

Penicillin V-induced Drug Rash with Eosinophilia and Systemic Symptoms

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ABSTRACT

DRESS syndrome (drug reaction with eosinophilia and systemic symptoms), previously named “drug hypersensitivity syndrome”, is a severe adverse drug reaction characterized by skin rash, fever, lymph node enlargement and internal organ involvement. We report on a 7-year old girl who developed DRESS syndrome caused by penicillin V treatment.

Keywords: Adverse reaction, child, DRESS syndrome, hepatitis, penicillin V, potassium

Erupción Cutánea Inducida por la Penicilina V con Eosinofilia y Síntomas Sistémicos

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RESUMEN

El síndrome DRESS (así llamado por las iniciales del inglés “drug reaction with eosinophilia y systemic symptoms”) es una reacción a medicamentos, acompañada por eosinofilia y síntomas sistémicos. Conocida anteriormente como “síndrome de hipersensibilidad a los medicamentos, se trata de una reacción adversa severa a los medicamentos, caracterizada por erupción cutánea, fiebre, agrandamiento de los ganglios y compromiso de órganos internos. El presente trabajo reporta el caso de una niña de 7 años de edad, que desarrolló el síndrome DRESS a partir de un tratamiento con penicilina V.

Palabras claves: Reacción adversa, niña, síndrome DRESS, hepatitis, penicilina V, potasio

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INTRODUCTION

DRESS syndrome (drug reaction with eosinophilia and systemic symptoms), previously named “drug hypersensitivity syndrome”, is a severe adverse drug reaction characterized by skin rash, fever, lymph node enlargement and internal organ involvement. The term DRESS syndrome was first introduced in 1996 by Bocquet to decrease the equivocality of the term “hypersensitivity syndrome” (1). This syndrome is a rare, idiosyncratic drug reaction and starts within 1–8 weeks after the offending drug exposure (2). The death rate is about 10%, mostly due to liver damage (2, 3). The aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine) and sulphonamides are the most common causes

of DRESS syndrome but a variety of other drugs was defined as causative agents (4).

Penicillin V potassium is an antibiotic which is used successfully for several infectious diseases in neonates, infants, children and adults. Anaphylactic and haematologic adverse reactions due to penicillin V, like other penicillin, is a well known adverse reaction (5, 6). Also, adverse skin reactions are common and usually their clinical manifestations include maculopapular and erythematous rashes and urticaria (5).

We did not find any adverse reaction due to penicillin V, like DRESS, in the English literature (PubMed). Here we reported a patient who developed DRESS syndrome caused by penicillin V potassium treatment, during upper respiratory tract infection.

Case report

A 7-year-old girl was admitted with protracted fever, pruritic skin rash, periorbital and perioral oedema (orofacial swelling). She was apparently well until 15 days previously. At

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that time she was given oral penicillin V because of tonsillitis. Three days later, her temperature increased and a widespread erythematous rash developed. She was hospitalized, in an urban institution and treated with parenteral penicillin V for 2 days and afterwards ceftriaxone for 4 days. However, the child's rash, fever and fatigue progressively increased and she was then referred to our hospital.

She had no history of allergy, previous operation or hospitalization. Immunization record was adequate and family history was unremarkable.

On physical examination, her body temperature was 38.5°C (axillary), heart rate was 144 /min, respiratory rate was 28 breaths/minute and blood pressure was 110/65 mmHg. She had generalized cutaneous maculopapular exanthem with desquamation (Fig. 1), facial oedema,



Fig. 1: Generalized maculopapular exanthem and desquamation

especially of the lips (Fig. 2) and hyperaemia of the eyes. She had no neurological findings, such as neck stiffness and pathological reflexes. Cardiac examination was normal. There were generalized peripheral lymphadenopathy (cervical, suboccipital, submandibular, axillary and inguinal) found. There was no hepatosplenomegaly. She had oedema in all extremities.

Laboratory tests found leucocytosis ($31.1 \times 10^3/\mu\text{L}$), absolute eosinophilia (16%) and atypical lymphocytes. The



Fig. 2: Facial erythema and orofacial oedema

haemoglobin level was 13.8 gm/dL, the platelet count was normal and the reticulocyte count was 0.8%. Liver and renal function tests were normal at admission except for the lactate dehydrogenase (LDH) level (602 IU/L) and gamma glutamyltransferase (GGT) level (36 mg/dL). The erythrocyte sedimentation rate was 30 mm/hr and C-reactive protein level was 1.2 mg/dL (range: < 0.5 mg/dL). Urinalysis was normal. Cultures obtained from urine, throat and blood were all negative. Total IgE level were high (875 mg/dL). Other immunoglobulins were at normal levels. Antibiotic was stopped on day three of hospitalization after liver function enzymes and lactate dehydrogenase levels were suddenly elevated. She was treated with antihistamines and low dose systemic glucocorticosteroids. Serologic tests for viral infections including hepatitis A, B and C, CMV, EBV, Brucella and rubella were negative.

