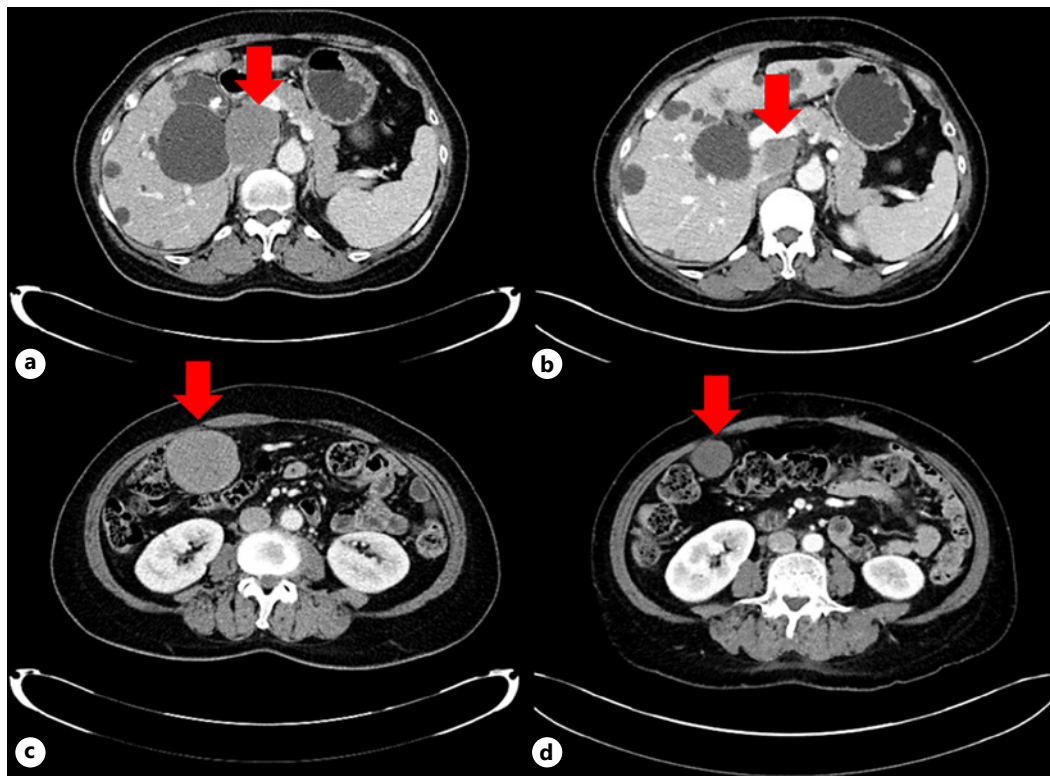


Fig. 3. CT scans of the abdomen. CT imaging before starting imatinib (**a, c**); CT imaging after 3 months of starting imatinib (**b, d**). These images show that sizes of metastatic masses (**a, c**) decreased after treatment with imatinib (**b, d**).

and the absolute eosinophil count was sustained in the normal range without administration of glucocorticoids. Lymphocyte count (1,900/ μ L, 26.2%, range: 24%–50%) and γ -GTP level (22 U/L, range: 0–50 U/L) returned to normal range.

Imatinib treatment was continued for 2 years until progression of the disease was observed on abdominal CT. During this period, the clinical symptoms did not reappear, and the absolute eosinophil count was sustained in the normal range, so no further reslizumab was administered. Despite the dose of imatinib being increased to 600 mg because of disease progression, the patient still tolerated the treatment well. However, since the disease progressed more, we changed treatment from imatinib to sunitinib.

Discussion

DRESS syndrome is a rare but potentially life-threatening cutaneous adverse drug reaction. This disease presents as a spectrum, ranging from mild rash with eosinophilia responding to withdrawal of the causative drug to multiple-organ involvement with high mortality. More than 50 drugs have been reported to induce DRESS syndrome, with allopurinol, anticonvulsants, and antibiotics commonly being implicated in this disease [5, 11]. The diagnosis of DRESS syndrome requires a high level of suspicion by clinicians, and the most widely used criteria were established by the RegiSCAR scoring system [10]. We diagnosed as “possible” DRESS syndrome with score 3 according to this scoring system; eosinophilia with 1,690/ μ L (2 points), skin rash over the entire body (1 point), skin rash suggesting DRESS with

facial edema and purpura (1 point), negative results of tests for anti-nuclear antibody, and hepatitis B and C (1 point), no fever (–1 point), and no skin biopsy (–1 point). To distinguish DRESS syndrome from maculopapular drug eruptions, it is important to note that systemic symptoms and visceral organ involvement are more common in DRESS syndrome, and the latency time of DRESS syndrome between drug exposure and disease onset (2–8 weeks) is longer than that of maculopapular drug eruptions (5–14 days) [11]. Although systemic symptoms and involvement of visceral organs were not prominent in this case, generalized skin rash occurred at 2 weeks after initiation of imatinib, and peripheral eosinophilia began to appear at 8 weeks.

