Netherlands
The Journal of Medicine

CASE REPORT

DRESS syndrome caused by nitrofurantoin

M.S. Velema, H.J. Voerman*

Department of Internal Medicine, Amstelland Hospital, Amstelveen, the Netherlands,
*corresponding author: tel.: +31 (0)20-247 47 47, fax: +31 (0)20-347 49 10, e-mail: bevo@zha.nl

ABSTRACT

Systemic side effects of nitrofurantoin are rare but can be life-threatening. Serious side effects are pulmonary involvement and Stevens-Johnson syndrome. We report a case of a patient developing circulatory and renal failure together with eosinophilia and a rash. This syndrome of drug rash, eosinophilia and systemic symptoms is called DRESS syndrome.

KEYWORDS

DRESS syndrome, nitrofurantoin, erythema multiforme, eosinophilia

INTRODUCTION

Nitrofurantoin is an antibiotic often prescribed for urinary tract infections. Side effects are usually mild, but may also be life-threatening. Pulmonary involvement and Stevens-Johnson syndrome are well known. We describe a patient who developed circulatory and renal failure together with eosinophilia and a rash. This is called DRESS syndrome (drug rash, eosinophilia and systemic symptoms). An overview of this syndrome is presented, together with the associated drugs.

CASE REPORT

A 77-year-old woman was admitted to our emergency room because a one-day history of confusion. Besides Meniere's disease and previous pyelonephritis she had no medical history of note. She experienced some pain in her upper abdomen and felt very weak. Anuria had been present for more than 12 hours. Four days earlier her general practitioner prescribed her nitrofurantoin for a urinary tract infection. She had also been taking betahistine for many years. Two days later she developed a rash, nevertheless she continued using this antibiotic.

On physical examination she was tachypnoeic and febrile (38°C). Blood pressure was 109/63 mmHg. The abdomen was tender. The skin showed red macules with target-shaped lesions on chest, back and extremities, including soles of her feet and palms of her hands.
Blood tests showed leucocytosis (31.4 x 10^9/l) partly based on an elevated eosinophil count (11.3 x 10^9/l), furthermore the level of creatinine was elevated (131 µmol/l). Alkaline phosphatase, gamma glutamyl transpeptidase, alanine aminotransferase and lactate dehydrogenase were slightly elevated. The arterial blood gas analysis showed a respiratory alkalosis due to hyperventilation (*table 1*). The urine showed some leucocytes, bacteria and granular casts. Electrocardiogram showed atrial fibrillation with a ventricular response of 181/min. Digoxin and metoprolol were administered. Blood pressure decreased to 85/50 mmHg. She was admitted to the intensive care unit.

Table 1. *Laboratory data at time of admission*

Haematology			**Chemistry**		
ESR	6	mm/hour	Sodium	132	mmol/l
Haemoglobin	9.7	mmol/l	Potassium	3.9	mmol/l
Thrombocytes	163	x 10^9/l	Creatinine	131	µmol/l
Leucocytes	31.4	x 10^9/l	Urea	15.6	mmol/l
Neutrophils	16.6	x 10^9/l	CRP	101	µmol/l
Eosinophils	11.3	x 10^9/l			
Liver enzymes			**Blood gas analysis (with 4 litres oxygen)**		
Bilirubin	13	µmol/l	PH	7.52	
ALP	177	IU/l	PCO_2	24	mmHg
γGT	42	IU/l	pO_2	139	mmHg
ASAT	27	IU/l	HCO_3^-	19.5	mmol/l
ALAT	67	IU/l	BE	-1.5	mmol/l
LDH	315	IU/l	sO_2	99	%

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; AP = alkaline phosphatase; γGT = gamma glutamyl transferase; ASAT = asparate aminotransferase; ALAT = alanine aminotransferase; LDH = lactate dehydrogenase.

Broad-spectrum antibiotics for a possible sepsis and norepinephrine were started. In addition corticosteroids were administered in a high dosage for the diagnosis of erythema multiforme. Urine production increased and the maximum creatinine concentration was 199 µmol/l. The eosinophil count increased to a maximum of 23.2 x 10^9/l after eight days. Bone marrow biopsy showed a high eosinophil count and normal haematopoiesis without signs of malignancy. Renal function normalised and the skin lesions disappeared in the following days. Cultures of urine, blood and faeces remained negative. One week after admission a pacemaker was implanted for a sick sinus syndrome. Creatinine concentration returned to normal level (54 µmol/l). She made an uneventful recovery and was discharged after 12 days.

