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LAMOTRIGIN-INDUCED DRESS SYNDROME: AN IDIOSYNCRATIC REACTION

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Abstract: Objective: This report demonstrates an unexpected, rare and severe reaction to drugs, which may evolve with severe organic dysfunction, mainly liver. **Introduction:** Drug reaction syndrome with eosinophilia and systemic symptoms (DRESS) is an idiosyncratic, potentially fatal form of drug-induced, T-cell-mediated hypersensitivity. It predominates in women and includes fever, rash, hematologic changes, lymph node enlargement, and organ involvement. The most related drugs are aromatic anticonvulsants and allopurinol. The trigger is herpes virus infection, in addition to association with HLA polymorphisms and enzymatic alterations of cytochrome P450, favoring the accumulation of toxic metabolites. The symptoms appear, on average, 3 weeks after the introduction of the drug, and may persist or even worsen after the drug is discontinued. The evolution to organic dysfunction is critical, with acute liver failure being infrequent, but predictive of mortality. **Case report:** Young female patient admitted for acute febrile icteric syndrome and history of previous pharyngotonsillitis. Started Lamotrigine 1 month ago. Upon admission, all drugs for continuous use were suspended. Within 3 days, a generalized rash, abdominal pain, persistent fever and hyperlactatemia appeared. Serologies and rheumatological tests were negative. Laboratory tests and imaging showed acute hepatitis. Evaluated by Gastroenterology and Infectology who suspected Epstein-Barr infection, dengue fever or drug-induced hepatitis. She had progressive organ dysfunction, associated with eosinophilia and the presence of atypical lymphocytes, suggesting DRESS. She evolved with liver failure, being referred to the transplant center, where she manifested encephalopathy, proceeding with the transplant. The patient reacted acutely to the graft, **Conclusion:** DRESS syndrome is a severe drug reaction involving viral, genetic,

enzymatic and autoimmune mechanisms. Early diagnosis, discontinuation of drugs and corticosteroid therapy are essential to improve outcomes.

Keywords: lamotrigine, DRESS, acute liver failure.

INTRODUCTION

Drug hypersensitivity results from unintentional and unwanted stimulation of immune or inflammatory cells by a drug. Dose is a factor related to late symptoms such as allopurinol and lamotrigine > 10 mg/day. [3]

Type IV reactions occur between 48-72 hours or even days to weeks after drug exposure, inducing unregulated expansion of T cells with greater drug reactivity. There is a greater risk in the presence of viral infections and autoimmune diseases, potentiating the activity of T cells, cytokines, high expression of MHC and costimulatory molecules. [3]

Drug reaction syndrome with eosinophilia and systemic symptoms (DRESS) is an idiosyncratic, rare, complex, potentially fatal form of T-cell mediated drug-induced hypersensitivity and includes rash, haematological changes, lymph node enlargement, and internal organ involvement. [1,2] The incidence ranges from 0.9 to 2 cases per 100,000 individuals, with a slight female predominance. It is associated with herpes virus infection, HLA B alleles, polypharmacy, autoimmune diseases and enzyme polymorphisms such as slow N-acetylator and cytochrome P450. [1,4,5]

The most related drugs are aromatic anticonvulsants (carbamazepine, phenytoin, phenobarbital, lamotrigine), allopurinol, minocycline, dapsone, vancomycin, sulfa drugs. Comorbidities that increase the risk include HIV, epilepsy, atopy, collagenosis, renal or hepatic failure. [1,2]

DRESS is characterized by fever, extensive mucocutaneous rash, lymphadenopathy, eosinophilia and atypical lymphocytes, evolving with organ dysfunction. Cutaneous manifestations are common due to the presence of memory effector cells. The main trigger is herpes virus infection. The symptoms appear between 2 and 8 weeks after starting to use the drug, and may persist or even worsen after discontinuing the drug. [2,3,4]

CASE REPORT

IARC female, 24 years old. Admitted on 8/27/2022 due to febrile jaundice and bronchospasm. History of myalgia, fever, abdominal pain, vomiting, headache, associated with disseminated petechiae for 2 weeks. Evolved with rash, loss of appetite, jaundice, choluria, acholia for 1 week and, for 4 days, odynophagia and retroauricular and cervical lymphadenopathy, receiving Norfloxacin, which aggravated the rash. He denies bleeding, mental confusion, recent trips, drug use, transfusions, sexual exposure, water consumption and suspicious foods. He denies smoking and alcoholism. Updated vaccination. Personal history of asthma, bipolar disorder, anxiety and depression.

In continuous use: Pantoprazole 40 mg, Desvenlafaxine 100 mg, Sertraline 100 mg, Lithium 450 mg, Frontal 0.25 mg, Quetiapine 25 mg, Lamotrigine 25 mg every 12 hours starting 1 month ago. All drugs were discontinued upon hospital admission.

On physical examination, jaundice 2+/4+, pallor 1+/4+, generalized and painful rash. Presence of exudate on the palate and oropharynx. Painful abdomen, palpable hepatomegaly 3 cm from the right costal margin.

