



Viral rashes mimicking drug reaction with eosinophilia and systemic symptoms syndrome in children after β -lactams intake: a diagnostic challenge

Arianna Dondi¹ · Roberta Parladori¹ · Francesca Mori² · Giulia Liccioli² · Andrea Bassi³ · Marcello Lanari¹ · Annalisa Patrizi⁴ · Iria Neri⁴

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Abstract

In cases of skin eruptions over the course of antibiotic therapy and concomitant viral infection, differential diagnosis is often challenging. Confirming or ruling out drug hypersensitivity is not always a clear-cut question. Drug reaction with eosinophilia and systemic symptoms (DRESS) cases, for example, is classified as severe cutaneous adverse reactions due to drugs, but frequently the clinical manifestations do not completely fit into the diagnosis of DRESS. The aim of the present paper is to highlight similarities and differences among DRESS syndrome and DRESS-like rashes during viral infections and amoxicillin intake in children, in order to highlight those aspects that can help clinicians in early detection. We describe the dermatological, clinical, and laboratory characteristics of five patients hospitalized for DRESS-like skin rashes appearing roughly 1 week since the start of an amoxicillin course for upper respiratory tract infection (URTI) symptoms. The data are compared with those of 3 patients with early-onset DRESS syndrome. The absence of eosinophilia might be an initial marker to help identifying DRESS-like rashes; a quick clinical improvement and the confirmation of a viral infection able to explain the symptoms can help to finally rule out DRESS syndrome.

Conclusion: A rapid, correct diagnosis of such DRESS-like rashes during viral infections allows more appropriate management and avoids unnecessary, life-long exclusion of useful and effective antibiotics because of a falsely “amoxicillin-allergy” labelling.

What is Known:

- *Viral infections are common causes of skin rashes in children during antibiotic intake and may require differential diagnosis with drug reactions.*
- *Early-onset DRESS syndrome is usually induced by antibiotics and appears ≤ 15 days after drug intake.*

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✉ Arianna Dondi
arianna.dondi2@unibo.it

Roberta Parladori
roberta.parladori@gmail.com

Francesca Mori
francesca.mori@meyer.it

Giulia Liccioli
giulia.liccioli@meyer.it

Andrea Bassi
bassi76@interfree.it

Marcello Lanari
marcello.lanari@unibo.it

Annalisa Patrizi
annalisa.patrizi@unibo.it

Iria Neri
iria.neri@aosp.bo.it

¹ Pediatric Emergency Unit, S.Orsola University Hospital, Scientific Institute for Research and Healthcare (IRCCS) Azienda Ospedaliero-Universitaria di Bologna, via Massarenti 9, 40138 Bologna, Italy

² Allergy Unit, Meyer Children's University Hospital, Florence, Italy

³ Dermatology Unit, San Luca Hospital, Lucca, Italy

⁴ Dermatology Unit, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy

What is New:

- Prominent midface edema, maculopapular rash, and mild-to-moderate systemic symptoms may appear in children during viral illnesses treated with amoxicillin few days after drug intake, and may require differential diagnosis with early-onset DRESS.
- In such cases, absence of eosinophilia, low (2–3) RegiSCAR score, confirmation of viral etiology, and a rapid resolution of the rash (2–5 days) might help to rule out DRESS; conversely, at an early stage, the presence of eosinophilia should suggest a diagnosis of DRESS.

Keywords Adverse drug reactions · Drug toxicity · Infectious mononucleosis · Drug reaction with eosinophilia and systemic symptoms · Viral rashes

Introduction

Viral infections are common causes of rashes in children during antibiotic intake and often require differential diagnosis with adverse drug reactions. The drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but serious condition with a 5.4% estimated mortality rate in the pediatric age and possible long-term and delayed sequelae, thus forbidding the use of the offending drug for life [1]. DRESS syndrome is characterized by widespread skin involvement, fever, lymphadenopathy, visceral involvement, and biological abnormalities (eosinophilia, mononucleosis-like atypical lymphocytes) [2]. It is more frequently caused by anticonvulsants and sulfonamides, but, in children, antibiotics are responsible for up to 30% of the cases [1, 2]. The disease usually starts abruptly 2–8 weeks after the start of the drug with a maculopapular or morbilliform rash and fever; upper respiratory tract infection (URTI)-like prodromes may be present, suggesting viral infections as possible triggers [2–4]. Despite this, there is no reliable standard for diagnosis. The European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) group established a clinical score (Table 1) that classifies a suspect patient into no, possible, probable, or definite DRESS case [5].

