DRESS syndrome with gadolinium contrast media in a 13-year-old boy

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Drug rash with eosinophilia and systemic symptoms (DRESS) is characterized by a combination of high fever, maculopapular eruption, lymphadenopathy, eosinophilia with atypical circulating lymphocytes, reactivation of herpes viruses, and multi-organ 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 drugs [2]. We report the case of a boy who developed a DRESS syndrome associated with different drugs, one of them a gadolinium-based contrast media.

A 13-year-old boy was admitted to the hospital due to a suspicion of pyelonephritis with positive blood culture for *S. aureus*, so treatment with intravenous cefotaxime and vancomycin was prescribed. Due to intense back pain, analgesia was added with metamizole, paracetamol and dexketoprofen. The next day, left paravertebral pyomyositis was confirmed by magnetic resonance image (MRI) with gadobutrol, a gadolinium-based contrast agent (GBCA).

After 23 days of treatment and 22 days after the MRI, the patient initiated fever and pruriginous maculopapular rash affecting the face and trunk, which worsened after administering each dose of cefotaxime; so it 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 because of a fever of 39ºC, aggravation of the exanthema, which spread in a cephalocaudal manner, facial edema and painful occipital lymphadenopathies.

Laboratory studies revealed 21,370/µl leukocyte with 8.3% of eosinophils (1,770/µl), increasing five days later to values of 22,270/µl leukocyte with 15.9% of eosinophils (3,530/µl), associated with abnormal liver enzymes and renal function profile (GOT: 152 U/L, GPT: 245 U/L, GGT: 123 U/L; urea: 50.0 mg/dL and creatinine: 1.19 mg/dL). Serology for HHV-6, HVV-7, and HHV-8, *Mycoplasma pneumoniae*, and blood cultures were negative.

All treatments were withdrawn with the suspicion of a drug hypersensitivity reaction (HSR), except metamizole and cloxacillin administered for six weeks. Systemic corticosteroids at the dose of 2 mg/kg and antihistamines were prescribed with a clinical and analytical improvement that resolved in two weeks. A few weeks later, the patient

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underwent an MRI with gadobutrol to monitor the infection, with the reappearance of the reaction that spontaneously resolved.
Once the patient was asymptomatic, an appointment for the allergy study was scheduled. The patient's parents signed the informed written consent.
Patch tests (PT) with all involved drugs were first performed. If negative, intradermal tests (IDT) with immediate and delayed readings were performed whenever possible. Readings were done as previously described [3]. Drug provocation tests (DPT) were not performed unless to check for alternative drugs considered by the team as necessary for the patient. Drug concentrations used skin test, and their results are presented in Table 1.

PTs were positive for cefotaxime, meropenem, metamizole, and doubtfully positive for vancomycin (Figure 1). IDTs were positive in delayed readings for ceftriaxone, teicoplanin, and doubtfully positive for disodium gadoxetate. Finally, single-blind placebo-controlled drug challenge tests (SBPCDC) with amoxicillin-clavulanic acid, paracetamol, and ibuprofen were negative. Due to the doubtfully positive result of gadoxetate disodium, an SBPCDC with gadoteric acid was performed to provide an alternative GBCA. Ten hours later, the patient developed a skin rash, high fever, and vomiting that spontaneously resolved. The patient was diagnosed with DRESS possibly caused by gadobutrol, metamizole, ceftriaxone, cefotaxime, meropenem, teicoplanin, and vancomycin. He received advice to avoid all GBCAs, cephalosporins, dipyrone, carbapenems, vancomycin, teicoplanin, and rifampicin.

DRESS represents a challenging diagnosis, reached after the exclusion of other diseases. The European Registry of Severe Cutaneous Adverse Reactions has developed a diagnostic validation score, combining clinical and biological criteria (Kardaun score) [4]. According to this, the patient had a definite DRESS since he reached 8 points [1].

Because of their safety and low side effect rates, GBCAs have been used in the last 25 years for contrast-enhanced MRI [5]. HSRs to GBCAs are rare, being immediate reactions, including anaphylaxis and fatality, the most frequently described [6, 7]. We have only found a delayed reaction described as exanthema [8]. Patients who react to one GBCA can frequently tolerate a different structured GBCA [5, 9].
Our patient suffered a reaction after administering gadobutrol -a macrocyclic nonionic GBCA- and had a doubtfully positive result to disodium gadoxetate, a linear ionic GBCA. Guides over DRESS usually recommends not performing DPTs with the suspicious drug and structurally related drugs due to the risk of eliciting a new reaction [1, 10]. Nevertheless, providing an alternative GBCA was considered essential for disease management by the attending physicians [9], so we decide to carry out a DPT with gadoteric acid, a macrocyclic ionic contrast media. The patient developed symptoms again, which confirmed the DRESS. Unfortunately, we had to recommend avoiding all GBCAs.
The pathogenesis of DRESS is not entirely understood. Proposed mechanisms are genetic deficiencies resulting in the accumulation of toxic drug metabolites, virus–drug

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interactions, and drug-specific T cell–mediated reactions [1]. A DRESS episode can elicit massive nonspecific activation of the immune system, decrease tolerance to drugs and lead to 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 immune response [1].

