CASE REPORT

Nitrofurantoin: cause of DRESS syndrome

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SUMMARY

Urinary tract infections (UTIs) are a common pathological entity among elderly patients. The widespread use of antibiotics for uncomplicated UTIs has gained many opponents mainly due to the increasing drug resistance observed. Nitrofurantoin is a commonly used antibacterial drug because it has low side effects and a good antiurinary bacterial profile. However, in this paper, we present a case of a nitrofurantoin-induced DRESS (drug reaction/rash with eosinophilia and systemic symptoms) syndrome in a 77-year-old woman. During UTI treatment, the patient developed an acute skin rash which spread all over the body and a considerable decrease in urine volume. At the emergency department, we found her developing eosinophilic pneumonia, anaemia and renal impairment that we relate to nitrofurantoin administration. To our knowledge, this is the second published case report which evokes nitrofurantoin as a possible cause of DRESS syndrome.

BACKGROUND

Nitrofurantoin is an antibacterial agent frequently used in the treatment and prevention of urinary tract infections (UTIs) being recommended by all major urological associations. Although generally well tolerated, it has a rare, but serious, side effect profile, including aplastic anaemia, peripheral neuropathy, liver toxicity, pulmonary toxicity and Stevens-Johnson syndrome (SJS). We report a case of a patient developing renal failure, eosinophilic pneumonia and anaemia together with eosinophilia and a rash. This syndrome of drug reaction with eosinophilia and systemic symptoms is called DRESS (drug reaction/rash with eosinophilia and systemic symptoms) syndrome, which is a rare and also a life-threatening condition. It is associated with adverse reactions most commonly to aromatic anticonvulsants with variable clinical presentation. It is important to recognise this entity because it is potentially severe, and withdrawal of the incriminating drug is imperative.

CASE PRESENTATION

A 77-year-old female patient was referred to our emergency room with acute rash and renal impairment. She had a previous history of type II diabetes mellitus and hypertension, both controlled with drugs.

One week before our observation, she was medicated with nitrofurantoin for a UTI. Two days after medication, her clinical status worsened. She had complaints of right lumbar pain, oliguria and acute skin rash. When questioned about drug allergies, she reported a skin rash 10 years ago during nitrofurantoin treatment.

Physical examination revealed pruriginous and erythematous macules spread all over the body associated with face and extremities oedemas. Moreover, she had no fever and low blood pressure (66/38 mm Hg).

At the third day of hospitalisation, despite total improvement in renal function, cutaneous alterations were present together with fever (38.8 °C) and dyspnoea with low-peripheral oxygen saturations. The aforementioned case is in accordance with a clinical condition as DRESS syndrome in the context of therapy with nitrofurantoin with skin, lung, renal and haematological commitment.

INVESTIGATIONS

Laboratory findings showed leucocytosis ($19.30 \times 10^9/l$), partly based on the eosinophil count ($8.5 \times 10^9/l$). In addition, the creatinine level was 1.87 mg/dl, urea was 150 mg/dl, sodium was 129 mEq/l, potassium was 5.9 mEq/l and haemoglobin was 7.9×10 g/l. Hepatic function was normal. Cultures of urine and blood were negative. Autoimmune studies (antinuclear antibodies, antineutrophil cytoplasmic antibody, complement components C3 and C4, rheumatoid factor and cryoglobulins) and viral serologies (hepatitis A virus, hepatitis B virus and hepatitis C virus) were performed to address the aetiology of the findings, but were negative.

Renal and bladder ultrasonography did not find any significant alteration.

A chest x-ray in a posteroanterior view showed bilateral pulmonary infiltrates (figure 1).

A CT of the chest revealed multiple hyperdense areas spread over both lung fields and bilateral

Figure 1 Chest x-ray in a posteroanterior view revealing bilateral pulmonary infiltrates.

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Figure 2 Chest CT: images were acquired using multislice CT (1.25 mm thickness). This section shows multiple hyperdense areas spread over both lung fields and bilateral pleural effusions.

pleural effusions likely of inflammatory origin, findings consistent with eosinophilic pneumonia (figure 2).

