Review

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome) associated with Acute Tubulointerstitial Nephritis in an adolescent

Inés Bibiana Bustamante Gañán [a]

[a] MD. Specialist in Pediatrics, MSc. in Public Health. Hospital Infantil Rafael Henao Toro, Manizales, Caldas. Faculty of health sciences, Universidad de Manizales, Caldas, Colombia. ORCID: https://orcid.org/0000-0002-2779-4862, i.bustamante@umanizales.edu.co

DOI: https://doi.org/10.22517/25395203.24661

Abstract

DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) is a rare pathology in Pediatrics, first described in 1996 by Bocquet et al. It can appear in a variable period of time after exposure to some medications, it is characterized by fever, skin involvement and internal organs. A 13-year-old patient is presented, with a history of use of Trimethoprim sulfa for two months, with a disease of three days of evolution, consisting of fever and skin rash, without mucosal involvement, with an unfavorable response to steroid management, requiring Intravenous inmunoglobulin. Weeks after the onset of symptoms and stable evolution, he presented acute renal failure that required renal replacement therapy. Other underlying autoimmune pathologies were ruled out. There was recovery of renal function test and normalization of the other paraclinical on day 40 of the disease. Patient remains asymptomatic four months later, with oral steroid treatment, in slow and gradual decline. Permanent evaluation of renal function tests should be considered in patients with DRESS syndrome, due to its association with acute tubulointerstitial nephritis and related complications.

Key words: DRESS Syndrome; Eosinophilia; Renal insufficiency; Nephritis interstitial; pediatric.

Síndrome de Reacción a drogas con Eosinofilia y Síntomas Sistémicos (DRESS) asociados a Nefritis Túbulo Intersticial Aguda en un adolescente

Resumen

El síndrome de DRESS (Reacción a drogas con eosinofilia y síntomas sistémicos) es una patología poco frecuente en Pediatría, descrita por primera vez en 1996, por Bocquet et al (1–4). Puede presentarse en un tiempo variable luego de exposición a algunos medicamentos, se caracteriza por fiebre, compromiso cutáneo y de órganos internos. En este caso, se presenta a un paciente de 13 años, con antecedente de uso de Trimetroprim sulfa desde hace 2 meses, con cuadro de 3 días consistente en fiebre y rash cutáneo, sin compromiso de mucosas, con respuesta no favorable al manejo con esteroide, requiriendo Inmunoglobulina IV. Semanas después del inicio de los síntomas y evolución estable presenta insuficiencia renal aguda que requirió terapia de reemplazo renal. Se descartaron otras patologías subyacentes de índole autoinmune. Hubo recuperación de azoados y normalización de los demás paraclínicos el día 40 de la enfermedad. El paciente continúa asintomático, 4 meses después, con tratamiento con esteroide oral, en descenso lento y gradual. Se debe considerar la evaluación permanente de las pruebas de función renal en los pacientes que presenten Síndrome de DRESS, por su asociación con Nefritis intersticial aguda y complicaciones relacionadas.

Palabras clave: Síndrome de hipersensibilidad a medicamentos, eosinofilia, insuficiencia renal, nefritis intersticial, Pediatría

Introduction

DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) is a rare disease in Pediatrics, with an incidence of 1: 1000 to 1: 10000, lower than in the adult population, first described in 1996 by Bocquet et al. (1–4). It can occur in a variable period of time after exposure to some medications, between 5 to 105 days post-exposure, and is mainly associated with the use of anticonvulsants (50%) and antibiotics (30.8%) (3.5).

It is characterized by fever, lymphadenopathy, skin involvement and internal organs, among which eosinophilia, the presence of atypical lymphocytes and liver involvement stand out, but it can also lead to kidney, pancreatic, myocardial and other organ damage. For its diagnosis, the Bocquet and RegiSCAR criteria (Registry of severe cutaneous adverse reactions to drugs) are taken into account, the latter being the most used in the pediatric population (3).

In the reported clinical case, the renal involvement of the patient is highlighted, with acute renal failure weeks after the onset of symptoms, requiring renal replacement therapy in the intensive care unit and the consideration of other underlying pathologies associated with rapid deterioration of the ill renal function, which were ruled out. The literature shows that the main affectation is at the liver level and renal involvement is reported to a lesser extent (2,3). The renal biopsy confirmed the diagnosis of Acute Tubulointerstitial Nephritis and 4 months after the presentation of the picture, the patient remains asymptomatic.