PTs have proven to be useful and valuable in the diagnosis of DRESS [1, 4]. In case of negative results, IDT can be performed. In our case, PT and IDT allowed us to identify involved drugs to provide safe alternatives for the patient. However, skin tests may show negative results, and drug challenges sometimes need to be performed [9]; our patient had a mild reaction after the DPT with gadoteric acid despite negative skin tests.

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

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References

1. Cabanas R, Ramirez E, Sendagorta E, Alamar R, Barranco R, Blanca-Lopez N, et al. Spanish Guidelines for Diagnosis, Management, Treatment, and Prevention of DRESS Syndrome. Journal of investigational allergology & clinical immunology. 2020;30(4):229-53.

2. Macias EM, Munoz-Bellido FJ, Velasco A, Moreno E, Davila I. DRESS syndrome involving 2 unrelated substances: imipenem and iodinated contrast media. Journal of investigational allergology & clinical immunology. 2013;23(1):56-7.

3. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Bilo MB, et al. Skin test concentrations for systemically administered drugs -- an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2013;68(6):702-12.

4. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? The British journal of dermatology. 2007;156(3):609-11.

5. Fok JS, Smith WB. Hypersensitivity reactions to gadolinium-based contrast agents. Current opinion in allergy and clinical immunology. 2017;17(4):241-6.

doi: 10.18176/jiaci.0742

6. Dillman JR, Ellis JH, Cohan RH, Strouse PJ, Jan SC. Frequency and severity of acute allergic-like reactions to gadolinium-containing i.v. contrast media in children and adults. AJR American journal of roentgenology. 2007;189(6):1533-8.
7. Jung JW, Kang HR, Kim MH, Lee W, Min KU, Han MH, et al. Immediate hypersensitivity reaction to gadolinium-based MR contrast media. Radiology. 2012;264(2):414-22.
8. Nagai H, Nishigori C. A delayed reaction to the magnetic resonance imaging contrast agent gadobutrol. The journal of allergy and clinical immunology In practice. 2017;5(3):850-1.
9. Moreno Escobosa MC, Cruz Granados S. Paramagnetic Contrast Media: Hypersensitivity and Cross-Reactivity. Journal of investigational allergology & clinical immunology. 2018;28(1):60-2.
10. Kidon M, Blanca-Lopez N, Gomes E, Terreehorst I, Tanno L, Ponvert C, et al. EAACI/ENDA Position Paper: Diagnosis and management of hypersensitivity reactions to non-steroidal anti-inflammatory drugs (NSAIDs) in children and adolescents. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2018;29(5):469-80.

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Table 1. Skin test concentrations and results.

DRUG	Drug concentrations		Test results		
	PT	IDT (mg/ml)	PT	IDT	DPT
Paracetamol	5% p	1	-	-	-
Dexketoprofen	1% p	1/100 1/10	-	-	NP
Ibuprofen	5% p	0,2	-	-	-
Metamizole	1% p	NP	+	NP	NP
BP-OL	20% p	0.04	-	-	NP
MDM	20% p	0.5	-	-	NP
BP	20% p	10000 UI/ml	-	-	NP
Amoxicillin	20% p	20	-	-	NP
Amoxicillin-clavulanic acid	20% p	20	-	-	-
Ceftriaxone	20% p	2	-	+	NP
Cefotaxime	20% p	NP	+	NP	NP
Cefuroxime	20% p	2	-	-	NP
Meropenem	10% p	NP	+	NP	NP
Teicoplanin	4% & 10% w	1	-	+	NP
Vancomycin	1% & 10% p	NP	+	NP	NP
Rifampicin	Pure	0.001	-	-	NP
Gadoteric acid	Undiluted	1/10	-	-	+
Gadobutrol	Undiluted	1/10	-	-	NP
Gadoxetate disodium	Undiluted	1/10	-	+	NP

PT: patch test; IDT: intradermal test; BP-OL: benzylpenicilloyl octa-L-lysine; MDM: minor determinant mixture; BP: Bencilpenicillin; w: water; p: petrolatum; DPT: drug provocation test; NP: not performed;