DIFFERENTIAL DIAGNOSIS

DRESS syndrome is clinically defined as combinations of symptoms including fever, skin rash and internal organ involvement. It could appear in an acute fashion or with a delayed onset (2–6 weeks after drug administration). Sometimes DRESS syndrome arises sooner which can be related to drug re-administration, as we described in this particular case.^{1–3}

Concerning the variability of its presentation, the diagnosis is a challenge and frequently done by exclusion. Severe skin reaction with systemic symptoms could be difficult to diagnose and clinicians should think in not only DRESS syndrome but also Toxic Epidermal Necrolysis (TEN) and SJS which always develop bullae. Moreover, we should also consider the Acute Generalised Exanthematous Pustulosis which is caused by β -lactam antibiotics and usually occurs within a few days.⁴ Furthermore, the causative drugs for SJS/TEN are nearly the same to those of DRESS syndrome and SJS has also been reported following treatment with nitrofurantoin.^{5 6} Accordingly, Bouvresse *et al*⁷ reported three cases in which these entities were overlapped.

In order to diagnose more precisely, the DRESS syndrome was created in a European registry of Severe Cutaneous Adverse Reactions (SCAR) that uses a scoring system to rank the cases of DRESS Syndrome as ‘no’, ‘possible’, ‘probable’ and ‘definite’—the RegiSCAR Scoring System (table 1).⁸

TREATMENT

Once the DRESS syndrome diagnosis is made, the discontinuation of all drugs potentially responsible for it is imperative. Early cessation of the drugs involved improves prognosis.⁹ The treatment depends on the presence of signs of severity (transaminases increased more than five times normal values, pneumonia, renal dysfunction, pancreatitis, pericarditis, myocarditis or haemophagocytosis syndrome).

Beyond cessation of nitrofurantoin, our patient was treated with prednisolone (1 mg/kg/day) and hydroxyzine (50 mg/day) with good clinical and laboratorial results.

Table 1 RegiSCAR diagnostic criteria for DRESS/DIHS

Score	–1	0	1	2	Minimum	Maximum
Fever $\geq 38.5^{\circ}\text{C}$	No/U	Yes			–1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils			$0.7\text{--}1499 \times 10^9 \text{ l}^{-1}$	$\geq 1.5 \times 10^9 \text{ l}^{-1}$		
Eosinophils, if leucocytes $< 4.0 \times 10^9 \text{ l}^{-1}$			10–19.9%	$\geq 20\%$		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					–2	2
Skin rash extent (% BSA)		No/U	$> 50\%$			
Skin rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement*					0	2
Liver		No/U	Yes			
Lung		No/U	Yes			
Kidney		No/U	Yes			
Muscle/heart		No/U	Yes			
Pancreas		No/U	Yes			
Other organs		No/U	Yes			
Resolution ≥ 15 days	No/U	Yes			–1	0
Evaluation of other potential causes						
Antinuclear antibody						
Blood culture						
Serology for HAV/HBV/HCV						
Chlamydia/mycoplasma						
If none positive and ≥ 3 of above negative			1		0	1
Total score					–4	9

*After exclusion of other explanations: 1, one organ; 2, two or more organs. Final score < 2 , no case; final score 2–3, possible case; final score 4–5, probable case; final score > 5 , definite case. Adapted from Kardaun *et al*.⁸

BSA, body surface area; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction/rash with eosinophilia and systemic symptoms; SCAR, Severe Cutaneous Adverse Reactions; U, unknown/unclassifiable.