Case report

13-year-old patient who received Trimethoprim sulfa for 2 months, formulated for the management of Acne, with no other pathological antecedents, with a 3-day evolution of fever and skin rash, without compromising the mucous membranes. Antibiotics are suspended, with partial improvement, but 2 days later, there is a reappearance of fever and an increase in skin lesions, with an erythematous, macular, generalized rash (approximately 80% of body surface involvement), pruritic, without bullous lesions. Covid19 is ruled out. He was hospitalized for paraclinical tests, among which there was an elevation of transaminases, twice above normal, the presence of eosinophilia greater than 1500 / mm^3, and atypical lymphocytes (see Table 1).

Table 1. Paraclinics

Days of evolution after onset of symptoms	5	10	17	23	30	40	120
Serum creatinine (mg/dl) Reference: Up to 0,83	0,46	0,45	0,4	3,1	1,23	0,7	0,5
Blood urea nitrogen (BUN) (mg/dl). Reference: Up to 20	8,6	7,8	14	82	34,5	20	9,2
White blood cell count (x10^3/uL) (Reference: Up to 10)	6,8	22,6	18,5	24,0	14,3	18,2	10,0
Eosinophils (Reference: Up to 5%)	2%	8%	6%	37%	4%	12%	1%
Absolute eosinophil count (Reference: Up to 500 eosinophil/mm^3)	136	1808	1110	8880	572	2184	100
Atypical lymphocytes (Reference: Up to 5%)	11%	17%	5%	4%	2%	2%	1%
GOT (Glutamic Oxaloacetic Transaminase) Reference: Up to 38 U/L	61	120	31	92	45	16	13
GPT (Glutamic Pyruvic Transaminase) Reference: Up to 40 U/L	45	358	227	138	62	49	21
Urinalysis	Normal			Normal			Normal

DRESS syndrome is suspected and management is started with 1 gram IV (intravenous) methylprednisolone for 3 days, with subsequent change to oral prednisone 1 mg / kg per day. A few days later, after receiving an IV steroid cycle, he again presented fever and exacerbation of skin lesions, as well as persistent elevation of transaminases and eosinophilia, for which management with IV Immunoglobulin 2 g / kg for 2 days was ordered, with good answer.

There is stable clinical evolution for a few days, but approximately 23 days after the onset of symptoms and having started the decrease in Prednisone, there is a reappearance of fever, persistence of skin lesions, to a lesser extent and significant elevation of nitrogen compounds, with acute renal failure. who required transfer to pediatric intensive care for hemodialysis. Second cycle of methylprednisolone is indicated; 1 gram daily for 3 days. Due to the rapid progression of his renal failure, another immunosuppressant, Cyclophosphamide in doses of 750 mg / m^2 (with adjustment to renal function) was added and studies were extended to rule out underlying autoimmune pathologies. The patient had an increase in nitrogen levels more than 1.5 times the baseline value, KDIGO 3 acute kidney injury, and creatinine clearance 36 ml / min / 1.73 m^2). With the described management, there was recovery of nitrogen compounds and normalization of the rest of the paraclinics on day 40 of the symptoms, and they remain so 4 months after the presentation of the clinical picture (Figure 1).

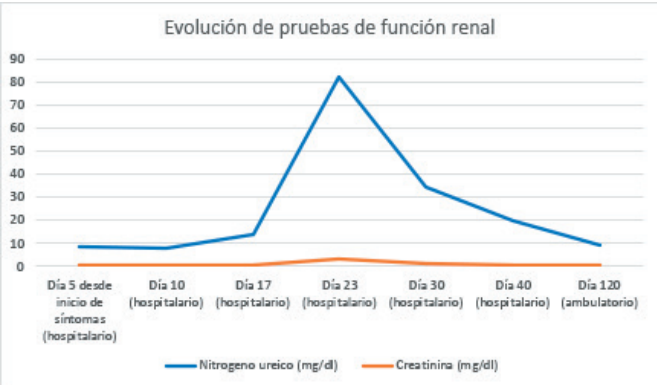

Figure 1. Evolution of kidneys function test

The urinalysis did not show alarm data at any time during the evolution of the disease, no hematuria, proteinuria or alterations in sediment were evidenced. Systemic lupus erythematosus was ruled out, after considering it due to its hypocomplementemia (C4 at 8.5 mg / dl, decreased and C3 at 97.2 mg / dl, normal) and renal deterioration described. Antiphospholipid syndrome was ruled out, he had altered studies in this phase of his disease: positive Ig M anticardiolipin, positive Ig M anti B2 glycoprotein and positive Ig G and M antiphospholipids, but on subsequent controls, all were found within normal limits. The other studies were negative (Anti-DNA negative; pANCA and cANCA negative; ANA negative; ENAS: antiRNP, antiLA, antiSm, antiRo negative¸ VDRL and direct negative Coombs). A possible relationship between this finding was considered with the administration of IV Immunoglobulin, which may be a transitory effect, with resolution several weeks later, as occurred in the patient. An echocardiogram was performed within normal limits. Four months after the onset of the symptoms, the patient is asymptomatic, with oral prednisone treatment with gradual and slow descent, as recommended in the literature

