DRESS Syndrome Induced by a Gadolinium-Based Contrast Agent in a 13-Year-Old Boy

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Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is characterized by a combination of high fever, maculopapular rash, lymphadenopathy, eosinophilia with atypical circulating lymphocytes, reactivation of human herpesvirus (HHV), and multiorgan involvement [1]. It is an uncommon, life-threatening syndrome that appears 2 to 8 weeks after the intake of the eliciting drug. Initially described with aromatic antiepileptic drugs, DRESS syndrome can be induced by many other agents [2]. We report the case of a patient who developed DRESS syndrome associated with several drugs, one of which was a gadolinium-based contrast agent (GBCA).

A 13-year-old boy was admitted to the hospital with suspected pyelonephritis. Blood culture was positive for *Staphylococcus aureus*, and treatment with intravenous cefotaxime and vancomycin was subsequently prescribed. Analgesia was added with metamizole, paracetamol, and dexketoprofen owing to intense back pain. The following day, left paravertebral pyomyositis was confirmed by magnetic resonance imaging (MRI) with the GBCA gadobutrol.

After 23 days of treatment and 22 days after the MRI, the patient developed fever and pruriginous maculopapular rash affecting the face and trunk. This worsened after each dose of cefotaxime, which was replaced by meropenem. Seven days later, the patient had only mild symptoms and was discharged with oral rifampicin and cloxacillin. A few hours later, the patient was readmitted with fever (39ºC) and aggravation of the rash (which had spread in a cephalocaudal manner), facial edema, and painful occipital lymphadenopathies.

Laboratory studies revealed a leukocyte count of 21 370/μL with 8.3% eosinophils (1770/μL), increasing 5 days later to 22 270/μL with 15.9% eosinophils (3530/μL). We also recorded abnormal liver enzymes and renal function profile

Table. Skin Test Concentrations and Results

Drug	Drug concentrations		Test results		
	PT	IDT, mg/mL	PT	IDT	DPT
Paracetamol	5% pet	1	-	-	-
Dexketoprofen	1% pet	1/100 1/10	-	-	NP
Ibuprofen	5% pet	0.2	-	-	-
Metamizole	1% pet	NP	+	NP	NP
BP-OL	20% pet	0.04	-	-	NP
MDM	20% pet	0.5	-	-	NP
BP	20% pet	10000 IU/mL	-	-	NP
Amoxicillin	20% pet	20	-	-	NP
Amoxicillin-clavulanic acid	20% pet	20	-	-	-
Ceftriaxone	20% pet	2	-	+	NP
Cefotaxime	20% pet	NP	+	NP	NP
Cefuroxime	20% pet	2	-	-	NP
Meropenem	10% pet	NP	+	NP	NP
Teicoplanin	4% and 10% aq	1	-	+	NP
Vancomycin	1% and 10% pet	NP	+	NP	NP
Rifampicin	Pure	0.001	-	-	NP
Gadoteric acid	Undiluted	1/10	-	-	+
Gadobutrol	Undiluted	1/10	-	-	NP
Gadoxetate disodium	Undiluted	1/10	-	+	NP

Abbreviations: BP, benzylpenicillin; BP-OL, benzylpenicilloyl octa-L-lysine; DPT, drug provocation test; IDT, intradermal test; MDM, minor determinant mixture; NP, not performed; PT, patch test.

(AST, 152 U/L; ALT, 245 U/L; GGT, 123 U/L; urea, 50.0 mg/dL; and creatinine, 1.19 mg/dL). Serology for HHV-6, HHV-7, HHV-8, and *Mycoplasma pneumoniae* was negative, as was blood culture.

All treatments were withdrawn because of suspected drug hypersensitivity reaction, except metamizole and cloxacillin, which were administered for 6 weeks. Treatment with systemic corticosteroids (2 mg/kg) and antihistamines led to improved clinical and laboratory findings. The patient's condition resolved completely in 2 weeks. A few weeks later, he underwent a new MRI examination with gadobutrol to monitor the infection. The reaction reappeared and resolved spontaneously.

