Journal of Research in Pharmacy Practice

Case Report

Drug reaction with eosinophilia and systemic symptoms syndrome associated with Nitrofurantoin

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Received: September 2015
Accepted: November 2015

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ABSTRACT

Drug reaction with eosinophilia and systemic symptom (DRESS) is a severe adverse drug-induced reaction with a prolonged latency period which is characterized by a variety of clinical manifestations, usually fever, rash, lymphadenopathy, eosinophilia, and a wide range of mild-to-severe systemic presentations. Drugs are an important cause of DRESS in most of the cases. It is challenging to diagnose DRESS because of the diversity of cutaneous eruption and visceral organs involvement. We hereby report a 34-year-old female who developed DRESS syndrome following ingestion of nitrofurantoin for the treatment of urinary tract infection. She was managed conservatively and recovered after few weeks. Our aim of this study is to raise awareness to suspect DRESS syndrome in patients who present with unusual clinical features with skin involvement after initiating any drug.

Keywords: Drug reaction; drug reaction with eosinophilia and systemic symptom syndrome; eosinophilia; Nitrofurantoin

INTRODUCTION

Nitrofurantoin is an antibacterial drug which was available in the 1950s.[1] It is frequently used in the treatment of urinary tract infections (UTIs). It is generally well-tolerated with common side effects including nausea and headache. The rare side effects are aplastic anemia, peripheral neuropathy, liver toxicity, pulmonary toxicity, and Stevens–Johnson syndrome (SJS).[2] Drug reaction with eosinophilia and systemic symptom (DRESS) due to nitrofurantoin may be life-threatening which is reported very rarely.[2,3]

CASE REPORT

A 34-year-old female patient was presented to our medicine emergency with acute skin rashes all over body for 4 days, fever for 3 days, and decreased urine output for 2 days, followed by dizziness. On detailed history, we found that she was on nitrofurantoin 100 mg thrice a day for UTI for 6 days, prescribed by a general physician. Her clinical status was worsening daily even though she continued nitrofurantoin. She was a known case of type II diabetes mellitus, and blood sugar was controlled with drugs. She had no history of asthma and similar episode in the past.

Physical examination revealed bilateral cheilitis [Figure 1] and pruriginous maculopapular eruptions with desquamation spread all over the body, predominantly over extremities [Figure 2a and b]. Vital signs were as temperature 102°F (febrile), pulse rate 102/min (tachycardia), respiratory rate 20/min (tachypnea), blood pressure 86/64 mmHg (hypotension), and SpO_2 87%. The chest auscultation revealed bilateral crepitations. Abdominal palpation did not found organomegaly. Investigations are summarized in

Access this article online

Website: www.jrpp.net

DOI: 10.4103/2279-042X.176560

How to cite this article: Singh J, Dinkar A, Atam V, Gupta KK, Sahani KK. Drug reaction with eosinophilia and systemic symptoms syndrome associated with Nitrofurantoin. J Res Pharm Pract 2016;5:70-3.

Table 1. Arterial blood gas analysis showed metabolic acidosis. Chest X-ray posterior-anterior view showed bilateral infiltrates. Urine analysis was normal. Serology of hepatitis A virus, hepatitis B surface antigen, and hepatitis C antibody were negative. Cultures of urine and blood were sterile. Result for antinuclear antibody was negative.

The aforementioned case was in accordance with a clinical condition as DRESS syndrome associated with nitrofurantoin therapy involving the skin, kidneys, lungs, and hematological abnormalities. Severe skin reaction with systemic symptoms may be challenging to diagnose by clinicians because of clinically close differential diagnosis of toxic epidermal necrolysis and SJS. Dermatology opinion was taken, and the case was managed on the line of DRESS syndrome.

Once the diagnosis was established with the help of clinical features and investigations, nitrofurantoin was stopped immediately. She was treated with intravenous corticosteroid and antihistamine. Broad-spectrum antibiotics were also administered for a possible sepsis. Blood pressure increased to normal on intravenous fluids. Supportive therapy for the management of the skin and temperature were done during hospitalization. Vitals were monitored closely. Urine production increased on the same day and was in adequate amount the next day. Renal and liver functions and hematological abnormalities normalized subsequently. Skin lesions subsided the following days. She made an uneventful recovery, and no sequelae were found during subsequent follow-up for 2 months.