Initially, he received Ceftriaxone, but there was an infectious worsening. Abdominal tomography on 08/27/2023 showed thickened gallbladder, small right pleural effusion, enlarged liver and spleen with blunt edges, free fluid in the pelvis.

Evolved with acute hepatitis, cholestatic syndrome and mononucleosis-like condition. On 08/29/2023, maintaining fever, abdominal pain mainly on palpation and hyperlactatemia. FAN requested, negative VHS. Serologies for HIV, syphilis, hepatitis B, hepatitis C and toxoplasmosis were negative. Epstein-Barr and immune cytomegalovirus.

Abdominal ultrasound on 08/29/2022 showed mild hepatosplenomegaly and thickening of the gallbladder walls secondary to liver disease.

Evaluated by Gastroenterology and Infectology who suspected Epstein-Barr infection, dengue and drug-induced hepatitis. Laboratory 08/27/2022: alanine phosphatase: 628; DHL: 1672; INR: 2.4 and aPTT: 34; total bilirubin: 9.4; direct bilirubin: 7.1; indirect bilirubin: 2.3; TGO: 1556; TGP: 1717; range GT: 924; normal amylase and lipase; Normal CPK; normal renal function and ions; negative cultures; lactate: 2.7. Blood count 08/29/2022: hemoglobin: 11.2; hematocrit: 34.6; VCM: 80; HCM: 26; platelets: 183000; leukocytes: 19300; neutrophils: 42% (8106); sticks: 5% (965); monocytes: 15% (2895); eosinophils: 10% (1930) reference value 0 to 4% (440) and presence of atypical lymphocytes.

The next day, he showed signs of liver failure such as increased INR, hyperbilirubinemia, hypoalbuminemia. Laboratory 08/29/2022: INR: 3.29; aPTT: 38; TGO: 2184; TGP: 2020; rangeGT: 897; albumin: 2.1; lactate: 2.9; PCR: 78.

Contact was made with Hospital das Clínicas USP-Ribeirão Preto and she was referred to the Hepatic Center due to acute liver failure. At that center, he progressed to encephalopathy, and a liver transplant was performed. However, the patient had a reaction to the graft, progressing to sepsis and death.

DISCUSSION

DRESS syndrome is a type of IV-b hypersensitivity, characterized by T cell action and release of IL-4, IL-5, IL-13 activating and recruiting eosinophils. IL-33 induces cutaneous macrophages, attracts type 2 innate lymphocytes and causes eosinophilia.[1]

There are 4 main mechanisms that induce the syndrome: polymorphisms of HLA alleles, polymorphisms of liver enzymes such as cytochrome P450 and N-acetyltransferase (NAT1 and 2), deficiency of the enzyme epoxy hydroxylase and reactivation of the herpes virus.[1,4]

HLA polymorphisms modify the histocompatibility complex (MHC) with interaction between the drug, the T cell receptor and antigen presenting cells (APCs). Functional alterations of liver enzymes contribute to the accumulation of toxic metabolites, for example, the enzyme epoxy hydroxylase generates hydroxylation of aromatic anticonvulsants and its deficiency produces free radicals and cell damage.[1,4]

After absorption, the drug or metabolite reaches the bloodstream and is captured by antigen-presenting cells that contain HLA in the membrane. In the HLA-drug complex, the hapten is presented to naive T cells through the T cell receptor and triggers several types of immune reaction. Expansion of dysregulated T lymphocytes occurs mediated by the Janus kinase signal transducer and transcription activator signal (JAK-STAT).[1,4]

It is believed that the imminent agent is the viral activity of herpes types 6 and 7, Epstein-Barr and Cytomegalovirus, present in 75% of cases. Viruses induce Treg expansion, reduction of B lymphocytes and immunoglobulins, simulating immunodeficiency. This effect also favors the spread of the virus, generating a cycle. Furthermore, they stimulate the expansion of clones and the transformation of CD4+ into CD8+ that are reactive to certain

drugs. Expression of regulatory CD4 and CD25 can inhibit antiviral T lymphocytes and facilitate viral replication. (1,4)

There is increased expression of plasmacytoid cells (CDp) accumulating in the skin and leading to the production of interferon (INF) with consequent stimulation of B cells for IgG synthesis. (4) There is a reduction in the pMO monocyte population and Treg expansion in the acute phase from cMO monocytes through IL-10 production. This also stimulates viral reactivation. (1,5)

In addition, the drugs inhibit the differentiation of B cells into immunoglobulin-producing cells, and the worsening of symptoms after discontinuing the drugs occurs with the reduction of the viral load in the acute phase. (5)

The clinical resolution of DRESS is justified by the change in Treg cell differentiation to Th17 due to the selective depletion of original pMOs in the subacute phase, mediated by IL-6. (5)

Histopathology demonstrates band infiltrate formation with atypical lymphocytes in the skin. In the organs, there is usually granulomatous infiltration secondary to the expansion of CD4+ and INF cells. There is a reduction of macrophages in cells that secrete TNF and promote fusion between multinucleated giant cells. (4)

The clinical picture may show prodromes of upper airway infections 4 weeks earlier, suggesting that the trigger is the viral infection. The acute phase is characterized by functional Treg expansions associated with sequential viral reactivations of the herpes virus. (4.5)