Once the patient was asymptomatic, an appointment for the allergy study was scheduled. The patient's parents signed the informed consent document.

Patch tests were performed with all the drugs involved. If negative, intradermal tests with immediate and delayed readings were performed whenever possible. Readings were taken as previously described [3]. Drug provocation tests (DPTs) were only performed to identify alternative drugs considered necessary by the team. The concentrations used in the skin tests and the test results are shown in the Table.

Patch tests were positive for cefotaxime, meropenem, and metamizole and doubtfully positive for vancomycin (Supplementary Figure). Intradermal tests were positive in delayed readings for ceftriaxone and teicoplanin and doubtfully positive for gadoxetate disodium. Finally, single-blind placebo-controlled drug challenge tests (SBPCDC) with amoxicillin-clavulanic acid, paracetamol, and ibuprofen were negative. Given the doubtfully positive result of gadoxetate disodium, an SBPCDC was performed with gadoteric acid to provide an alternative GBCA. Ten hours later, the patient developed rash, high fever, and vomiting, which resolved spontaneously. The patient was diagnosed with DRESS syndrome, possibly caused by gadobutrol, metamizole, ceftriaxone, cefotaxime, meropenem, teicoplanin, and vancomycin. He was advised to avoid all GBCAs, cephalosporins, dipyrone, carbapenems, vancomycin, teicoplanin, and rifampicin.

DRESS syndrome is challenging in terms of diagnosis, which is reached after the exclusion of other diseases. The European Registry of Severe Cutaneous Adverse Reactions has developed a diagnostic validation score that combines clinical and biological criteria (Kardaun score) [4]. The patient's score (8 points) confirmed that he had definite DRESS syndrome [1].

Because of their safety profile and low frequency of associated adverse effects, GBCAs have been used in contrast-enhanced MRI over the last 25 years [5]. Hypersensitivity reactions to GBCAs are rare and involve mainly immediate reactions, including anaphylaxis and, occasionally, fatal reactions [6,7]. We found only 1 case of a delayed reaction described as exanthema [8]. Patients who react to a GBCA

can frequently tolerate a differently structured GBCA [5,9]. In the case we report, the patient experienced a reaction after receiving gadobutrol, a macrocyclic nonionic GBCA, and had a doubtfully positive result to gadoxetate disodium, a linear ionic GBCA.

Guidelines on DRESS syndrome usually recommend not performing DPTs with the suspect drug or structurally related drugs owing to the risk of eliciting a new reaction [1,10]. Nevertheless, since providing an alternative GBCA was considered essential for disease management by the attending physicians [9], we decided to carry out a DPT with gadoteric acid, a macrocyclic ionic contrast agent. The patient developed symptoms again, thus confirming DRESS syndrome. We therefore recommended avoiding all GBCAs.

The pathogenesis of DRESS syndrome is not entirely understood. Proposed mechanisms include genetic deficiencies resulting in the accumulation of toxic drug metabolites, virus–drug interactions, and drug-specific T cell–mediated reactions [1]. An episode of DRESS syndrome can elicit massive nonspecific activation of the immune system, decreasing tolerance to drugs, and, consequently, sensitization to chemically and antigenically unrelated drugs [1,2]. Costimulatory signals provided by viral reactivation or first drug sensitization could act as cofactors that enhance the stimulation of the immune response [1].

Patch testing has proven useful and valuable in the diagnosis of DRESS [1,4]. Intradermal tests can be performed in the case of negative results. In the present case, patch and intradermal testing enabled us to identify the drugs involved and thus provide safe alternatives for the patient. However, skin tests may show negative results, and DPT may be necessary [9]. In the present case, the patient had a mild reaction after the DPT with gadoteric acid despite negative skin test results.

In conclusion, we present a case of DRESS syndrome in a child sensitized to chemically and antigenically unrelated substances, namely, antibiotics, NSAIDs, and gadolinium-based contrast media. To our knowledge, this is the first reported case of DRESS syndrome involving a GBCA.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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