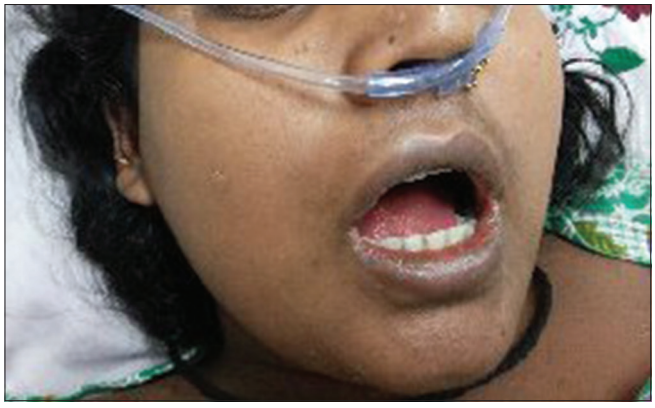

Figure 1: Cheilitis over both angles of mouth

DISCUSSION

In 1950, Chaiken described DRESS syndrome first, and he called it the drug-induced hypersensitivity syndrome. It has an incidence of 1 in 1000–10,000 exposures to drug and death rate of about 10%.[4] In 1996, Bocquet introduced first the acronym "drug rash with eosinophilia and systemic symptoms"

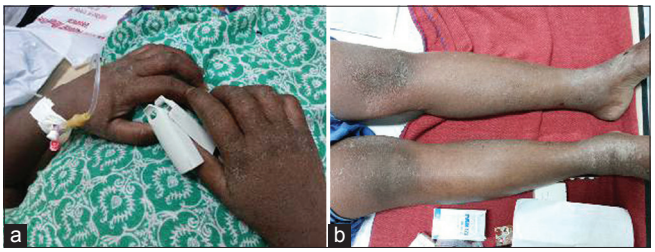

Figure 2: (a and b) Maculopapular eruptions with desquamation seen on bilateral hands and lower limbs

Table 1: Laboratory parameters of patient

Laboratory parameters	During hospitalization				On follow-up	
	1st day	3rd day	8th day	2nd week	1st month	2nd month
Hb (g/dl)	13.2	12.8	12.8	13.0	13.6	14.2
TLC ($10^3/\mu L$)	16.4	14.0	12.2	10.4	9.8	8.8
DLC (%)	N55L13E21	N58L13E22	N62L16E14	N60L18E12	N57L20E10	N60L18E5
PC ($10^3/\mu L$)	98.0	96.0	122	138	154	218
Serum Na^+ (mmol/L)	134	145	135	148	136	-
Serum K^+ (mmol/L)	5.3	4.8	4.6	4.6	4.2	-
Serum urea (mg/dl)	102.4	88	86	56	50	33
Serum creatinine (mg/dl)	2.4	2.1	1.8	1.0	1.1	0.86
RBS (mg/dl)	110	98	118	102	98	104
ALT (IU/L)	218.0	190.0	160.0	56	78	56
AST (IU/L)	190.0	188.0	148.0	54	62	64
Serum ALP	140.0	154.0	128.0	112	110	102
Serum protein (g/dl)	7.0	-	7.1	-	6.8	7.4
Serum albumin (g/dl)	4.2	-	4.0	-	3.8	4.0
Serum amylase (U/L)	124	100	88	-	-	-
Serum lipase (U/L)	104	92	72	-	-	-

N=Neutrophil, E=Eosinophil, ALT=Alanine transaminase, ANA=Antinuclear antibody, AST=Aspartate transaminase, ALP=Alkaline phosphatase, RBS=Random blood sugar, TLC=Total leukocyte count, DLC=Differential leukocyte count, PC=Platelet counts

to describe patients exhibiting a drug-induced condition characterized by an extensive rash, fever, lymphadenopathy, hematological abnormalities, hepatitis, and involvement of the kidneys, lungs, heart, or pancreas.[5] It may appear in an acute fashion or with a delayed onset (2–6 weeks after drug administration.[2] The cutaneous manifestations in DRESS are urticaria, maculopapular eruption; however, in some instances, vesicles, bullae, pustules, purpura, target lesions, facial edema, cheilitis, and erythroderma may be there.[6] Lesions may later become exfoliated. Desquamation/scaling may occur with healing.[7] While, visceral involvement are as hepatitis, pneumonitis, myocarditis, pericarditis, nephritis, and colitis which remains the major cause of morbidity and mortality in this syndrome. Hematological manifestations may be leukocytosis with eosinophilia (90%) and/or mononucleosis (40%).[6] Literature has showed has that the severity of organ dysfunction does not always correlate with the extent of skin involvement.[7]

All kinds of drugs can be involved. This syndrome is most frequently seen in association with anticonvulsants and antibiotic agents. A number of drugs including anticonvulsants-carbamazepine (phenytoin, lamotrigine, zonisamide, and phenobarbital), antibiotic agents (sulfonamides, minocycline, and cefadroxil), anti-inflammatory agents (salazosulfapyridine and sulfasalazine), antiretroviral drugs (nevirapine and abacavir), and others–fluoxetine, calcium channel blockers, imatinib, nonsteroidal anti-inflammatory drugs, allopurinol, mexiletine, hydroxychloroquine, esomeprazole, efalizumab, ranitidine, sorbinil, gold salt, zalcitabine, thalidomide, and dapsone.[3]