Recently, an early-onset DRESS syndrome has been described: it differs from the most frequent delayed-onset type because of the time latency (≤ 15 days versus >15 days after starting the drug), the drugs involved (mainly antibiotics and iodinated contrast media), and a significantly higher presence of lymphadenopathy; there are no differences in terms of severity, visceral involvement, resolution, RegiSCAR score, and mortality rate [2, 6].

At an early stage, the differential diagnosis between early-onset antibiotic-driven DRESS syndrome, viral infections, and other drug eruptions may be challenging, but, because of severe consequences of DRESS, it is important to define the diagnosis as early as possible [2]. Moreover, such cases are not rare in daily practice. We decided to revise our patients' medical records to identify and describe these situations in

detail, to highlight and delineate the differences between the two entities for an easier differential diagnosis.

Methods

We performed a retrospective analysis of 5 patients admitted to the Pediatric Emergency Unit of S.Orsola University Hospital in Bologna, Italy, from January 2016 to December 2019 because of suspecting DRESS syndrome, but in whom the final diagnosis was a viral rash. Moreover, we included a group of three children affected by clinically diagnosed DRESS syndrome for comparison. The diagnosis was made by a pediatrician and a dermatologist, and the data collected were as follows: the offending drugs, the day of symptoms appearance, the time of onset and of improvement of the rash, fever, eosinophil count, presence of lymphadenopathy or of organ involvement. The RegiSCAR score was calculated according to Kardaun et al. [5]. Patients were included in the DRESS group only if their RegiSCAR score was >5 ("definite"). On the other hand, patients with a RegiSCAR score <2 were excluded, as well as if their records were incomplete or unclear. When available, pictures were reviewed and included in the study after obtaining a signed informed consent from the parents/caregivers.

Results

We identified 5 patients hospitalized for DRESS-like rashes during viral infections (Fig. 1). Table S1 reports a detailed description of our cases and of the rash characteristics. All of them had dermatological characteristics that were similar to the DRESS syndrome: the rash extension was $\geq 50\%$ of the body surface area (5/5) with maculopapular characteristics and sometimes confluent (3/5), and prominent midface edema (5/5). Skin involvement appeared 6–7 days since the start of amoxicillin (with or without clavulanate) for an URTI; atypical lymphocytes were present in most of them (3/5), and a

Table 1 The European Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) score. From Kardaun et al. (7)

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

^a After exclusion of other explanations. BSA, body surface area. Final score: minimum -4, maximum 9; <2 no drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, 2–3 possible DRESS syndrome, 4–5 probable DRESS syndrome, >5 definite DRESS syndrome

viral infection was demonstrated in all (5/5); cervical lymphadenopathy and fever were always present, and a mild liver

involvement, assessed by liver function tests, was also shown in most of them (3/5); resolution was always rapid within a

Fig. 1 Pictures in the upper line: rash with edema of the midface area (from left to right: patients 1, 3, and 5); in the lower line: diffuse, sometimes confluent, maculopapular rash (left: patient 1, right: patient 5)



few days from stopping the drug and starting treatment with antihistamines sometimes associated with corticosteroids; the RegiSCAR score was 2–3 (“possible case”) in all. None of our patients had eosinophilia. In all patients a viral infection, namely Epstein-Barr virus (EBV) in 4/5 and parainfluenza virus in 1/5, that could explain the symptoms was demonstrated after a few days, which are necessary for the performance of the microbiological tests. All of them had a quick resolution of the rash (range 2–5 days) without relapses.

