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HEMOPHAGOCYTIC SYNDROME SECONDARY TO ANTICONVULSANT-RELATED DRESS SYNDROME: A CASE REPORT

SÍNDROME HEMOFAGOCÍTICA SECUNDÁRIA À SÍNDROME DRESS RELACIONADA AO USO DE ANTICONVULSIVANTE: UM RELATO DE CASO

SÍNDROME HEMOFAGOCÍTICO SECUNDARIO A SÍNDROME DRESS RELACIONADO CON ANTICONVULSIVOS: REPORTE DE UN CASO

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ABSTRACT

DRESS (Drug Reaction with Eosinophilia and Systemic Inflammation) is a serious adverse reaction that can present with significant multivisceral involvement. The exacerbated immune activation that occurs in DRESS syndrome can trigger hemophagocytic syndrome, generating intense systemic inflammation with unfavorable and potentially fatal clinical evolution. The association between hemophagocytic syndrome and DRESS is rare; however, early recognition of signs and symptoms is fundamental for timely diagnosis and treatment, reducing the likelihood of adverse outcomes and increasing the chances of therapeutic success.

Keywords: Hemophagocytic Syndrome. DRESS Syndrome. Eosinophilia.

RESUMO

A Síndrome DRESS (Drug Reaction with Eosinophilia and Systemic) é uma reação adversa grave, podendo apresentar acometimento multivisceral importante. A ativação imunológica exacerbada que ocorre na síndrome DRESS pode desencadear a síndrome hemofagocítica, gerando uma inflamação sistêmica intensa com evolução clínica desfavorável e potencialmente fatal. A associação entre síndrome hemofagocítica e a DRESS é rara, contudo, o reconhecimento precoce dos sinais e sintomas é fundamental para a realização do diagnóstico e tratamento oportunos, reduzido a probabilidade de desfechos adversos e aumentando as chances de sucesso terapêutico.

Palavras-chave: Síndrome Hemofagocítica. Síndrome DRESS. Eosinofilia.

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RESUMEN
El síndrome DRESS (Reacción a Medicamentos con Eosinofilia e Inflamación Sistémica) es una reacción adversa grave que puede presentarse con afectación multivisceral significativa. La activación inmunitaria exacerbada que se produce en el síndrome DRESS puede desencadenar un síndrome hemofagocítico, generando una inflamación sistémica intensa con una evolución clínica desfavorable y potencialmente mortal. La asociación entre el síndrome hemofagocítico y el síndrome DRESS es poco frecuente; sin embargo, el reconocimiento temprano de los signos y síntomas es fundamental para el diagnóstico y tratamiento oportunos, lo que reduce la probabilidad de resultados adversos y aumenta las probabilidades de éxito terapéutico.

Palabras clave: Síndrome Hemofagocítico. Síndrome DRESS. Eosinofilia.

1 INTRODUCTION

DRESS Syndrome (Drug Reaction with Eosinophilia and Systemic), also known as systemic drug hypersensitivity syndrome (SHD), is a severe drug reaction characterized by rash associated with multivisceral involvement, lymphadenopathy, eosinophilia. In general, the adverse reaction occurs after the first contact with the drug, starting between 2 weeks and 2 months after its introduction. The exacerbated immune activation seen in DRESS syndrome may, in rare cases, trigger hyperactivation of T lymphocytes and macrophages, resulting in systemic hyperinflammation and possible progression to hemophagocytic syndrome. The association between DRESS syndrome and hemophagocytic syndrome is considered a marker of severity and is related to increased morbidity and mortality, causing severe and potentially fatal organ dysfunctions.

2 OBJECTIVE

This article aims to report the clinical case of a previously healthy male patient whose clinical history and laboratory tests showed hemophagocytic syndrome secondary to a severe drug reaction after the initiation of anticonvulsants, in addition to discussing the diagnosis, the therapy adopted and the clinical outcome.

3 METHODOLOGY

The information was obtained through a review of the electronic medical record and interviews with the patient.

4 CASE REPORT

A 35-year-old male patient had been in an institution for 30 days for treatment of alcohol and psychoactive substance dependence, and the use of valproic acid was initiated. In the four days prior to hospital admission, the patient developed asthenia, inappetence, jaundice, diffuse abdominal pain, and oliguria. He denied fever, gastrointestinal and respiratory symptoms, neurological alterations and skin alterations. He denied choluria, fecal acholia, as well as recent travel and exposure to contaminated water or floods. He was referred to a tertiary referral hospital and on admission he was hemodynamically stable, vital signs within normal ranges, presence of jaundice ++++/4+, oriented in time and space, cardiac and pulmonary auscultation without alterations and presence of mild abdominal pain in the right hypochondrium with palpable liver two centimeters from the right costal margin,