DISCUSSION

To our knowledge this is the first reported case of DRESS syndrome caused by nitrofurantoin. DRESS syndrome, previously called hypersensitivity syndrome, describes a collection of symptoms and signs occurring at the severe end of a spectrum of drug hypersensitivity reactions.[1,2] Symptoms occur within eight weeks after starting the drug, usually after more than one week.[3] Various diagnostic criteria have been suggested. The criteria most often used are: (1) cutaneous eruption; (2) absolute eosinophilia (≥1500/µl) with or without atypical lymphocytes; and (3) systemic involvement (lymphadenopathy ≥2 cm, *aspartate* aminotransferase ≥2x upper limit, interstitial nephritis, interstitial pneumonitis, or carditis). Diagnosis can be made if all three of the criteria are present. Skin biopsy is widely used to confirm the diagnosis but is non specific.[4]

DRESS syndrome has recently been classified under a delayed type IV b hypersensitivity reaction with T helper type II cells playing a significant role. Furthermore there are some studies suggesting that viral infections, especially reactivation of human herpes virus type 6, commonly occur. Whether this plays a causal role or represents a consequence of DRESS syndrome is not clear.[5,6] Eosinophil accumulation is thought to account for internal organ involvement.[1]

All kinds of drugs can be involved. The syndrome is most frequently seen in association with anticonvulsants and antibiotic agents. An overview is shown in *table 2*.

Other diagnoses for skin abnormalities after drug use include Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), pustular drug eruptions and erythematous drug eruptions in general. The causative drugs for SJS/TEN are for the greater part similar to those of DRESS syndrome. SJS has also been reported after taking nitrofurantoin.[7] One of the most frequently seen pustular drug eruptions is generalised exanthematous pustulosis, which is caused by β-lactam antibiotics and usually occurs within a few days in contrast to DRESS syndrome. Also erythematous drug eruptions tend to present within days.

It can be difficult to differentiate between the above-mentioned diagnoses. Important is that patients with SJS/TEN always develop bullae (SJS <10% and TEN >30% of body surface area). In most patients with SJS/TEN the mucosa of mouth, genitalia and/or conjunctivae are involved in contrast to those with erythema multiforme, which presents with target lesions. In TEN internal epithelial surfaces (lung, gastrointestinal tract) may also be affected and multiorgan failure can occur as in DRESS syndrome. The most important laboratory finding to differentiate DRESS syndrome from other diagnoses is eosinophilia. Mortality in DRESS syndrome is 10%, with hepatic involvement being a bad prognostic factor.[8] Earlier discontinuation of the causative drug improves the prognosis.[9] Determinants of number and severity of organ involvement is unclear; however, genetic factors may be important.[10] This has led to the suggestion of avoiding the same drugs for first-degree family members.[11]

Once the diagnosis is made, corticosteroids are prescribed in a majority of patients. Corticosteroids might inhibit eosinophilic accumulation, which is thought to account for organ involvement, probably by inhibiting the effect of interleukin 5.[1] No randomised controlled trials of corticosteroids in the treatment of DRESS syndrome are available.[12]

It is remarkable that our patient's symptoms started within three days after taking nitrofurantoin. However, eosinophil count reached its maximum after ten days.

Table 2. *DRESS-associated drugs*[13-23]

Anticonvulsants	**Others**
Carbamazepine	Fluoxetine
Phenytoin	Calcium channel blockers
Lamotrigine	Imedeen
Zonisamide	NSAIDs
Phenobarbital	Allopurinol
Antibiotic agents	Mexiletine
Sulphonamides	Efalizumab
Minocycline	Hydroxychloroquine
Cefadroxil	Esomeprazole
Anti-inflammatory agents	Sorbinil
Salazosulfapyridine	Gold salt
Sulfasalazine	Ranitidine
Antiretroviral drugs	Thalidomide
Nevirapine	Dapsone
Abacavir	Zalcitabine

CONCLUSION

DRESS syndrome should always be considered in case of high eosinophil count *and* skin eruption. Multiple organs can be affected causing a wide range of symptoms.