The patients with DRESS-like viral rash were compared to 3 patients with a definite diagnosis of DRESS which are described in Table S2. Two of them were hospitalized for severe infections (cellulitis and encephalitis) and treated with multiple systemic drugs, whereas in one case, DRESS had been triggered by amoxicillin/clavulanate administered for URTI-like symptoms. All had an early-onset form, meaningful eosinophilia, cervical or diffuse lymphadenopathy, and an itchy maculopapular rash with desquamation occurring some days after rash appearance. In 2/5, a mild liver enzymes elevation was reported. In none of them a viral agent could be identified by laboratory exams. In one case, DRESS resolved in 4 days, whereas in 2, in more than 3 weeks. All the patients with definite DRESS were treated with IV antihistamines and 2 with IV corticosteroids.

Discussion

The aim of the present paper is to highlight similarities and differences among early-onset DRESS syndrome and DRESS-like rashes during viral infections and amoxicillin intake, to help clinicians in early detection (Table 2).

In a recent systematic review about pediatric DRESS syndrome, the most common clinical symptoms were rash (99%), more frequently morbilliform (89%), fever (96%), eosinophilia (90%), and lymphadenopathy (74%); the most commonly affected organ was the liver (80%) [1]. Moreover, antibiotics are reported to induce roughly 1/3 of the cases of DRESS syndrome in the pediatric population [1].

However, similar findings are also typical of EBV-infectious mononucleosis (IM) [7], which was diagnosed in 4 out of 5 children in our series. Therefore, it can be difficult to clinically differentiate an antibiotic-associated rash during IM from an antibiotic-driven DRESS before obtaining results of microbiological tests.

EBV infection itself can induce a skin eruption, usually erythematous, maculopapular, and involving the trunk and the extremities [8]. Moreover, up to 30% of the patients treated with amoxicillin or amoxicillin/clavulanate during IM will develop a pruritic and prolonged maculopapular rash. Other less frequent manifestations can be urticarial, purpuric and vesicular rashes, pustular erythematous rash, diffuse

Table 2 Factors that help distinguish between early-onset antibiotic-induced DRESS syndrome, DRESS-like rashes during viral infections and antibiotic intake, and β -lactam-induced rashes in mononucleosis (1, 2)

Item	Early-onset antibiotic-induced DRESS syndrome	DRESS-like rashes during viral infections and antibiotic intake	β -lactam-induced rashes in mononucleosis
Causative drugs	Antibiotics, iodinated media contrast, others	Amoxicillin +/- clavulanate	Amoxicillin +/- clavulanate
Time of onset since initial drug intake (days)	7–19	6–7	7–10
Rash	Diffuse, morbilliform, with facial edema, possible mucosal involvement	Diffuse, morbilliform, sometimes pomphoid, with facial edema	Morbiliform rash of the trunk usually with sparing of the extremities
Fever $\geq 38.5^{\circ}\text{C}$	+++	++	++
Atypical lymphocytes	++	++	++
Eosinophilia	+++	-	-
Lymphadenopathy	+++	+++	+++
Liver involvement	+++	++	++
Other organ involvement	++	-	-
Significant improvement	3–5 weeks with corticosteroid therapy	2–5 days with antihistamine and/or corticosteroid therapy	Usually up to 7 days, no treatment required
RegiSCAR	>5	2–3	Undefined (if 2 or higher, DRESS should be ruled out)

erythema, or cutaneous vasculitis in the erythema multiforme pattern [9, 10].

These systemic manifestations probably reflect hypersensitivity to the antibiotic or its metabolites during the viral infection; a delayed-type time-limited hypersensitivity reaction and transient loss of tolerance to the antibiotic due to the immunostimulatory properties of EBV have been hypothesized and future adverse reactions to the same drug are not predictable [10]. Among the potential mechanisms which cannot be excluded lies molecular mimicry between amoxicillin and viral molecules, and high affinity of β -lactams for viral proteins [9]. Moreover, some patients with skin eruptions after drug intake during EBV infection may exhibit true sensitization to penicillins [11].