non-palpable spleen, bowel air noise present and no other alterations. On admission laboratory tests, the patient had renal dysfunction (serum creatinine: 18.2; Serum urea: 225); hepatic cholestasis (Total bilirubins: 41.3, direct bilirubin: 27.4, and indirect bilirubin: 13.9; TGO: 136; TGP: 136; INR: 1.03; albumin: 3.1; alkaline phosphatase: 343; GAMAGT: 836); hematological disorders (Hb: 9.9/ MCV: 74/ HCM: 28/ Leukocytes: 9,640/ eosinophils: 400/ platelets: 139,000); amylase: 102; lipase: 46; Serology: HIV and syphilis (FTABS and VDRL): non-reactive, HbsAg: non-reactive, Anti-Hbc: non-reactive, Anti-Hbs: reactive (previous vaccination); Anti-HCV: non-reactive, hepatitis A IgG: reactive and IgM: non-reactive; Epstein Baar: Non-reactive IgM; Toxoplasmosis: IgG reactive and IgM non-reactive; HTLV I and II: Non-reactive; Cytomegalovirus: IgG reactive and IgM non-reactive; Leptospirosis IgM: non-reactive; Varicella Zoster: Non-reactive IgM and reactive IgG; RT-PCR for dengue, chiungunya and zika virus: non-reactive; C-reactive protein: 2.02; Uric acid: 9.7; corrected calcium: 8.02; serum phosphorus: 7.8; serum potassium: 6.7; serum sodium: 113; ferritin: 6,866; serum iron: 288; Serum lithium: 0.1; Anti LKM antibody: non-reactive, anti-smooth muscle antibody: non-reactive; direct Coombs test: negative; Lactate Dehydrogenase: 492; PTH: 30.7. Magnetic resonance cholangiography showed signs of acute hepatitis; Thick bile in the bile ducts and gallbladder suggesting mild cholestasis associated with the inflammatory process and slight increase in the caliber of the common bile duct and bile ducts; Globose kidneys with an appearance of acute nephropathy and small bilateral pleural effusion.

Due to significant changes in the admission exams, the patient was referred to the Intensive Care Unit, where he was evaluated by the nephrology team, which indicated intermittent hemodialysis. During the following days, the patient developed daily fever peaks > 38.5°C, as well as worsening in laboratory tests, such as: Total bilirubins: 62.1; right bilirubin: 39.3; indirect bilirubin: 22.8; ferritin: 17,857; Triglycerides: 476; alkaline phosphatase: 773; GT range:1661; albumin: 2.1; Heb: 7:4; Leukocytes: 8,340; eosinophils: 2,080; platelets 170,000; C-reactive protein: 2.55; Blood cultures (2 samples): negative; Uroculture: negative. Patient presented HScore with a score: 189 points - Probability of Hemophagocytic of 70-80% and RegiSCAR DRESS: 6 points - definitive diagnosis. The patient remained hemodynamically stable and with normal vital signs, despite the worsening seen in laboratory tests. To complement the diagnostic investigation, a myelogram was performed, which showed hypercellular bone marrow with eosinophilia, mild plasmacytosis, and no signs of hemophagocytosis were found. In view of the clinical history, laboratory tests, HScore: 189 points and RegiScar: 6 points, the diagnostic hypothesis of Hemophagocytic

Syndrome secondary to DRESS syndrome related to the use of anticonvulsant (valproic acid) of recent onset was suggested. Therefore, treatment with prednisone 1mg/kg/day was initiated. After 10 days of corticosteroid use, the patient evolved with gradual clinical and laboratory improvement, such as: Total bilirubins: 8.3; direct bilirubin: 5.2; indirect bilirubin: 2.1; triglycerides: 65; creatinine: 1.7; urea 50; blood count: Hb 8.0; leukocytes: 9,870; eosinophils: 20; platelets 230,000; ferritin: 4,211; Albumin: 3.5. However, after this period, the patient presented subfebrile episodes associated with laboratory increases in hepatic transaminases (AST/ALT), alkaline phosphatase, and GAMAGT. Therefore, research for opportunistic infectious diseases was performed and PCR for cytomegalovirus was found with 73,000 IU/mL. Due to cytomegalovirus reactivation after initiation of prednisone, treatment with intravenous ganciclovir was initiated. Currently, the patient is in a ward unit, under daily renal and hepatic surveillance, evolving with significant clinical and laboratory improvement, without the need for dialysis, with gradual weaning from prednisone and finishing treatment for cytomegalovirus reactivation. In addition, it presents a hospital discharge schedule for the next few days with continuity of care in outpatient returns.