Figures 2 and 3 show the behavior of nitrogen compounds in relation to transaminases and hemogram during the evolution of the patient in the initial 4 months of care:

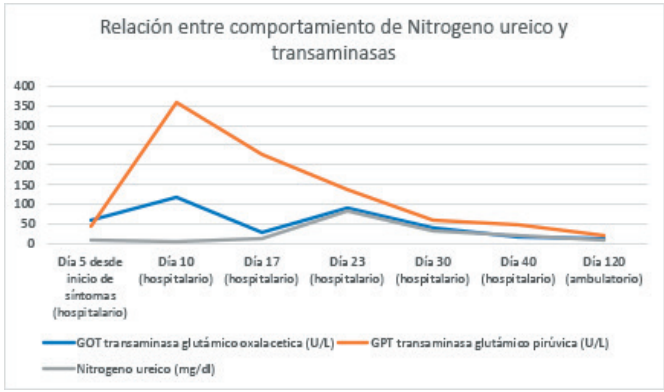

Figure 2. Relation between the evolution of Blood Urea Nitrogen and Transaminases

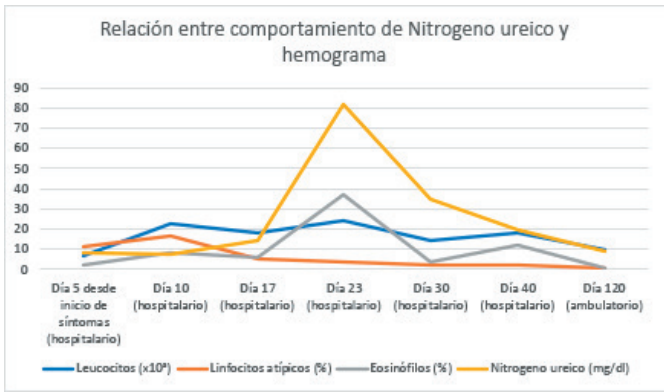

Figure 3. Relation between the evolution of Blood Urea Nitrogen and Complete Blood Count

Renal biopsy reported severe acute tubulointerstitial nephritis, histological changes compatible with drug hypersensitivity. Presence of Ig A in immunofluorescence suggestive of background Ig A nephropathy with minimal mesangial proliferation, no endocapillary proliferation, segmental sclerosis, no presence of extracapillary proliferation, and no changes suggesting superimposed podocytopathy.

Discussion

DRESS syndrome is a multiorgan systemic reaction, characterized by a clinical triad (rash, fever and systemic compromise) accompanied by alterations in the blood such as eosinophilia and the presence of atypical lymphocytes and liver and kidney dysfunction, as the main affectations mentioned. The average time of presentation of symptoms is variable after exposure to the drug, ranging from 3 to 8 weeks or up to 100 days according to other authors (1–4,6–10).

The incidence in the pediatric population is not well established, but it is estimated that the entity presents between 1: 1,000 to 1: 10,000 exposures to medications, with anticonvulsants (50%) and antibiotics (30.8%)

being the most common causes. with reports of mortality rates up to 10% (3,5,9,11).

Similar diseases have been mentioned in the literature for several decades, but it was in 1996 that Bocquet et al. coined the term DRESS for the description of hypersensitivity reactions to drugs and defines criteria for their diagnosis, requiring 3 criteria for their consideration: Drug-associated skin rash; fever, adenopathy greater than 2 cm, hepatitis with increased transaminases (more than 2 times normal), interstitial nephritis or myocarditis, and hematologic abnormalities such as eosinophilia greater than 1500 / mm^3 and atypical lymphocytes. Subsequently, in 2007, the RegisCAR (Registry of Severe Cutaneous Adverse Reaction) scoring system was developed in Europe, which classifies cases as "Not a case", "Possible", "Probable" and "Definitive", taking into account clinical and laboratory elements. This score was originally published by Kardaun et al, with an initial score (inclusion criteria), followed by confirmation (validation criteria) (3,11–14).

