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Presence of a single nucleotide polymorphism (RS3758581) in a boy with DRESS syndrome

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Abstract

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, potentially life-threatening, drug-induced hypersensitivity reaction that includes rash, hematologic abnormalities, lymphadenopathy, and internal organ involvement. The pathogenesis of DRESS syndrome is partially understood. Various medications have been described as the cause of DRESS syndrome. Phenytoin and allopurinol are the most commonly reported culprit drugs, although more than 50 drugs can induce DRESS syndrome. Members of the cytochrome P450 (CYP) superfamily are the most commonly involved enzymes in metabolism of drugs such as phenytoin. This case report addresses the influence of CYP2C9 genetic polymorphism (a single nucleotide polymorphism) on phenytoin drug metabolism, thereby causing DRESS syndrome.

Key words: *DRESS syndrome, phenytoin, CYP2C9 gene polymorphisms.*

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Introduction

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, potentially life-threatening, drug-induced hypersensitivity reaction that includes rash, hematologic abnormalities, lymphadenopathy, and internal organ involvement [1, 2]. The pathogenesis of DRESS syndrome is partially understood. Various medications have been described as the cause of DRESS syndrome. Phenytoin and allopurinol are the most commonly reported culprit drugs, although more than 50 drugs can induce DRESS syndrome [3-6]. Members of the cytochrome P450 (CYP) superfamily are the most commonly involved enzymes in metabolism of drugs such as phenytoin. Genetic variation in the CYP2C9 gene can affect metabolism of phenytoin leading to altered phenotypes. Individuals with CYP2C9 gene polymorphisms were found to have an increased risk of severe cutaneous adverse reactions such as DRESS syndrome compared with the normal population [7, 8]. This case report addresses the influence of CYP2C9 genetic polymorphism (a single nucleotide polymorphism) on phenytoin drug metabolism, thereby causing DRESS syndrome.

Case description

A 6-year-old boy presented to the clinic with complaints of fever and rash lasting for about a week. He had no specific medical history before phenytoin was prescribed upon the suspicion of epilepsy. Three weeks later, he started to complain of fever (highest 38.8°C) and rash involving the trunk and extremities. Five days after the onset of symptoms, he presented to our clinic with these symptoms. On examination, maculopapular eruptions consisting of erythematous lesions varying from pin point in size up to a few millimeters across, through a wider range of rashes, were seen predominantly on the trunk and extremities. The skin rash tended to be confluent and was widespread on the body. He had submandibular and cervical lymphadenopathies about 2 × 2 cm confirmed by ultrasonography. His vital signs upon admission to the service were 90/60 mmHg for blood pressure, 80/min for pulse rate, 28/min for respiratory rate and 38.8°C for body temperature.

Figure 1 shows generalized erythematous maculopapular rash in the patient's abdomen and leg.

Laboratory findings showed leucocytosis (white blood cell 22 900/µl), hyper-eosinophilia (eosinophil 4000/µl, 17.4%), hepatitis (AST 1492 IU/l [10-40 IU/l], ALT 702 IU/l [10-40 IU/l]), hyperbilirubinemia (total bilirubin 5.08 mg/dl [0.3-1.3 mg/dl], and direct bilirubin 4.23 mg/dl [0.05-0.40 mg/dl]).

Diagnosis

Work-up for eosinophilia showed normal levels of serum IgE and complement. Stool studies failed to show any evidence of parasites. Blood and urine cultures were all negative. Furthermore, serological studies for rheumatoid

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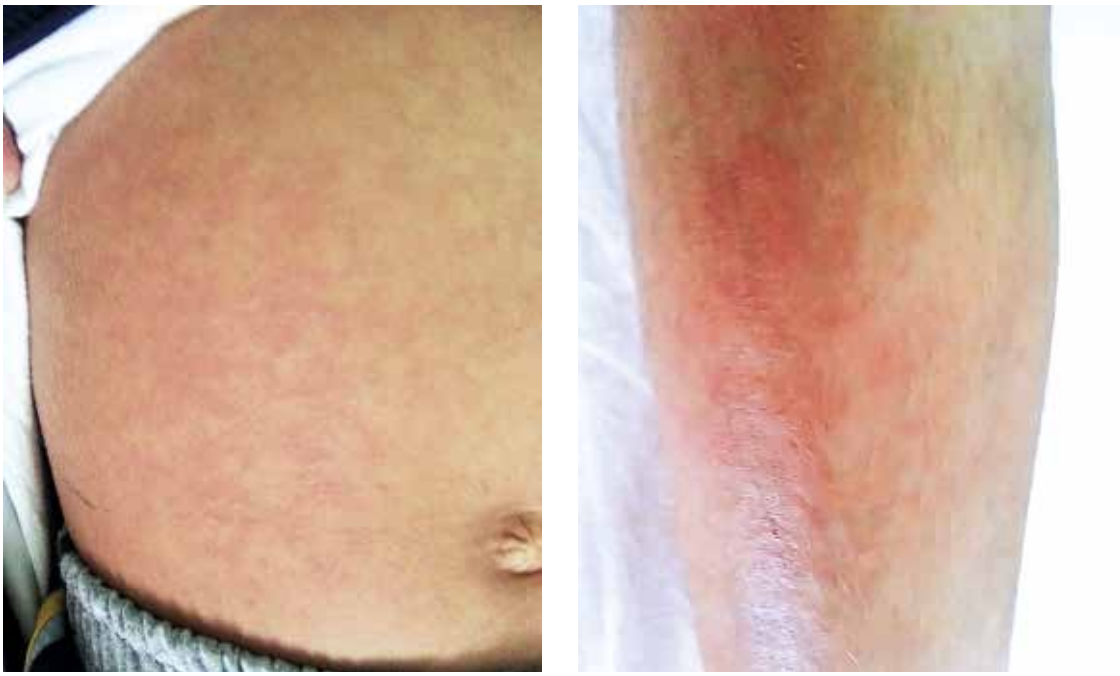

