

# The efficacy of oral cyclosporine in a patient with drug reaction with eosinophilia and systemic symptoms probably due to cefadroxil

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**Abstract** Drug Reaction with Eosinophilia and Systemic Symptom (DRESS) is a rare but potentially life-threatening adverse drug reaction. Antibiotics especially cephalosporin often cause DRESS. The gold standard for diagnosing DRESS is by RegiSCAR criteria. Systemic corticosteroid is the first line therapy of DRESS but in certain cases, steroid sparing agents such as cyclosporine can be used to reduce side effects and accelerate patient recovery. **Case:** A 36-years-old man admitted to Moewardi General Hospital, Surakarta with recalcitrant DRESS due to melena after treated with methylprednisolone 125 mg/day. He presented with itchy red patches three weeks after taking cefadroxil 500 mg twice daily. Dermatovenereological status showed generalized scaly erythematous partially hyperpigmented patches. The regiSCAR obtained 6 points (definite) and was diagnosed with DRESS. After administered with methylprednisolone 93.75 mg/day IV tapering off followed by oral cyclosporine 100 mg twice a day in a week showed clinical and laboratory improvement on the seventh days after therapy. **Discussion:** Cyclosporine as an adjuvant therapy for recalcitrant treatment of DRESS showed good improvement. It can be considered in cases where systemic corticosteroids are contraindicated, inadequate response to conventional therapy or long-term use of corticosteroids. The use of cyclosporine 100 mg twice daily for one week can lower the dose of systemic corticosteroid, furthermore can decrease the potential adverse events. **Conclusion:** This case reports a man with recalcitrant DRESS. The patient was treated with methylprednisolone 93.75 mg/day IV tapering off followed by oral cyclosporine 100 mg twice a day in a week showed clinical and laboratory improvement.

**Key words**

Cefadroxil; Cyclosporine; DRESS.

## Introduction

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a rare but potentially life-threatening severe drug hypersensitivity reaction with clinical manifestations fever, skin rash, abnormal blood laboratory results (eosinophilia or atypical lymphocytes) and

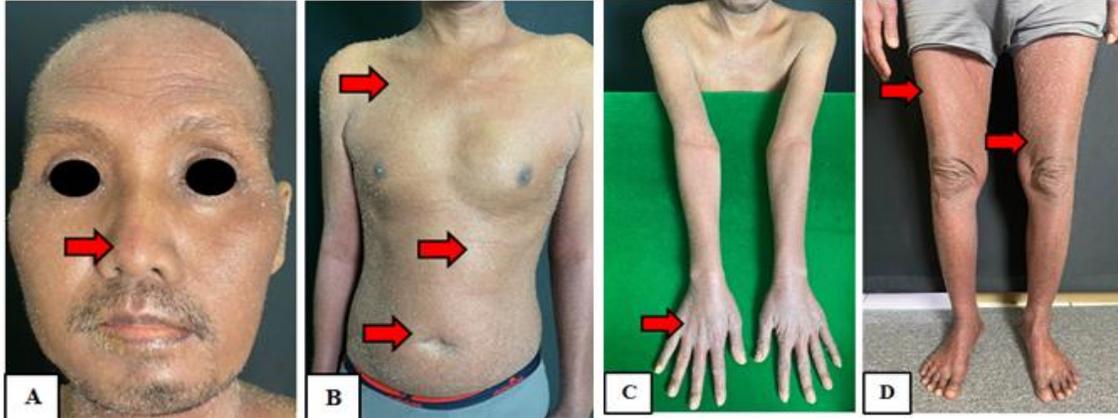
multiple organ involvement.<sup>1</sup> The worldwide incidence of DRESS is not known certainly but estimated between 1 per 1000 and 1 per 10,000 drug exposure.<sup>2</sup> The incidence of DRESS in Asia accounts for 10% of all cases of drug hypersensitivity reactions with mortality rates ranging from 3-10% and most often caused by multiple organ failure and sepsis.<sup>3</sup>

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Antibiotics such as penicillins, glycopeptides, tetracyclines and cephalosporins can cause DRESS.<sup>4</sup> Cefadroxil is a third-generation of cephalosporin that used to treat infections of soft tissues such as the skin, upper respiratory tract, pharyngitis and urinary tract.<sup>5</sup> Lin *et al.* reported