5 DISCUSSION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a serious and potentially fatal adverse reaction, with a mortality rate ranging from 2% to 10%, and is considered a dermatological urgency. DRESS is estimated to occur in 0.9 to 2 per 100,000 patient-years, and the main medications related to DRESS include: aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital, lamotrigine); sulfonamides; NSAID; antibiotics; allopurinol and antiretrovirals. The pathophysiological mechanism is not yet exactly known, however, there are three essential components: I) Presence of genetic susceptibility (HLA); II) **Presence of** alterations in drug metabolism pathways; III) Presence of reactivation of the virus of the Herpesviridae family, which may occur in up to 75% of patients. The clinical presentation is characterized by cutaneous involvement, (morbilliform rash with cephalocaudal progression, evolving to purpuric and desquamative lesions), hepatitis and liver failure (liver injury is the most common visceral manifestation of DRESS and the main cause of death), lymphocytic interstitial pneumonia, pleuritis, interstitial nephritis, hematuria, proteinuria, renal failure, carditis (severe complication and with poor prognostic factor), peripheral neuropathy, eosinophilia, lymphocytosis with atypia, fever and lymph node enlargement. The most commonly used diagnostic criterion is RegiSCAR : Fever >38.5°C,

enlarged lymph nodes in at least two different areas of the body, Eosinophilia, Atypical lymphocytes, skin involvement, organ involvement, resolution >15 days. Score 2-3: probable cases; score 4-5: possible cases; score > 5: definitive diagnosis. Early recognition as well as immediate discontinuation of the causal medication are essential for clinical and therapeutic response in DRESS. In milder cases, topical corticosteroids and antihistamines may be considered. In more severe cases, with significant multivisceral involvement, the use of systemic corticosteroids can be considered until clinical improvement and laboratory normalization, with a reduction in the dose in the following 8 to 12 weeks, to avoid relapses.

Hemophagocytic syndrome (HPS) is characterized by excessive inflammation resulting from a failure in the normal regulatory mechanisms of macrophages and lymphocytes, leading to tissue damage due to uncontrolled immune activation. Hemophagocytosis is characterized by the presence of red blood cells, platelets, white blood cells or fragments of these cells, within the cytoplasm of macrophages causing cytopenias, however, hemophagocytosis alone is neither pathognomonic nor necessary for diagnosis. HPS may be related to infection (EBV, cytomegalovirus, varicella zoster virus), cancer (especially lymphomas), rheumatologic disorder (systemic juvenile idiopathic arthritis, Sjogren's disease, vasculitis, systemic lupus erythematosus), or an alteration in homeostasis. Clinical and laboratory manifestations include: hepatitis with elevated transaminases, fever, splenomegaly, encephalitis, increased lactate dehydrogenase (LDH) and bilirubins, elevated D-dimer and triglycerides, hypofibrinogenemia, hematological disorders, exacerbated increase in ferritin, presence of hemophagocytosis in the bone marrow or other tissues. The diagnosis can be made by the HLA-2024 criteria, and the diagnosis is established in the presence of at least 5 of the 8 criteria: 1) fever> 38.5°C; 2) splenomegaly; 3) cytopenias (two or more of the following: Hb <9 g/dL, platelets < 100,000, neutrophils < 1,000); 4) triglycerides >265 mg/dL and/or fibrinogen <150 mg/dL; 5) ferritin >500 g/mL; 6) Soluble CD25 >2,400 u/mL; 7) presence of hemophagocytosis in the bone marrow or other tissues. The Hscore was developed in 2014 to assess secondary hemophagocytic syndrome in adults and presents the following criteria: fever, organomegaly, immunosuppression, increased serum ferritin, elevated triglycerides and AST, low fibrinogen, cytopenias, and hemophagocytosis in the bone marrow or other tissues. The total score ranges from 0 to 337. A cut-off point of 169 offers good sensitivity and specificity, correctly classifying about 90% of cases. In the case reported, in the HLA-2024 criteria, the patient scored 4 items out of the 8 total, as well as an Hscore with a score: 189 points with a Probability of Hemophagocytic of 70-80%. The

treatment of HPS is stratified according to the patient's clinical condition and takes into account the triggering factor (infection, neoplastic disease, autoimmune diseases). In stable patients, treatment of the underlying disease is recommended. In severe cases or cases with clinical deterioration, high-dose corticosteroids (prednisone, methylprednisone, dexamethasone) can be used in association with etoposide. In cases with central nervous system involvement, Etoposide, intrathecal methotrexate and preferably dexamethasone (crosses the blood-brain barrier) are used.

6 FINAL CONSIDERATIONS

The case reported here highlights the importance of clinical and theoretical knowledge about the associations between rare syndromes, such as hemophagocytic syndrome related to DRESS syndrome. Clinical suspicion, early diagnosis, and timely treatment are essential for better clinical outcomes, since these associated conditions have a higher probability of unfavorable and sometimes fatal outcome. It is noteworthy that, in the case reported, both the diagnosis and the treatment were carried out at an opportune time, contributing to the improvement of the clinical condition and the therapeutic success of the patient.

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