Cutaneous reactions during imatinib treatment occur in 31–44% of patients, and most cases are self-limiting and can be manageable without cessation of the drug [12]. However, imatinib can induce severe cutaneous adverse reactions (SCARs) that are potentially fatal, such as Stevens-Johnson syndrome/toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and DRESS syndrome [13]. There were 7 case reports of DRESS syndrome associated with imatinib; 5 cases in patients with chronic myeloid leukemia, one in a patient with GIST, and one in dermatofibrosarcoma protuberance. The starting dose of imatinib was 400 mg in all cases, except in 1 case with dermatofibrosarcoma protuberance whose dose started at 800 mg. The latency time varied from 2 to 15 weeks, and there were no fatal cases [14–20].

Identification and withdrawal of the causative drug are the first steps in the management of SCARs. For Stevens-Johnson syndrome/toxic epidermal necrolysis, early withdrawal of the causative drugs is associated with a better prognosis [21]. Although there are no randomized clinical trials for treatment of SCARs, topical corticosteroids are helpful in mild cases, and systemic corticosteroids are used for moderate to severe cases. Rechallenge of the offending drug is not recommended because the relapse can be worse than the initial reaction [22]. However, in cases wherein the causative drug is associated with anticancer treatment, especially for patients with advanced disease, discontinuation of the drug causes disease progression and leads to an undesired outcome. In case reports of imatinib-induced DRESS syndrome, the clinical symptoms and laboratory abnormalities returned to normal after cessation of imatinib [14–20]. In 2 cases, imatinib was restarted, although at half the original dose, and a small dose of oral glucocorticoid was administered concomitantly [16, 19]. Our patient's clinical symptoms also improved after discontinuation of the drug. Then, desensitization treatment to rechallenge imatinib was attempted twice, but the clinical symptoms reappeared more severely, and the peripheral eosinophilia persisted. Because this patient had metastatic cancer that showed good tumor response to imatinib, it was not easy to stop the medication for her.

DRESS syndrome is considered a T-cell-mediated hypersensitivity reaction with a drug-specific immune response and involvement of the human herpes virus reaction with a subsequent antiviral immune response [23]. Interestingly, imatinib is suspected to induce clonal T-cell subsets producing IL-5 [24]. Thus, other mechanisms may be involved in imatinib-induced DRESS syndrome, unlike conventional cases. However, the pathogenesis of DRESS syndrome remains unclear. Reslizumab, a monoclonal anti-IL-5 antibody, has been approved for add-on maintenance therapy of severe asthma of eosinophilic phenotype. IL-5 is a pro-eosinophilic cytokine that is a potent mediator of eosinophilic hematopoiesis and plays a pivotal role in eosinophil accumulation and activation [25]. Although the exact role of IL-5 in pathogenesis of DRESS syndrome is not fully understood, the elevation of plasma IL-5 levels was observed in patients with early DRESS syndrome, and IL-5 could be used as a target for treatment of DRESS syndrome [26]. There was a case report in which DRESS syndrome was treated with mepolizumab, another humanized monoclonal antibody targeting IL-5 [27]. Because the clinical symptoms of our patient worsened as peripheral eosinophilia appeared,

we administered reslizumab without cessation of imatinib. Afterward, the peripheral eosinophil count immediately returned to normal, and the clinical symptoms improved gradually. Reslizumab enabled the patient to safely maintain imatinib treatment for 2 years until disease progression was observed. In this patient, desensitization treatment was attempted when the symptoms first appeared, and the patient tolerated imatinib well after desensitization. However, DRESS syndrome developed after 2 months. Imatinib is likely to induce clonal T-cell subsets producing IL-5, which may lead to desensitization failure. Our case suggests that sequential therapy with an anti-IL-5 agent during desensitization in imatinib-induced DRESS syndrome can improve the therapeutic success. However, further studies are needed.

Conclusion

Herein, we report a patient with imatinib-induced DRESS syndrome successfully treated with reslizumab. Reslizumab could be considered in the management of DRESS syndrome in patients who need to continue the causative medication. However, the exact role of reslizumab in the pathophysiology of DRESS syndrome remains unclear, and further clinical studies are required to confirm its efficacy.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The institutional review board of our hospital approved this case report (KUGH 2021-07-032).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors did not receive any funding.

Author Contributions

H. Park and E.M. Lee reviewed the literature and contributed to manuscript drafting; G.S. Choi and E.M. Lee contributed to the conception, design, acquisition, analysis, and interpretation of data; E.M. Lee was responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

Data Availability Statement

All data underlying the results are available as part of the article, and no additional source data are required.