**Figure 1** Dermatological status. (A) Facial region shows multiple discrete, partially confluent erythematous patches with thin scales (red arrow). (B-D) Anterior trunk et superior et inferior bilateral extremities show multiple discrete, partially confluent erythematous patches with thin scales (red arrow).

that cefadroxil was the second most common cause of cephalosporin class in DRESS patients.<sup>6</sup>

Cyclosporine is a class of calcineurin inhibitors that can be used as an alternative therapy in patients with contraindications or whom do not respond to corticosteroids.<sup>7</sup> Cyclosporine has strong immunosuppressant effect by inhibit cytotoxic T cell activation which is the main pathogenesis of DRESS. The addition of cyclosporine in the therapeutic regimen can reduce the dose and duration of systemic corticosteroid and thereby reduce the potential severe side effects.<sup>8</sup>

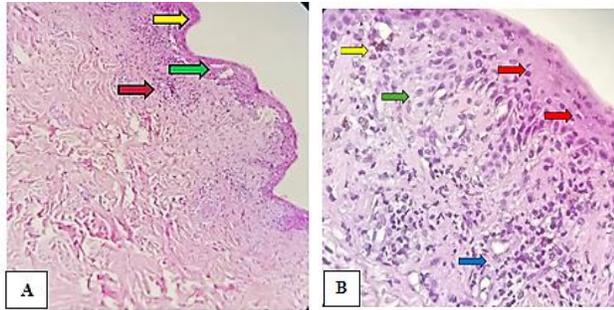
### Case report

A 36-years-old man admitted to Dr. Moewardi General Hospital, Surakarta with chief complaint itchy red spots on almost all parts of his body. Red spots initially appeared on both armpits since 1 month ago. Three days after, the itchy red spots spread all over the body. The patient also complained of painful when swallowing and mouth sores. Patient was consuming cefadroxil capsule 500 mg twice daily and paracetamol tablet 500 mg three times daily after mandibular surgery 7 weeks ago. He denied any fever, watery eyes, painful urination

and defecation. Physical examination revealed icteric sclera and enlargement of supraclavicular, axillary and left inguinal lymphnodes. Dermatovenereological status showed generalized scaly erythematous partially hyperpigmented patches (**Figure 1**).

Routine blood tests obtained abnormal results with increase of leukocyte 14.78 thousand/ul (N: 4.5-11.0 thousand/ul), eosinophils 15.7% (N: 0-4%), lymphocytes 57.7% (N: 22.00-44.00%), urea 138 mg/dl (N: <50 mg/dl) and creatinine 2.65 mg/dl (normal: 0.6-1.1 mg/dl) and decrease of hemoglobin 10.8 g/dl (N: 13.5-17.5 g/dl), hematocrit 30% (N: 33-45%), erythrocytes 3.68 million/ul (N: 4.50-5.90 million/ul), neutrophils 21.6% (N: 55.00-80.00%), albumin 2.7 g/dl (N: 3.5-5 g/dl), sodium 127.66 mmol/L (N: 136-145 mmol/L), potassium 3.04 mmol/L (N: 3.5-5.1 mmol/L), chloride 93.45 mmol/L (N: 98-106 mmol/L), calcium 0.88 mmol/L (N: 1.17-1.29 mmol/L), serum glutamic oxoacetic transaminase (SGOT) 43 U/l (N: <31 U/l) and serum glutamic piruvic transaminase (SGPT) 181 U/l (N: <34 U/l).

Histopathological examination on epidermal layer showed severe spongiosis (vacuolization), few neutrophils and proliferation of basal cells while dermal layer showed perivascular



**Figure 2** Histopathology (A) Hyperkeratotic epidermal layer (yellow arrow) with spongiosis (green arrow), upper dermis showed an inflammatory cell infiltrates (red arrow). (HE 10x) (B) Thinning of epidermal layer with spongiosis (red arrow) and basal cell vacuolar degeneration (green arrow), dermal layer showed dropping melanin (yellow arrow) and lymphocytic infiltrates (blue arrow). (HE 40x)

infiltrates, dropping of melanin and fibrin (Figure 2). The regiSCAR obtained 6 points (definite) and patient was diagnosed with DRESS.