After 10 days of hospitalization, liver function tests began to decrease and the fever returned to normal and the IgE level decreased to 345 mg/dL. Eosinophilia was 12%. One month later, liver function tests were normal, IgE level was 196 mg/dL and eosinophilia was 10%. In the second month, IgE level and eosinophilia returned to normal. Over the subsequent 6 months, the patient did not demonstrate eosinophilia. Evolution of AST, ALT, LDH and IgE levels are shown in Table 1. The patient was told to avoid all penicillin in the future in order to prevent a recurrence.

Table 1: Evolution of AST, ALT, LDH and IgE levels

	Day of Admission							Standard
	1	3	7	10	20	30	60	
AST (IU/L)	28	608	1092	722	31	24	–	< 31
ALT (IU/L)	31	479	1751	1351	38	12	–	< 31
LDH (IU/L)	602	1338	838	746	309	210	–	80–225
GGT	36	414	415	267	44	28	–	< 30
IgE (mg/dL)	875	–	–	345	–	196	132	1–161

DISCUSSION

The most common differential diagnoses include Stevens-Johnson syndrome, toxic epidermal necrolysis, hypereosinophilic syndrome, Kawasaki disease and Still's disease whose diagnostic criteria are very similar to those of DRESS syndrome (4, 7). Also, they have no clear and strict definitions (8).

DRESS syndrome points to two important characteristics as well as cutaneous features: multisystemic involvement (adenopathies, hepatitis and other organ involvement) and haematological abnormalities [eosinophilia and atypical lymphocytes] (4). Skin lesions were reported in 73–100% of cases reported in the literature (9). The type of cutaneous eruption was not well documented in most cases; the most frequent skin lesion was a diffuse maculopapular inflammatory rash (9). As in the index case in that study, it was reported that eosinophilia was the most frequent haematological abnormality (in more than 50% of cases) (9). Another study suggested that a key feature of DRESS syndrome was eosinophilia (10). Other haematological abnormalities (thrombocytopaenia, anaemia, neutropaenia, and leukocytosis and presence of large, activated lymphocytes) were more rarely reported (9). Although peripheral adenopathy were rarely observed (< 30%) except in cases related to minocycline (80%), the index patient had generalized peripheral lymphadenopathy (9). In some large-scale retrospective study, liver abnormalities were the most frequent systemic symptoms in more than 60% of cases. (9). The main liver abnormality was hepatocellular necrosis although cholestasis was observed rarely (9). Liver biopsy was not performed in our patient for hepatitis. Hepatic parameters slowly improved within one month. Diagnostic criteria were based on drug exposure, eosinophilia or monocytosis and at least two visceral localizations outside the skin such as the liver, kidney, heart and lung (1). The index case had these diagnostic criteria. Serum LDH and GGT levels were elevated several days before serum AST and ALT levels increased. On review of the literature, we found one case who had high serum GGT and LDH levels on admission compared to serum AST and ALT levels (7).

A median time interval between the first intake of the causative drug and the onset of adverse reactions were between 11 and 47 days for most drugs in cases of drug-induced cutaneous side-effects associated with various systemic syndromes (9). The symptoms of DRESS syndrome usually begin 2–6 weeks after drug administration. This interval time was short (3 days) in our patient.

The pathogenesis is not fully understood and may be multifactorial. The activation of a population of T cells, induced by a specific recognition of the drug or one of its metabolites, is supposed to stimulate eosinophilic proliferation through secretion of IL-5. Visceral involvement is a consequence of eosinophilic infiltrate, with direct toxicity of eosinophilic peroxidase (11). Currently, an association of drug reactions with viral infection, especially Human Her-

pesvirus 6 (HHV-6) and other Herpesviridae species infection, has been discussed, although the exact pathophysiological pathway is unidentified (12). Viruses might interfere with the clearance of the drug and result in accumulation of a metabolite (13). In the literature, there were reports of DRESS syndrome with concomitant human herpesvirus 6 reactivation (13, 14); and it was determined that hypoinmunoglobulinaemia and a decreased B-cell count was associated with HHV-6 reaction. Although there is no strong evidence about the link between HHV-6 infection and DRESS syndrome, serologic tests for HHV-6 is recommended routinely in patients with suspected DRESS syndrome.

