HK J Paediatr (new series) 2016;**21**:102-104

Case Reports

Drug Rash with Eosinophilia and Systemic Symptoms Syndrome Induced by Cefazolin and Gentamicin in a Child

K ***Yilmaz***, Z ***Gunduz***, F ***Tahan***, HH ***Akar***

Abstract Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, is an uncommon, acute and severe life-threatening systemic disease. DRESS syndrome is characterised by fever, skin rash, lymph node enlargement, and internal organ involvement. The most common culprit drugs are anticonvulsants and allopurinol. We first reported a case of DRESS syndrome induced by cefazolin and gentamicin in a child. We aimed to emphasize the severity of renal damage and the dramatic response to short term intravenous and oral steroid therapy.

Key words DRESS syndrome; Drug hypersensitivity; Eosinophilia; Interstitial nephritis

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, also known as drug-induced hypersensitivity syndrome, is characterised by fever, cutaneous eruption, systemic findings including haematologic abnormalities, interstitial nephritis, pneumonitis, myocarditis, and life threatening fulminant hepatitis.[1] DRESS syndrome could be differentiated from Stevens-Johnson syndrome and toxic epidermal necrolysis in terms of the dermis involvement. The most common culprit drugs are carbamazepine, sulfonamides, and allopurinol.[2] Here, we report the first case of DRESS syndrome that resulted in severe interstitial nephritis, secondary to usage of cefazolin and gentamicin in the literature.

Department of Pediatric Nephrology, Erciyes University, Kayseri, Turkey

K **Yilmaz** *MD*
Z **Gunduz** *MD(Prof)*

Department of Pediatric Allergy, Erciyes University, Kayseri, Turkey

F **Tahan** *MD(Prof)*
HH **Akar** *MD*

Correspondence to: Dr K **Yilmaz**

Received June 4, 2015

Case Report

A previously healthy 12-year-old child developed fever and swelling in the left knee after trauma. He was given cefazolin and gentamicin for suspected septic arthritis because of the increased leukocyte count in synovial fluid without bacterial growth. A couple of days later, his fever disappeared. He returned to normal activity two weeks after treatment was initiated. Blood urea nitrogen and creatinine at 18th day of admission were normal. However, 21 days later, his fever recurred (of 39.4°C) and he developed a maculopapular rash characterised by widespread erythematous eruption with mild exfoliation and facial oedema. Then, hepatomegaly, elevated liver enzymes and increased blood urea nitrogen and creatinine was found on the visit. He had no mucous membrane involvement. Laboratory findings at 23rd day of admission were as follows: Hb 11.8 g/dL (11.5-16 g/dL), leukocyte count 13700/μL (normal, 4800-10800/μL), eosinophilia 5.1% (normal, 0-2.9%) platelet count 136000/μL (normal, 150000-450000/μL), Blood urea nitrogen 90 mg/dL (normal, 8-26 mg/dL), creatinine 6.2 mg/dL (normal, 0.5-0.8 mg/dL), AST 146 IU/L (0-40 IU/L), ALT 102 IU/L

(0-50 IU/L), sodium 130 mmol/L (normal, 136-145 mmol/L), potassium 4.4 mmol/L (normal, 3.5-5.5 mmol/L), uric acid 8.7 mg/dL (normal, 3.5-7.2 mg/dL). He was referred to department of allergy with suspicious DRESS syndrome and it was diagnosed based on the following findings; fever and rash, hepatosplenomegaly, hepatic and renal failure and haematologic abnormalities (leukocytosis, eosinophilia, thrombocytopenia). On hospital day 24, drug-induced DRESS was suspected, therefore cefazolin and gentamicin therapy were stopped. His renal failure needed to be created by haemodialysis two times using a temporary haemodialysis catheter. Serological tests for Epstein-Barr virus, parvovirus, cytomegalovirus, hepatitis A, B, C were negative. Antinuclear antibody and rheumatoid factor were also negative. His echocardiogram and chest X-ray were unremarkable for major organ involvement. Because of the unclear origin of the persisting renal failure, a percutaneous renal biopsy was performed. Histological examination revealed interstitial nephritis with a dense peritubular infiltrate of lymphocytes, monocytes and granulocytes (Figure 1). Light microscopy showed no glomerular lesions and immunofluorescence staining was negative. Therefore, he was given pulse methylprednisolone therapy (30 mg/kg per day for 3 days) and oral prednisolone (1 mg/kg per day) with gradual tapering. His clinical and laboratory findings returned to normal. Blood urea nitrogen and creatinine at 42nd day of admission were normal. The patient was advised to definitely avoid cephalosporins and gentamicin. More than 7 months after the event he remains healthy with normal creatinine and without proteinuria.

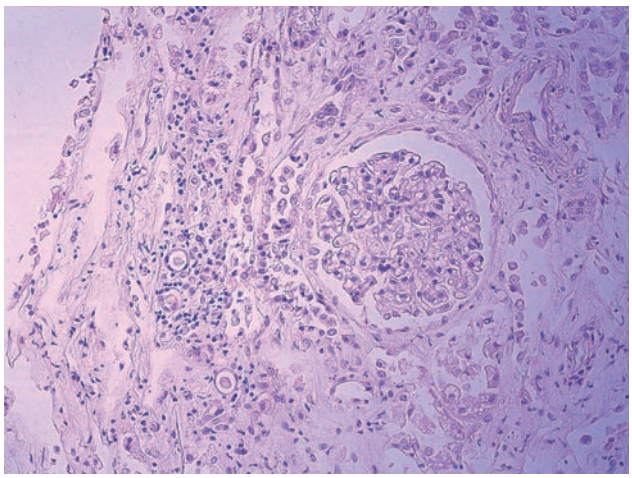

Figure 1 Renal biopsy: Consistent with tubulointerstitial nephritis.