References

- 1 Joensuu H, Roberts PJ, Sarlomo-Rikala M, Andersson LC, Tervahartiala P, Tuveson D, et al. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med*. 2001;344(14):1052–6.
- 2 Joensuu H, Eriksson M, Sundby Hall K, Hartmann JT, Pink D, Schütte J, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. *JAMA*. 2012;307(12):1265–72.
- 3 Corless CL, Ballman KV, Antonescu CR, Kolesnikova V, Maki RG, Pisters PW, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. *J Clin Oncol*. 2014;32(15):1563–70.
- 4 Guillhot F. Indications for imatinib mesylate therapy and clinical management. *Oncologist*. 2004;9(3):271–81.
- 5 Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS syndrome: a literature review. *Am J Med*. 2011;124(7):588–97.
- 6 Deeks ED, Brusselle G. Reslizumab in eosinophilic asthma: a review. *Drugs*. 2017;77(7):777–84.
- 7 Coffey K, Fajt ML, Acho M, Gladwin M, Petrov AA. Successful treatment of corticosteroid-refractory hypereosinophilia with reslizumab. *J Investig Allergol Clin Immunol*. 2019;29(3):241–2.
- 8 Buttgereit T, Bonnekoh H, Church MK, Bergmann KC, Siebenhaar F, Metz M. Effective treatment of a lymphocytic variant of hypereosinophilic syndrome with reslizumab. *J Dtsch Dermatol Ges*. 2019;17(11):1171–2.
- 9 Kuruvilla M. Treatment of hypereosinophilic syndrome and eosinophilic dermatitis with reslizumab. *Ann Allergy Asthma Immunol*. 2018;120(6):670–1.
- 10 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(3):609–11.
- 11 Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *Br J Dermatol*. 2013;169(5):1071–80.
- 12 Deininger MW, O'Brien SG, Ford JM, Druker BJ. Practical management of patients with chronic myeloid leukemia receiving imatinib. *J Clin Oncol*. 2003;21(8):1637–47.
- 13 Chen CB, Wu MY, Ng CY, Lu CW, Wu J, Kao PH, et al. Severe cutaneous adverse reactions induced by targeted anticancer therapies and immunotherapies. *Cancer Manag Res*. 2018;10:1259–73.
- 14 Le Nouail P, Viseux V, Chaby G, Billet A, Denoeux JP, Lok C. [Drug reaction with eosinophilia and systemic symptoms (DRESS) following imatinib therapy]. *Ann Dermatol Venereol*. 2006;133(8–9 Pt 1):686–8.
- 15 Goldman J, Duval-Modeste AB, Lambert A, Contentin N, Courville P, Musette P, et al. [Imatinib-induced DRESS]. *Ann Dermatol Venereol*. 2008;135(5):393–6.
- 16 Kumar M, Mandal PK, Dolai TK, Bhattacharrya M. Imatinib causing drug rash with eosinophilia and systemic symptoms: a rare cutaneous reaction. *Indian Dermatol Online J*. 2014;5(Suppl 2):S120–2.
- 17 Saidi W, Lahouel I, Laarif M, Aounallah A. A new case of imatinib-induced drug reaction with eosinophilia and systemic symptoms. *Indian J Dermatol Venereol Leprol*. 2017;83(2):224–6.
- 18 Vatel O, Aumont C, Mathy V, Petit M, Feriel J, Sloma I, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS) induced by imatinib in chronic myeloid leukemia. *Leuk Lymphoma*. 2017;58(2):473–4.
- 19 Ben-Ami E, Castells MC, Connell NT, Rutherford AE, Thornton KA. Imatinib-induced drug reaction with eosinophilia and systemic symptoms in solid tumors: a patient with dermatofibrosarcoma protuberans and successful desensitization management. *Anticancer Drugs*. 2018;29(9):919–23.
- 20 Zgolli F, Aouinti I, Charfi O, Badri T, Elaidli S, Kastalli S, et al. Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome induced by imatinib. *Curr Drug Saf*. 2019;14(2):151–4.
- 21 Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol*. 2000;136(3):323–7.
- 22 Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. *Lancet*. 2017;390(10106):1996–2011.
- 23 Ganeshanandan L, Lucas M. Drug reaction with eosinophilia and systemic symptoms: a complex interplay between drug, T cells, and herpesviridae. *Int J Mol Sci*. 2021;22(3):1127.
- 24 McGrath K, Stein B, Kalhagen L, Leighton L. Imatinib mesylate- and dasatinib-induced eosinophilia in a patient with chronic myelocytic leukemia. *Ann Allergy Asthma Immunol*. 2017;119(1):85–6.
- 25 Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev*. 2017;9(9):Cd010834.
- 26 Choquet-Kastylevsky G, Intrator L, Chenal C, Bocquet H, Revuz J, Roujeau JC. Increased levels of interleukin 5 are associated with the generation of eosinophilia in drug-induced hypersensitivity syndrome. *Br J Dermatol*. 1998;139(6):1026–32.
- 27 Ange N, Alley S, Fernando SL, Coyle L, Yun J. Drug Reaction with eosinophilia and systemic symptoms (DRESS) syndrome successfully treated with mepolizumab. *J Allergy Clin Immunol Pract*. 2018;6(3):1059–60.