Fig. 1. Generalized erythematous maculopapular rash in the patient's abdomen and leg

factor, ANA and anti-DNA were also negative. According to serum tests, all herpes simplex virus, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus (HIV), and hepatitis A, B, and C viruses, were negative too. Biopsy of the skin lesions showed mild spongiotic epidermis and a mild dermal chronic inflammatory cell infiltrate composed of lymphocytes, histiocytes and occasional eosinophils with focal exocytosis of lymphocytes into the epidermis and associated vacuolar damage to the basal layer. These findings were consistent with the histological description typically found in this syndrome; however, it was not pathognomonic.

The laboratory and clinical findings, coupled with associated fever, generalized rash, eosinophilia, hepatic dysfunction, and lymphadenomegaly, led to the diagnosis of DRESS syndrome. Phenytoin was stopped when he was admitted to the hospital and prednisolone was started on the fifth day of hospitalization. The clinical course was favorable, with progressive regression of symptoms after steroid initiation. We planned a pharmacogenetic study for CYP2C9 gene polymorphisms two months after the steroid therapy.

Discussion

"Drug rash with eosinophilia and systemic symptoms" was first introduced in 1996 by Bocquet, to describe patients exhibiting a drug-induced condition characterized by an extensive rash, fever, lymphadenopathy, hematologic abnormalities, hepatitis, and involvement of the kidneys, lungs, heart, or pancreas [1]. The initial symptoms in the present case were fever and skin eruption three weeks after being exposed to the drug. Cutaneous lesions can range from erythematous papules to plaques, pustules, and eczematous lesions [8]. The laboratory abnormalities in our case included elevated white blood cell count with increased eosinophils, hepatitis, and direct hyperbilirubinemia. RegiSCAR proposes a series of criteria for DRESS, according to which hospitalized patients with drug rash must have at least 3 of 4 systemic features (fever, lymphadenopathy, internal organ involvement, hematological abnormalities) [10]. In the present report, our patient developed all 4 criteria of the DRESS syndrome, and the Kardaun score was 7 [11].

Phenytoin is a first-line antiepileptic drug but can cause adverse reactions from maculopapular exanthema to life-threatening reactions. It is estimated that about 19% of patients taking phenytoin develop hypersensitivity reactions [8]. Not all patients taking phenytoin develop phenytoin-induced severe cutaneous adverse reactions such as DRESS, Steven-Johnson syndrome and toxic epidermal necrolysis [12]. Evidence suggests that genetic factors also might have a significant role in the pathogenesis of phenytoin-induced severe cutaneous adverse reactions [8, 12-16].

Phenytoin is metabolized primarily by the cytochrome P450 (CYP) enzyme. CYP2C9, a member of the cytochrome-P450 enzyme superfamily, is a monooxygenase that metabolizes drugs such as phenytoin [18]. Genetic variation in the *CYP2C9* gene can affect the metabolism, leading to altered phenotypes. It was discovered that *CYP2C9* gene

polymorphisms known to cause a 93% to 95% reduction in phenytoin clearance are important genetic factors for phenytoin-related severe cutaneous adverse reactions [8, 12-16]. To investigate the genetic factors associated with phenytoin-related DRESS syndrome, we carried out a genome-wide association study, followed by direct sequencing of the associated gene and replication analyses.

Here we report a case of DRESS secondary to phenytoin, in which an underlying genetic predisposition (a single nucleotide polymorphism) was found. Genetic analysis showed a missense mutation in CYP2C9 exon 7 called rs3758581. Single nucleotide polymorphisms on the *CYP2C9* gene which can cause amino acid changes, such as rs3758581 (Ile331Val), affect CYP2C9 enzyme activity and its substrate specificity; thus rs3758581 is significantly associated with severe cutaneous adverse phenytoin reactions (e.g. Steven Johnson, DRESS syndrome) [8].

Conclusions

DRESS syndrome is a possible complication of phenytoin treatment that clinicians should keep in mind. We recommend that, wherever possible, clinicians should carry out CYP2C9 genotyping of epileptic patients before prescribing phenytoin, with progress in molecular technology. Thus identification of patients' genotype prior to phenytoin administration could potentially prevent life-threatening reactions such as DRESS syndrome.

The authors declare no conflict of interest.

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