REFERENCES

1. Tas T, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS Syndrome): An update. Dermatology. 2003;206:353-6.
2. Lerch M, Pichler WJ. The immunological and clinical spectrum of delayed drug-induced exanthems. Curr Opin Allergy Clin Immunol. 2004;4:411-9.
3. Tas S, Simonart T. Drug rash with eosinophilia and systemic symptoms (DRESS syndrome). Acta Clin Belg. 1999;54:197-200.
4. Roujeau JC. Treatment of severe drug eruptions. J Dermatol. 1992;26:718-22.
5. Kim JW, Kim JS, Kim KJ. A clinical observation of drug hypersensitivity syndrome and serological and molecular genetic analyses of human herpesvirus-6 reactivation. Korean J Dermatol. 2005;43:143-5.
6. Shiohara T, Lijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. Br J Dermatol. 2007;156:1083-4.
7. Chan HL, Stern RS, Arndt KA, Langlois J, Jick SS, Jick H, Walker AM. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population based study with particular reference to reactions caused by drugs among outpatients. Arch Dermatol. 1990;126:43-7.
8. Ghislain PD, Roujeau JC. Treatment of severe drug reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity syndrome. Dermatol Online J. 2002;8:5.
9. Garcia-Doval I, Le Clach 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;136:323-7
10. Pirmohamed M, Kitteringham MR, Guenthner TM, Breckenridge AM, Park BK. An investigation of the formation of cytotoxic, protein-reactive and stable metabolites from carbamazepine in vitro. Bioch Pharmacol. 1992;43:1675-82
11. Rzaby B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. Lancet. 1999;353:2190-4.
12. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med. 1994;331:1272-85.
13. Peyrière H, Dereure O, Breton H, Demoly P, Cociglio M, Blayac JP, Hillaire-Buys. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2006;155:422-8.
14. Syn WK, Naisbitt DJ, Holt AP, Primohamed M, Mutimer DJ. Carbamazepine-induces acute liver failure as part of the DRESS syndrome. Int J Clin Pract. 2005;50:988-1.
15. Michel F, Navellou JC, Ferraud D, Toussirot E, Wendling D. DRESS syndrome in a patient on sulfasalazine for rheumatoid arthritis. Joint Spine Bone. 2005;72:82-5.
16. Van Leeuwen JF, van der Hooft CS, os LE, Bekkenk MW, van Zuuren EJ, Stricker BH. Geneesmiddelenexantheem met eosinofilie en systemische symptomen (DRESS) in verband gebracht met het orale huidverzorgingssupplement Imedeem. Ned Tijdschr Geneeskd. 2005;149:1353-6.
17. White JM, Smith CH, Robson A, Ash G, Barker JN. DRESS syndrome caused by efalizumab. Clin Dermatol. 2007;33:50-2.
18. Volpe A, Marchetta A, Caramaschi P, Biasi D, Bambara LM, Arcaro G. Hydoxychloroquine-induced DRESS syndrome. Clin Rheumatol. 2008;27:537-9.
19. Caboni S, Gunera-Saas N, Ktiouet-Abassi S, Berard F, Nicolas JF. Esomeprazol-induces DRESS syndrome. Studies of crossreactivity among proton-pump inhibitor drugs. Allergy. 2007;62:1341-2.
20. Suswardana, Hernanto M, Yudani BA, Pudjiati SR, Indrastuti N. DRESS syndrome from cefadroxil confirmed by positive patch test. Allergy. 2007;62:1216-7.
21. Claudio GA, Martin AF, Dios Perrino S, Velasco AA. DRESS syndrome associated with nevirapine therapy. Arch Intern Med. 2001;16:2501-2.
22. Seishima M, Yamanaka S, Fujisawa T, Tohyama M, Hashimoto K. Reactivation of human herpesvirus (HHV) family members other than HHV-6 in drug induces hypersensitivity syndrome. Br J Dermat. 2006;155:344-9.
23. Kano Y, Hirharas K, Sakuma K, Shiohara T. Several herpesviruses can reactivate in a severe drug-induced multiorgan reaction in the same sequential order as in graft-versus-host disease. Br J Dermat. 2006;155:301-6.