In our case series, 2 of the 3 patients with definite DRESS syndrome were already hospitalized for severe infections and had multiple drugs which could be the potential offending agents. However, one patient with early-onset DRESS caught our attention because his rash was triggered by amoxicillin/clavulanate administered for URTI-like symptoms, even if no viral agents could be identified by microbiological tests. In such cases, in which the rash appears a few days after the intake of oral amoxicillin or amoxicillin/clavulanate in a patient with URTI symptoms, an elevated eosinophil count might be the only feature to help distinguishing DRESS or DRESS-like rashes before the availability of microbiological investigations and before time shows the complete clinical course.

Up to now and to the best of our knowledge, no DRESS-like rashes during IM have been described. We also found a similar rash in a child who did not have IM, but a parainfluenza viral infection. Nevertheless, in 2016, Descamps and Brunet-Possenti discussed these clinical pictures as triggered by Herpes viruses reactivation and defined them by the acronym VRESS (virus reactivation with eosinophilia and systemic symptoms) [12].

When facing rashes that might underlie a DRESS syndrome, a key point is to decide whether to stop or continue the possibly causative antibiotic before a definite diagnosis is done. We believe that the medication should be stopped in any case, either the rash is a real DRESS or if it is a DRESS-like viral rash. In fact, in the former situation, stopping the drug is mandatory, and in the latter, the antibiotic is useless to heal the viral infection and might contribute to the rash onset and persistence, as previously discussed. The final diagnosis will allow to decide whether the drug should be avoided for life or can be taken again in the future. For any rash in which diagnosis is uncertain, it is mandatory to stop the drug immediately in case danger signs occur: painful skin, atypical target lesions, erosions of mucosa, fever $> 38.5^{\circ}\text{C}$, skin extension $> 50\%$, centropalpebral edema, purpuric infiltrates, papules, necrosis, organ involvement, hematological abnormalities, lymphadenopathy, etc. [13].

In conclusion, we observed that healthy children treated with amoxicillin during viral illnesses may develop a maculopapular rash with prominent midface edema and mild-to-moderate systemic symptoms, particularly liver involvement assessed by liver function tests, leading to consider early-onset DRESS syndrome as a possible diagnosis. In our cases, the absence of eosinophilia, a low (2–3) RegiSCAR score, and the confirmation of viral etiology cleared the diagnosis; a rapid resolution of the rash (2–5 days) was helpful to rule out DRESS. Conversely, at an early stage, the presence of eosinophilia in a child with a maculopapular rash with edema of the midface region appearing ≤ 7 days after oral penicillin intake should suggest a diagnosis of DRESS. Even if the case series is limited in the number of patients, we think that

describing them is important to spot some clues to distinguish DRESS from DRESS-like rashes in order to render a precise diagnosis and provide appropriate management. Larger population studies might help to confirm our observations and to explain the mechanisms that underlie such rashes.

Abbreviations DRESS, Drug rash with eosinophilia and systemic symptoms; EBV, Epstein-Barr virus; IM, Infectious mononucleosis; RegiSCAR, Registry of Severe Cutaneous Adverse Reactions; URTI, Upper respiratory tract infection; VRESS, Virus reactivation with eosinophilia and systemic symptoms

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Code availability N/A

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by AD, IN, RP, GL, AB, and FM. The first draft of the manuscript was written by AD and RP and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability N/A

Declarations

Ethics approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate Written informed consent was obtained from the parents.

Consent for publication Patients' parents or caregivers signed informed consent regarding publishing their data and photographs.

Conflict of interest The authors declare no competing interests.