Discussion

DRESS syndrome is a very rare, potentially life-threatening, drug-induced hypersensitivity reaction with cutaneous manifestations and internal organ involvement that occurs in both adults and children.[3] Currently, there is no standard criterion for establishing the diagnosis of DRESS syndrome. However, recently, two different scoring systems based on diagnostic criteria have been developed by the European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) and the Japanese Research Committee on Severe Cutaneous Adverse Reaction (J-SCAR) (Table 1).[2] Our patient's documented findings at the time of diagnosis were fever, facial oedema, generalised erythematous rash, pruritus, leukocytosis, eosinophilia, thrombocytopenia, hepatosplenomegaly, renal failure, interstitial nephritis, and

Table 1 Diagnostic criteria for drug reaction with eosinophilia and systemic symptoms syndrome[2]

RegiSCAR	J-SCAR
Skin rash	Maculopapular rash developing >3 weeks after starting culprit drug
Reaction suspected to be drug-related	Prolonged clinical symptoms after discontinuation of the causative drug
Hospitalisation	Fever >38°C
Blood count abnormalities	Leukocyte abnormalities (≥1)
Lymphocytosis or lymphopenia	Leukocytosis (>11 x 10^9/L)
Eosinophilia	Atypical lymphocytes (>5%)
Thrombocytopenia	Eosinophilia (>1.5 x 10^9/L)
Enlarged lymph nodes involving ≥2 sites	Lymphadenopathy
Involvement of ≥1 internal organ	HHV-6 reactivation Liver abnormalities (ALT >100 U/L) or other organ involvement

hepatitis. These findings are typically seen in this syndrome.

The pathogenesis is not fully understood and may be multifactorial, involving immunological mechanisms, particular drug detoxification pathways and reactivation of human herpes, including cytomegalovirus, Epstein-Barr virus and human herpesvirus-6 and -7.[3,4]

Several drugs may cause DRESS syndrome, including aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital), vancomycin, sulfasalazine, lamotrigine, allopurinol, isoniazid, minocycline, ranitidine, and celecoxib.[4] To the best of our knowledge, this is the first case of DRESS syndrome induced by combination of cefazolin and gentamicin in childhood. Patients with DRESS are induced by a single drug, but some cases of DRESS are known to be at risk for multiple drug hypersensitivity.[5] Typically, DRESS syndrome begins within 8 weeks of ingestion of the culprit drug, usually 2 to 6 weeks after its first use.[6] In our patient, at 3 weeks after the administration of cefazolin and gentamicin, DRESS syndrome developed with typical findings and, cefazolin and gentamicin therapy was stopped. Nevertheless, patient's clinical and laboratory findings continued to deteriorate with progressive involvement of the other organs. Therefore, renal biopsy was done and histopathological findings were compatible with interstitial nephritis.

The kidney is frequently affected in DRESS syndrome, with 11% of patients presenting renal disease. Clinical symptoms are generally absent, however microscopic haematuria and proteinuria can be found on admission in these patients.[2] In the most of the cases, there is only mild renal impairment. However, severe interstitial nephritis may develop and progress to severe renal failure. Haemodialysis is rarely needed for treatment of kidney failure like our case.[7]

The use of systemic corticosteroids accompanied with discontinuation of the suspicious medicine for the treatment of DRESS syndrome with organ involvement, especially in patients with renal and/or pulmonary involvement is suggested as a treatment option.[8]

The use of cyclosporine, cyclophosphamide and intravenous immunoglobulin to treat DRESS is currently anecdotal and controversial, and its mechanism of action is unknown.[9]

Conclusion

We report the first case of DRESS syndrome associated with cefazolin and gentamicin in children. We aimed to emphasize the severity of renal damage and the dramatic response to short term intravenous and oral steroid.

Acknowledgement

Patient and the parents have given informed consent.

Conflict of interest

We declare that we have no conflict of interests.

References

1. Eshki M, Allanore L, Musette P, et al. Twelve-year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms: a cause of unpredictable multiorgan failure. Arch Dermatol 2009;145:67-72.
2. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part I. Clinical perspectives. J Am Acad Dermatol 2013;68:693.
3. Newell BD, Moinfar M, Mancini AJ, Nopper AJ. Retrospective analysis of 32 pediatric patients with anticonvulsant hypersensitivity syndrome (ACHSS). Pediatr Dermatol 2009;26: 536-46.
4. Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. Am J Med 2011;124:588-97.
5. Daubner B, Groux-Keller M, Hausmann OV, et al. Multiple drug hypersensitivity: normal Treg cell function but enhanced in vivo activation of drug-specific T cells. Allergy 2012;67:58-66.
6. Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol 2010;146:1373-9.
7. Ang CC, Wang YS, Yoosuff EL, Tay YK. Retrospective analysis of drug-induced hypersensitivity syndrome: a study of 27 patients. J Am Acad Dermatol 2010;63:219-27.
8. Walsh SA, Creamer D. Drug reaction with eosinophilia and systemic symptoms (DRESS): a clinical update and review of current thinking. Clin Exp Dermatol 2011;36:6-11.
9. Lee JH, Park HK, Heo J, et al. Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome induced by celecoxib and anti-tuberculosis drugs. J Korean Med Sci 2008;23:521-5.