High fever affects 90% of cases, associated with pruritic morbilliform rash on the face, neck, upper limbs and trunk in 87% of cases, in addition to periorbital edema. In 25% of cases, it affects the buccal mucosa and pharynx. Generalized and diffuse lymph node enlargement is documented in 70% to 75% of cases. (1,2,4)

Eosinophilia defines the organic infiltrate, evidenced in 85% to 96% and determines the severity of the condition. Targets include lymphatic, hematologic, liver, kidneys, heart, lungs, and pancreas. Acute interstitial nephritis is another frequent complication, usually induced by allopurinol. (1,2) On the other hand, acute liver failure is rare; however, it is the main cause of death, more frequent in women. (4,5)

The diagnosis is made with at least 3 of the following criteria:

- Symptoms after 3 weeks of drug use.
- Fever.
- Lymphadenomegaly in at least two distinct chains.
- Eosinophilia > 1500 mm^2.
- Atypical lymphocytes.
- Skin wrapping.
- Organic dysfunction.
- Interstitial nephritis.
- Hepatitis.
- Pneumonia.
- Myocarditis
- Pancreatitis (2,4)

Symptoms may persist after discontinuing the drug due to immunoglobulin synthesis deficiency status. 5)

Management of the DRESS syndrome requires support in an intensive care setting, immediate withdrawal of the triggering agent, avoid introducing other drugs due to the risk of cross-reaction, monitoring cytomegalovirus reactivation, and instituting high-dose corticosteroid therapy. (2,4,5)

Corticosteroids reduce tissue damage and the gradual loss of Treg function by restoring impaired Treg activity. They also reduce the viral load of cytomegalovirus and Epstein-Barr. It is recommended to use them for 6 to 8 weeks with gradual weaning over 4 to 8 weeks, avoiding organic deterioration. In some cases, ganciclovir is indicated to avoid

viral complications. [5]

In renal or pulmonary disease, oral prednisone 0.5 to 1 mg/kg/day is administered, with progressive withdrawal for 8 to 12 weeks. In potentially fatal cases, such as hemophagocytosis with bone marrow failure, encephalitis, severe hepatitis, renal or respiratory failure, combine prednisone and immunoglobulin 2 mg/kg for 5 days. [2,4]

If symptoms worsen, start intravenous methylprednisolone 30 mg/kg, immunoglobulin or plasmapheresis. Cases of severe hepatitis must be referred to the transplant center. [2,4]

The prognosis of DRESS is unpredictable and variable. Complications are pneumocystosis, myocarditis, sepsis, gastrointestinal bleeding, increasing morbidity and mortality. [5]

The worst prognostic factors involve viral reactivation by herpes or cytomegalovirus, severe liver damage, atypical lymphocytosis, advanced age, and multiple organ dysfunction. In these situations, the estimated mortality ranges from 2% to 10%. [2]

Late symptoms on exposure and visceral involvement differentiate DRESS from other pharmacodermias. The main differential diagnoses include Stevens-Jhonsons syndrome, toxic epidermal necrolysis, acute cutaneous lupus, mononucleosis-like, vasculitis, lymphoproliferative diseases, Still's disease, Kawasaki disease. [2,4,5]

CONCLUSION

DRESS syndrome is a severe reaction to drugs, involving viral, genetic, enzymatic and autoimmune mechanisms, distinguishing it from other pharmacodermias due to organ involvement. Early diagnosis, discontinuation of drugs and corticosteroid therapy are the cornerstones of the approach. In the face of severe complications, immunosuppression with high-dose methylprednisolone, immunoglobulin or even plasmapheresis can alter outcomes. Genetic counseling for patients and their families is also paramount. The report denotes the evolution to acute liver failure with indication for transplantation, but there was death motivated by factors related to the host, septic shock and the morbidity and mortality inherent to the procedure.

REFERENCES

1. CÁBANAS, R; RAMÍREZ E; SENDAGORTA E, et al. **Diretrizes espanholas para diagnóstico, manejo, tratamento e prevenção da síndrome de DRESS.** J Investig Allergol Clin Immunol 2020; Vol. 30(4): 229-253.

2. LEE, Haur Yueh. **Reação medicamentosa com eosinofilia e sintomas sistêmicos (DRESS).** UpToDate, USA, maio 2023.

3. PICHLER, Werner J. **Hipersensibilidade a drogas: classificação e características clínicas.** UpToDate, USA, dezembro 2019.

4. RICARDO, Paulo; AVANCINI, João; JARDIM, Roberta Fanchini; SANTI, Claudia Giuli. **Reação a drogas com eosinofilia e sintomas sistêmicos (DRESS) / Síndrome da hipersensibilidade induzida por droga (DIHS): revisão dos conceitos atuais.** Um Bras Dermatol. 2012;87(3):427-51.

5. SHIOHARA Tetsuo; MIZUKAWA Yoshiko. **Síndrome de hipersensibilidade induzida por drogas (DiHS)/reação a drogas com eosinofilia e sintomas sistêmicos (DRESS): Uma atualização em 2019.** Allergology International 68 (2019) 301-308.