Although there are no randomised clinical trials demonstrating its benefit, oral corticosteroids are used in these clinical cases. In severe cases, it is recommended to initiate methylprednisolone, intravenous immunoglobulin (IVIg), plasmapheresis or a combination of these therapies. In the case of significant demonstration of viraemia measured by quantitative PCR, antiviral therapy (ganciclovir, cidofovir) may be offered in combination with corticosteroids and/or IVIg.^{2 10 11}

OUTCOME AND FOLLOW-UP

After hospital discharge, it is recommended to follow the patient for at least 3 months due to frequent recurrences particularly in the context of prior corticosteroid therapy.^{2 10}

In this case, we found a progressive imagiological and laboratorial improvement and cutaneous lesions disappeared. Analytically, there was a decrease in eosinophil count ($1.38 \times 10^9/l$) and an increase in haemoglobin ($9.7 \times 10 g/l$).

Owing to the favourable outcome, the patient was discharged on the eighth day of steroid therapy with an indication to tapering during two more weeks.

The patient has been referred to her general practitioner for regular follow-up. She was cautiously warned not to take nitrofurantoin in the future.

Three months after the end of treatment, the patient remains asymptomatic.

DISCUSSION

The DRESS syndrome was first described in 1950 by Chaiken who called it the Drug-Induced Hypersensitivity Syndrome. It has an incidence of 1 in 1000–10 000 exposures to drug and has a death rate of about 10%; therefore, its early recognition is very important.¹²

The pathogenesis of DRESS syndrome has not been fully explained. Some different mechanisms have been implicated like the metabolic pathways; immune response related to human leukocyte antigen; and reactivation of human herpes virus (HHV; Epstein-Barr virus, HHV-6 and HHV-7).^{2 13}

This syndrome may occur with various types of drugs with anticonvulsants, antidepressants, sulfonamides and sulfones, anti-inflammatory drugs, anti-infectives, ACE inhibitors and β -blockers being the most common.^{14 15} In a recent systematic review of DRESS cases reported in the literature between January 1997 and May 2009, Cacoub *et al*¹⁶ found 44 drugs related to 172 case reports (table 2) and about 30% were associated aromatic anticonvulsants. During our literature review, we only found one case of DRESS syndrome caused by nitrofurantoin.¹⁷

In our case, according to the criteria published by Kardaun *et al*,⁸ the diagnosis of definite nitrofurantoin-induced DRESS was made. Consequently, we believe that nitrofurantoin can be added to the list of drugs as having the possibility of DRESS syndrome.

Learning points

- ▶ The key to diagnose DRESS (drug reaction/rash with eosinophilia and systemic symptoms) syndrome is a high degree of suspicion.
- ▶ Although diagnosed by elimination, a complete investigation of DRESS syndrome is essential in clinical practice.
- ▶ Any skin rash in a patient taking drug therapy should focus our attention for a serious systemic skin reaction to the drug, as diseases such as DRESS syndrome can be undercover.
- ▶ DRESS syndrome may be caused by all kinds of drugs and the withdrawal of the incriminating drug is vital.

Table 2 Drugs related to DRESS/DIHS

Drug	Cases related to the drug
Abacavir	5
Allopurinol	19
Amoxicillin plus clavulanic acid	1
Amitriptyline	2
Atorvastatin	1
Aspirin	1
Captopril	1
Carbamazepine	47
Cafadroxil	1
Celecoxib	1
Chlorambucil	1
Clomipramine	1
Clopidogrel	1
Codein phosphate	1
Cotrimoxazole/Cefixime	1
Cyanamide	1
Dapsone	4
Diaphenylsulfone	1
Efalizumab	1
Esomeprazole	1
Hydroxychloroquine	2
Ibuprofen	2
Imatinib	1
Lamotrigine	10
Mexiletine	5
Minocycline	3
Nevirapine	8
Olanzapine	1
Oxycarbamazepine	3
Phenobarbital	10
Phenylbutazone	1
Phenytoin	7
Quinine and thiamine	1
Salazosulfapyridine	2
Sodium meglumine ioxitalamate	1
Sodium valproate/ethosuximide	1
Spironolactone	1
Streptomycin	1
Strontium ranelate	2
Sulfalazine	10
Sulfamethoxazole	2
Tribenoside	1
Vancomycin	4
Zinosamide	1

Adapted from Cacoub *et al*.¹⁶

DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction/rash with eosinophilia and systemic symptoms.

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Competing interests None.

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