Patient was treated with methylprednisolone 125 mg/day IV, mometasone furoate 0.1% cream twice daily apply to red patches on facial area, desoximetasone 0.25% cream twice daily apply to red patches on the body and urea 10% cream twice daily all over the body. One week after, he complained of melena and the dose of methylprednisolone was reduced. After two days, the itchy red patches was getting worse and spreading more throughout the body. He

was then diagnosed with recalcitrant DRESS and treated with methylprednisolone 93.75 mg/day IV tapering off followed by oral cyclosporine 100 mg twice a day in a week showed clinical and laboratory improvement on the seventh days after therapy (Figure 3).

## Discussion

DRESS syndrome is a severe drug hypersensitivity reaction which was first observed in patients treated with anticonvulsants in the early 1930s.<sup>9</sup> Wang *et al.* reported that DRESS contributed to 10% of cases of severe drug hypersensitivity reactions in Asia.<sup>10</sup>

The European Registry of Severe Cutaneous Adverse Reaction study group proposes a DRESS diagnostic assessment that meets at least three of seven criteria include the presence of fever, enlarged lymph nodes, eosinophilia, atypical lymphocytes, skin involvement >50% of body surface area (BSA), involvement of internal organs and resolution in  $\geq 15$  days.<sup>11</sup> Patient in this case had acute skin rash >50% BSA, lymphadenopathy in >2 locations, internal organ involvement characterized by increased liver and kidney function, presence of lymphocytosis and eosinophilia with total score of 6 (definite DRESS).



**Figure 3** Follow up (A) Facial region shows no abnormalities (B-D) Anterior trunk et superior et inferior bilateral extremities show multiple discrete hyperpigmented patches with thin white scales (red arrows).

DRESS syndrome caused by cefadroxil has been described in several literatures.<sup>12-15</sup> Farhat *et al.* reported a 46 years old female with DRESS. She had previously taken oral cefadroxil 4 weeks before the onset of symptoms. She underwent a patch test and obtained a strong positive result for cefadroxil.<sup>12</sup> Patch test is the gold standard examination to identify the causative drug in DRESS. Intradermal test and prick test is the second diagnostic step if a negative patch test was found.<sup>16</sup>

Cyclosporine acts by inhibit calcineurin, which is a calcium-dependent serine/threonine protein phosphatase and calmodulin. Activated calcineurin dephosphorylates several transcription factors, especially nuclear factor of activated T cells (NFATs). Inhibition of calcineurin by cyclosporine occurs via binding to immunophilins and cyclophilins which prevent NFAT dephosphorylation and subsequent translocation from the cytoplasm to the nucleus in an interleukin (IL)-2-mediated process. Inhibition at this level thereby prevents activation of the T-cell activation promoter and the overall immune response.<sup>17</sup>

The use of cyclosporine has been reported as an alternative treatment for DRESS in which cyclosporine can reduce the dose and duration of systemic corticosteroid use and thereby reduce its potential severe side effects.<sup>8,18</sup> Kirchoff *et al.* reported the use of cyclosporine in two patients with DRESS. The first patient was given oral cyclosporin 100 mg twice daily for 1 week and the second patient was given 5 mg/kgbw/day divided into two doses for 3 days. Clinical improvement in the form of skin lesions and kidney function was found on seventh day of treatment in both patients.<sup>19</sup>

Cyclosporine as a steroid sparing agent in recalcitrant and relapse DRESS had been reported in several clinical studies.<sup>8</sup> Zuliani *et al.*

reported the use of oral cyclosporine 200 mg daily for 5 days in recalcitrant DRESS patients after administration of intravenous methylprednisolone injection for 3 weeks and improved skin lesions and kidney function were seen after administration of cyclosporine.<sup>20</sup> Cyclosporine at a lower dose of 1-3 mg/kgbw/day was reported by Su *et al.* The reason for using a lower dose was because the patient had been given long-term systemic corticosteroids previously and cyclosporine was used together with systemic corticosteroids and the duration of cyclosporine therapy was 7-10 days.<sup>8</sup> The patient in this case was given oral cyclosporine 100 mg twice daily for 7 days and intravenous injection of methylprednisolone 93.75 mg/24 hours IV. Clinical and laboratory improvement was obtained on the seventh day of treatment.