There is no clear consensus on the treatment of DRESS syndrome beyond stopping the causative agent. There was no definitive evidence that the administration of corticosteroids is beneficial. In some cases, systemic corticosteroid therapy in combination with the rapid withdrawal of the responsible drug represents the basic therapeutical principles (2).

The clinical history mimics severe sepsis. On the other hand, DRESS syndrome may be lifethreatening, with a mortality rate of about 10%. Mortality is mostly due to liver damage thought to be mediated by infiltration of eosinophils (15, 16).

We think that this case is penicillin V induced-DRESS syndrome, based on the history and timing of the events and laboratory tests although *in vivo* investigations of allergy (such as prick tests or patch tests) were not performed. To the best of our knowledge, this is the first time that DRESS syndrome resulted from use of penicillin V potassium, although cases with DRESS syndrome caused by administration of a beta-lactam antibiotic were reported (10,17). We also emphasize that LDH is the first enzyme to rise in Dress syndrome.

REFERENCES

1. 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.
2. Tas S, Simonart T. Drug rash with eosinophilia and systemic symptoms (DRESS syndrome). *Acta Clin Belg* 1999; **54**: 197–200.
3. Roujeau JC, Stern RS. Severe adverse reactions to drugs. *N Engl J Med* 1994; **331**: 1272–85.
4. Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. *Dermatology* 2003; **206**: 353–6. <http://www.nlm.nih.gov/medlineplus/druginformation.html> (16.01.2009).
5. Linares T, Marcos C, Gavilan M, Arenas L. Hypersensitivity to penicillin V with good tolerance to other beta-lactams. *J Investig Allergol Clin Immunol* 2007; **17**: 50–1.
6. Allam JP, Paus T, Reichel C, Bieber T, Novak N. DRESS syndrome associated with carbamazepine and phenytoin. *Eur J Dermatol* 2004; **14**: 339–42.
7. Ronni W, Hagit M, Batsheva M, Edith O. Drug rash with eosinophilia and systemic symptoms vs toxic epidermal necrolysis: the dilemma of classification. *Clin Dermatol* 2005; **23**: 311–4.

8. Peyrière H, Dereure O, Breton H, Demoly P, Cociglio M, Blayac J-P, Hillaire Buys D and the Network of the French Pharmacovigilance Centers. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a Drees syndrome really exist? *Br J Dermatol* 2006; **155**: 422–8.
10. Horsfield P, Deshpande S, Ellis R. Killing with kindness? Drug reaction eosinophilia with systemic symptoms (DRESS) masquerading as acute severe sepsis. *J Antimicrob Chemother* 2009; **64**: 663–5.
11. Sullivan JR, Shear NH. The drug hypersensitivity syndrome: What is the pathogenesis? *Arch Dermatol* 2001; **137**: 357–64.
12. Descamps V, Valance A, Edlinger C, Fillet AM, Grossin M, Lebrun-Vignes B et al. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol* 2001; **137**: 301–4.
13. Kano Y, Inaoka M, Shiohara T. Association between anticonvulsant hypersensitivity syndrome and human herpesvirus 6 reactivation and hypogammaglobulinemia. *Arch Dermatol* 2004; **140**: 183–8.
14. Schauer P, Salaun N, Bazin S, Labrouze JM, Bourguignon G. DRESS syndrome with bilateral panuveitis, elevated intraocular pressure, and HHV-6 reactivation: a case report. *J Fr Ophtalmol* 2006; **29**: 659–64.
15. Roujeau JC. Treatment of severe drug eruptions. *J Dermatol* 1999; **26**: 718–22.
16. Callot V, Roujeau JC, Bagot M, Wechsler J, Chosidow O, Souteyrand P et al. Drug-induced pseudolymphoma and hypersensitivity syndrome: two different clinical entities. *Arch Dermatol* 1996; **132**: 1315–21.
17. Amoxicillin/piperacillin/tazobactam: DRESS syndrome: case report. <http://www.ingentaconnect.com/content/adis/rea/2009/00000001/00001279/art00019>.

ERRATUM

In Issue No. 2, March 2010, re: Article entitled “A Survey of Physicians’ Knowledge and Attitudes Regarding Antimicrobial Resistance and Antibiotic Prescribing Practices at the University Hospital of the West Indies, pages 165–170. The name of the 4th author should be ‘C Thoms’ instead of ‘C Thomas’.