The case presented had a score greater than 5, according to RegisCAR, being classified as a definitive case, with the presence of fever, skin involvement suggestive of noxa of more than 50% in extension, eosinophilia (absolute count greater than 1500), atypical lymphocytes and liver involvement (transaminase increase above 2 times normal) and kidney (nitrogen elevation more than 1.5 times the baseline value, KDIGO 3 acute kidney injury and creatinine clearance 36 ml / min / 1.73 m^2)

The behavior of the patient shows typical data of the disease, with the aforementioned compromise in skin and hemogram (eosinophilia and atypical lymphocytes), but in this case kidney damage is also highlighted, so the patient required renal therapy (hemodialysis), which little is mentioned in the literature. The involvement of other internal organs, such as the liver, is reported in 50-80% of patients, the kidney between 11-28% and less frequent the lung in 2-5%, the gastrointestinal system in 8% and the heart in 4% (3,4).

The differential diagnoses associated with the rapid renal involvement detected in this patient include autoimmune pathologies, such as lupus erythematosus, antiphospholipid syndrome, hematologic neoplasms of eosinophilic precursors, Kawasaki disease, other erythroderma, and bacterial and viral infections. The studies requested in this regard ruled out these diseases and the clinical evolution and renal biopsy confirm the diagnosis of severe acute tubulointerstitial nephritis, compatible with drug hypersensitivity.

Acute tubulointerstitial nephritis (ITN) is a potentially reversible type of kidney damage, with a variable course, ranging from subclinical manifestations to kidney failure, with multiple etiologies, the most frequent being drug reactions, in approximately 70% to 90% of cases, followed by infections and autoimmune diseases. In children, genetic mutations are also reported. Medications include NSAIDs (non-steroidal anti-inflammatory drugs), antibiotics such as beta-lactams, sulfa drugs, and cephalosporins, anticonvulsants, and proton pump inhibitors. NTI is responsible for 5–15% of acute kidney injury in children and adults and can develop chronic kidney disease (15–17).

Finally, regarding the management in this patient, the initial use of intravenous steroid (methylprednisolone 1 g / day, maximum dose for its weight) for 3 days, with subsequent use of oral steroid (Prednisone 1 mg / kg / day) is highlighted. No response expected in the following days, given the persistence of skin and systemic symptoms, which required the application of Intravenous Immunoglobulin (2 g / kg) and a second cycle of Methylprednisolone in the same dose. Prednisone dose 1 mg / kg / day was continued. The response was favorable with improvement of skin lesions and with controlled biochemical parameters, but 23 days after receiving treatment with oral steroid and having started its dose decrease, the patient presented the described renal complication that leads to hospitalization in intensive care for hemodialysis. In parallel, pediatric nephrology indicates management with cyclophosphamide, one dose and other etiologies are ruled out. The patient has a favorable response, which is maintained after 4 months of outpatient management and follow-up, with a more gradual decrease in treatment with Prednisone, according to what the literature suggests in these cases of renal involvement to avoid relapses (8-10, 12,13,16).

Conclusions

DRESS syndrome is a rare entity in Pediatrics, finding more and more case reports, with commonly used medications, for which the medical staff must closely monitor and monitor their patients at the time of formulating them and suspecting the entity promptly. in the face of classic symptoms such as fever, skin rash, lymphadenopathy and changes in basic laboratories that can be performed in primary care levels such as eosinophilia, presence of atypical lymphocytes, elevated transaminases and nitrogen compounds, for the initiation of timely management, which, In the first instance, it is the immediate suspension of the suspected drug and the use of steroids (oral or intravenous) and subsequent recommendations, depending on the clinical evolution of the patient, which must be defined in more complex centers. It should be borne in mind that the recommendations against outpatient oral steroid use include a much more gradual and slow decline (weeks or months).

Renal involvement can be found in late stages of the disease (weeks after the initial presentation of systemic symptoms), so it is recommended within the follow-up of the patient, the performance of these renal function tests, even months after the initial diagnosis. In addition, in the face of rapid and aggressive renal involvement, diagnostic tests that rule out other underlying pathologies in the patient, such as autoimmune diseases, should be considered.

Early diagnosis and interdisciplinary management are essential to obtain favorable results in patients and reduce the risk of serious complications and unfavorable prognosis.

Financing: There is no source of external financing.

Conflict of interests: There is no conflict of interests.