## Conclusion

Cyclosporine as an adjuvant therapy for recalcitrant treatment of DRESS showed good improvement. It can be considered in cases where systemic corticosteroids are contraindicated, inadequate response to conventional therapy or long-term use of corticosteroids. The use of cyclosporine 100 mg twice daily for one week can lower the dose of systemic corticosteroid, furthermore can decrease the potential adverse events. In this case, patient was given cyclosporine 100 mg twice daily for 7 days orally and methylprednisolone 93.75 mg/24 hours IV. Clinical and laboratory improvement was found at the seventh day after the treatment.

## References

1. Kardaun SH, Sekula P, Valeyrie-Allanore L. 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.
2. Cho YT, Yang CW, Chu CY. Drug reaction with eosinophilia and systemic symptoms (DRESS): An interplay among drugs, viruses and immune system. *Int J Mol Sci.* 2017;**18**(6):1-12.
  3. Hiransuthikul A, Rattananupong T, Klaewsongkram J, Rerknimitr P, Pongpruthiphan M, Ruxrungtham K. Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS): 11 years retrospective study in Thailand. *Allergol Int.* 2016;**65**(4):1-7.
  4. Eatemadi A, Arzaghi MR, Matroushi F Al, Baluki T Al, Mohammadi I, Eatemadi R. Antibiotic associated DRESS syndrome: Maleficent DRESS? *Int J Innov Sci Res Rev.* 2021;**3**(2):840-3.
  5. Chatterjee J, Rai N, Sar SK. Determination of cefadroxil antibiotic by an analytical method. *Selected from International Conference on Recent Trends in Applied Sciences with Engineering Applications.* 2013;**11**(1):28-31.
  6. Lin YF, Yang CH, Sindy H. Severe cutaneous adverse reactions related to systemic antibiotics. *Clin Infect Dis.* 2014; **58**(10):1377-85.
  7. Ackermann G, Hartmann M, Scherer K. Evaluation of cyclosporin for the treatment of DRESS syndrome. *JAMA Dermatology.* 2020;**156**(6):704-6.
  8. Su HJ, Chen CB, Yeh TY, Chung WH. Successful treatment of corticosteroid-dependent drug reaction with eosinophilia and systemic symptoms with cyclosporine. *Ann Allergy, Asthma Immunol.* 2021; **127**(6):1-8.
  9. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part I. Clinical perspectives. *J Am Acad Dermatol.* 2013;**68**(5):1-14.
  10. Wang L, Mei XL. Drug reaction with eosinophilia and systemic symptoms: Retrospective analysis of 104 cases over one decade. *Chin Med J (Engl).* 2017;**130**(8):944-9.
  11. Paulmann M, Mockenhaupt M. Severe skin reactions: Clinical picture, epidemiology, etiology, pathogenesis and treatment. *Allergo J Int.* 2019;**28**(8):1-16.
  12. Farhat L, Vastardi M. Dress syndrome demystified using patch testing. *Ann Allergy, Asthma Immunol.* 2019;**123**(5):77.
  13. Mian S, Bilal H, Bernshteyn, Perl A. A rare case of cefadroxil induced DRESS syndrome leading to severe acute liver failure necessitating liver transplantation evaluation. *Am J Gastroenterol.* 2020; **115**(6):73.
  14. Alkhatib A, Nader CM. A unique presentation of DRESS. *Case Rep Immunodeficient Allergy.* 2016;**1**(4):1-3.
  15. Wicaksono RB, Djatmiko W, Putranti IO. Drug-induced hypersensitivity syndrome in a breast cancer patient: A case report. *Sci Technol Publ.* 2021;**21**(2):241-4.
  16. Groot AC. Patch testing in drug reaction with eosinophilia and systemic symptoms (DRESS): A literature review. *Contact Dermatitis.* 2022;**12**(10):1-37.
  17. Tedesco D, Haragsim L. Cyclosporine: A review. *J Transplant.* 2012;**1**(2):1-7.
  18. Kuschel SL, Reedy MS. Cyclosporine treatment of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: A case report and brief review of the literature. *Pract Dermatology.* 2018; **1**(8):41-3.
  19. Kirchhof MG, Wong A, Dutz JP. Cyclosporine treatment of drug-induced hypersensitivity syndrome. *JAMA Dermatology.* 2016;**152**(11):1-4.
  20. Zuliani E, Zwahlen H, Gilliet F, Marone C. Vancomycin-induced hypersensitivity reaction with acute renal failure: Resolution following cyclosporine treatment. *Clin Nephrol.* 2005;**64**(2):155-8.