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Supplementary tables

Patient	Age (yrs), sex	Rash	Max body temperature (°C)	Systemic symptoms	Leukocytes (%Lymphocytes, %Eosinophils)	AST/ALT (UI/ml)	Drug	Disease for which the drug was started	Viral infection	Appearance after drug intake (days)	Treatment	Disappearance (days)	RegiSCAR
1	13, F	Mid-face swelling with diffuse ($\geq 50\%$ BSA), itchy, maculopapular skin rash	38.5	Cervical lymphadenopathy, hepatosplenomegaly	6040/mm ³ (50%, 3.3%)	31/23	Amoxicillin	Non-streptococcal tonsillitis	EBV : IgM + IgG + EBNA +; DNA PCR +	6	IV antihistamines and corticosteroids	2	2
2	4, F	Generalized ($\geq 50\%$ BSA) macular rash with	38.7	Cervical lymphadenopathy, splenomegaly	9650/mm ³ (70%, 1.5%)	70/40	Amoxicillin/clavulanate	URT I	EBV : IgM + IgG-	7	IV antihistamines and corticosteroids	3	3

		facial involvement and swelling of the eyelid											
3	3, M	Face swelling, diffuse maculopapular rash (≥50% BSA) with swelling of the skin	40.1	Cervical and inguinal lymphadenopathy, hepatosplenomegaly	12780/mm ³ (77%, 3.1%) Atypical lymphocytes	155/110	Amoxicillin/clavulanate	Streptococcal tonsillitis	EBV : IgM + IgG-, DNA PCR +	6	oral antihistamines	4	3
4	4, M	Face swelling, pomphoid, sometimes coalescing, diffuse itchy	37.7	Cervical lymphadenopathy	2240/mm ³ (60%, 0%) Atypical lymphocytes	33/25	Amoxicillin/clavulanate	URT I	Parainfluenza virus (antigen detection)	7	oral antihistamines and corticosteroids	3	2

		lesions mainly of the limbs ($\geq 50\%$ BSA)											
5	7, F	Facial and cervical swelling, generalized urticarial rash with polymorpho-like appearance on the trunk ($\geq 50\%$ BSA)	38.3	Cervical and inguinal lymphadenopathy, hepatosplenomegaly	8580 (75%, 3.8%) Atypical lymphocytes	74/110	Amoxicillin/clavulanate	Otitis media	EBV : IgM + IgG+ EBNA-; DNA PCR +	6	oral antihistamines	5	3

Table S1 –Case series of 5 previously healthy, pediatric patients with DRESS-mimicking rashes during viral infections and b-lactams intake. URTI = Upper Respiratory Tract Infection. BSA =

Body Surface Area. EBV = Epstein Barr Virus. AST = Aspartate aminotransferase. ALT = Alanine aminotransferase.

Patient	Age (yrs), sex	Rash	Max body temperature (°C)	Systemic symptoms	Leukocytes (%Lymphocytes, %Eosinophils)	AST/ALT (UI/ml)	Drug	Disease for which the drug was started	Viral infection	Appearance after drug intake (days)	Treatment	Disappearance (days)	RegiSCAR	DRESS onset
2	8, F	Itchy MPE	40.4	Cervical lymphadenopathy	6820/mmc (42.3%, 13%)	90/113	oxacillin, clindamycin	Cellulitis and infection of the foot	none	5	IV antihistamines	4	6	early
3	13, M	Itchy MPE and desquamation	39	Multiple lymphadenopathies	6100/mmc (30%, 18.5%)	Within normal range	Amoxicillin-clavulanic acid	URTI	none	3	IV antihistamines and corticosteroids	21	6	early
4	3, F	Itchy MPE and desquamation	39	Multiple lymphadenopathies	9430/mmc (37.9%, 28.7%)	106/104	enoxaparin, cotrimoxazole, fluconazole, acyclovir,	Encephalitis and thrombosis	none	15	IV antihistamines and corticosteroids	30	7	early

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Table S2 – Case series of 3 previously healthy, pediatric patients with definite, early-onset DRESS (RegiSCAR scoring 6 or higher). MPE = maculopapular exanthema. URTI = Upper Respiratory Tract Infection. AST = Aspartate aminotransferase. ALT = Alanine aminotransferase.