Confidentiality of the data and informed consent: The author declares that she has followed the protocols of her work center on the publication of patient data, with the respective approval of the Investigations Committee, with the informed consent of the guardian and the consent of the patient.

References

1. Karakayali B, Yazar AS, Çakir D, Cetemen A, Kariminikoo M, Deliloglu B, et al. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome associated with cefotaxime and clindamycin use in a 6 year-old boy: a case report. Pan Afr Med J [Internet] 2017; 28:1–5. DOI: 10.11604/pamj.2017.28.218.10828.

2. Shiohara T, Mizukawa Y. Drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS): An update in 2019. Allergol Int [Internet] 2019; 68(3):301–8. DOI: 10.1016/j.alit.2019.03.006

3. Mori F, Caffarelli C, Caimmi S, Bottau P, Liotti L, Franceschini F, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS) in children. Acta Biomed 2019; 90(8):66–79. DOI: 10.23750/abm.v90i3-S.8167

4. Criado PR, Criado RFJ, Avancini JM SC. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) / Drug-induced Hypersensitivity Syndrome (DIHS): A review of current concepts. An Bras Dermatol 2012; 87(3). p. 435–49.

5. Metterle L, Hatch L, Seminario-Vidal L. Pediatric drug reaction with eosinophilia and systemic symptoms: A systematic review of the literature. Pediatr Dermatol [Internet] 2020 Jan 5; 37(1):124–9. DOI: 10.1111/pde.14044

6. Watanabe H. Recent Advances in Drug-Induced Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms. J Immunol Res [Internet] 2018; 2018:1–10. DOI: 10.1155/2018/5163129

7. Nguyen M, Chen Y, Tartar D. Characteristics of patients hospitalized for drug reaction with eosinophilia and systemic symptoms (DRESS) at a level 1 trauma center. J Invest Dermatol [Internet] 2019 Sep; 139(9):B13. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022202X19316926

8. Del Olmo-Gil E, Galindo-López MP, Maya-Gutiérrez A, Maya-Granados N, Barragán-Martínez JA, Alexanderson-Rosas G, et al. Síndrome de DRESS. Presentación de 2 casos y revisión de la literatura [Internet] Vol. 77, Rev Med Hosp Gen Méx. 2014. Available from: www.elsevier.es/

9. Silva-Feistner M, Ortiz E, Rojas-Lechuga MJ, Muñoz D. Síndrome de sensibilidad a fármacos con eosinofilia y síntomas sistémicos en pediatría. Caso clínico. Rev Chil Pediatr. 2017; 88(1):164–8. DOI: 10.1016/j.rchipe.2016.05.010

10. Cabañas R, Ramírez E, Sendagorta E, Alamar R, Barranco R, Blanca-López N, et al. Spanish guidelines for diagnosis, management, treatment, and prevention of dress syndrome. J Investig Allergol Clin Immunol. 2020; 30(4):229–53.

11. Tomani M, Caridi C, Charlot C. Complicated Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome History in a 14-Year-Old. Am J Case Rep 2021; 22: 1–7. DOI: 10.12659/AJCR.927951

12. Shanoj K, Joseph S, Shenoy P. Drug reaction with eosinophilia and systemic symptoms syndrome. Indian J Rheumatol. 2019; S59-66. DOI: 10.4103/0973-3698.272151

13. Fernández-Reyes MM, Ramírez-Rosales A, Guerrero-Izaguirre I, López-Romo A. DRESS syndrome. Dermatologia Rev Mex. 2018; 62(6):522–8.

14. Kardaun SH, Mockenhaupt M, Roujeau JC. Comments on: DRESS syndrome. J Am Acad Dermatol [Internet] 2014; 71(5):1000-1000.e2. DOI: 10.1016/j.jaad.2013.11.053

15. Nieto-Ríos JF, Ruiz-Velásquez LM, Álvarez L, Serna-Higuita LM. Nefritis tubulointersticial aguda. Revisión bibliográfica. Iatreia. 2020; 33(2):155–66. DOI: 10.17533/udea.iatreia.45

16. Ruebner RL, Fadrowski JJ. Tubulointerstitial Nephritis. Pediatr Clin North Am [Internet] 2019; 66(1):111–9. DOI: 10.1016/j.pcl.2018.08.009

17. Higashi Y, Baba N, Yoshimine H, Sakaguchi I, Kanekura T. Late-onset interstitial nephritis in a patient with drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms. J Dermatol. 2020;47(2):174–7. DOI: 10.1111/1346-8138.15175