The diagnostic criteria are based on clinical and laboratory findings as mentioned [Table 2].[6] DRESS syndrome can be diagnosed if all three of following criteria are present. These are (1) cutaneous eruption; (2) absolute eosinophilia (≥1500/μl) with or without atypical lymphocytes; and (3) systemic involvement (lymphadenopathy ≥2 cm, aspartate aminotransferase ≥2 × upper limit, interstitial nephritis, interstitial pneumonitis, or carditis).[3] The skin biopsy may support diagnosis though nonspecific. The skin biopsy findings may be lymphocytic infiltrate with or without eosinophils in the papillary layer of the dermis.[7]

The pathogenesis of DRESS syndrome is not well clear and is hypothesized to consist of a complex interaction of the following which includes detoxification defects leading to reactive metabolite formation and subsequent immunological reactions slow acetylation, and reactivation of human herpes including Epstein–Barr virus and human herpesvirus-6 and -7. Other types of viral infection were also reported such as cytomegalovirus reactivation and paramyxovirus infection. It is increasingly apparent that there is a genetic predisposition to adverse drug reactions. It is hoped that further research may define pharmacogenetic disease susceptibility markers to identify people at high risk of developing HSS/DRESS.[5] The DRESS syndrome is treated with corticosteroids in a most of the cases. Corticosteroids inhibit eosinophilic accumulation. It is thought that organ involvement is due to eosinophilic accumulation which acts probably by inhibition of interleukin 5. Unfortunately, use of corticosteroids in the management of DRESS is not well-supported by strong evidence-based data.[8] Our case fulfilled the diagnostic criteria of DRESS syndrome with dermatology opinion. To our best knowledge, there are only few cases of nitrofurantoin-induced DRESS syndrome and no report from India.[2,3]

Many drugs have been reported causing DRESS syndrome in India; at present, nitrofurantoin has also included in this category. Early diagnosis with appropriate management improves prognosis. Therefore, the patient must be counseled for an adverse reaction before starting any drug.

Table 2: Diagnostic criteria of DRESS syndrome

Criteria	Inclusion criteria for potential case of HSS/DRESS in RegiSCAR	Japanese group's criteria
1	Hospitalization	Maculopapular rash developing >3 weeks after starting with the suspected drug
2	Reaction suspected to be drug-related	Prolonged clinical symptoms 2 weeks after discontinuation of the suspected drug
3	*Acute skin rash	Fever >38°C
4	*Fever >38°C	Liver abnormalities (alanine aminotransferase >100 U/L)
5	*Enlarged lymph nodes at a minimum of 2 sites	Leukocyte abnormalities
6	*Involvement of at least 1 internal organ	Leukocytosis (>11×10^9/L)
7	*Blood count abnormalities	Atypical lymphocytosis (>5%)
8	Lymphocytes above or below Normal limits	Eosinophilia (>1.5×10^9/L)
9	Eosinophils above the laboratory limits	Lymphadenopathy
10	Platelets below the laboratory limits	Human herpes 6 reactivation
Diagnosis	Diagnosis *Three or more asterisked (*) criteria	Presence of the 7 criteria (typical DHS)

SCAR=Severe cutaneous adverse reactions, DHS=Drug hypersensitivity syndrome, DRESS=Drug reaction with eosinophilia and systemic symptom

AUTHORS' CONTRIBUTION

This manuscript is designed, studied, prepared and reviewed by all contributors.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Gupta K, Trautner BW. Urinary tract infection, pyelonephriti, and prostitis. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, *et al*. editors. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw Hill; 2012. p. 2387-95.
2. Leão RN, Barreto P, Leão RR, Ribeiro JV. Nitrofurantoin: Cause of DRESS syndrome. BMJ Case Rep 2013;2013. pii: Bcr2013008991.
3. Velema MS, Voerman HJ. DRESS syndrome caused by nitrofurantoin. Neth J Med 2009;67:147-9.
4. E L omairi N, Abourazzak S, Chaouki S, Atmani S, Hida M. Drug reaction with eosinophilia and systemic symptom (DRESS) induced by carbamazepine: A case report and literature review. Pan Afr Med J 2014;18:9.
5. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug rash with eosinophilia and systemic symptoms: DRESS). Semin Cutan Med Surg 1996;15:250-7.
6. Choudhary S, McLeod M, Torchia D, Romanelli P. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. J Clin Aesthet Dermatol 2013;6:31-7.
7. Agu CC, Basheer H. DRESS syndrome associated with allopurinol. Int J Case Rep Images 2014;5:145-9.
8. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994;331:1272-85.