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Sulfasalazine: Adverse Effects and Literature Review - Case Report

Christian Camilo Lasso Maldonado
Universidad del Rosario
Escuela de Medicina y Ciencias de la Salud – Fundación Santa Fe de Bogotá
Programa Medicina de Emergencias
Bogotá D.C. – Colombia

Dalyla Leal Vargas
Specialist in Internal Medicine
Universidad de los Andes – Fundación Santa Fe de Bogotá
Bogotá D.C. - Colombia

Abstract:- DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) is a very rare and potentially fatal drug-induced delayed hypersensitivity syndrome. We present the case of a 60-year-old woman who had been on sulfasalazine for 2 months to treat rheumatoid arthritis. She was admitted for 4 days presenting a pruriginous maculopapular erythema predominantly on the trunk and fever of 39.5 °C. Blood tests showed marked eosinophilia (800/mm3), a cholestatic pattern, and severe inflammation. Sulfasalazine-induced DRESS syndrome was diagnosed.

Keywords:- *"DRESS Syndrome", "Sulfasalazine Induced DRESS Syndrome", "Sulfasalazine Adverse Effects", "Sulfasalazine"*

I. CASE REPORT

60-year-old woman with seropositive rheumatoid arthritis diagnosed on tocilizumab treatment with persistent polyarthralgias and functional limitation. Since 20 days ago with additional management with sulfasalazine who after its initiation presents fine maculopapular exanthema scarce in thorax and extremities associated in the last 4 days with febrile peaks quantified up to 39.5 degrees predominantly at night with increased arthralgia of the right knee and local edema for which she consults. Physical examination: normal vital signs with few papular lesions in lower limbs and thorax with marked edema in the right knee with limited arc of movement, without other alterations.

Paraclinical admission with hemogram with leukocytes of 7800/mm3 with eosinophils of 800/mm3 (9.7%) with marked elevation of inflammatory reactants (C-reactive protein: 9,626 mg/dl, erythrocyte sedimentation: 47 mm/hour), altered liver profile with discrete elevation of bilirubins (total bilirubin 1. 46 mg/dl direct bilirubin 0.60 mg/dl indirect bilirubin 0.86 mg/dl, alkaline phosphatase 384 u/l, gamma glutamyl transferase: 445 u/l, lactate dehydrogenase: 247 u/l and elevated liver enzymes (aspartate aminotransferase: 128u/l, alanine aminotransferase: 135u/l), Laboratory studies are presented in Table 1. Due to the presence of a cholestatic pattern, liver ultrasound was performed, documenting cholelithiasis without signs of cholecystitis or choledocholithiasis by cholangioresonance. She was evaluated by the orthopedics department with knee imaging, who ruled out the presence of septic arthritis, so it was decided not to start antibiotic therapy.

Table 1. Summary Laboratory tests at Diagnosis

Paraclínicos				
	Dia 1	Dia 2	Dia 3	Dia 5
Conteo Absoluto Eosinófilos	800/mm3	300/mm3	500/mm3	500/mm3
Bilirrubina Total	1,46mg/dL	1,28mg/dL	1,24mg/dL	1,08 mg/dL
AST	128 u/l	56 u/l	74 u/l	143 u/l
ALT	135 u/l	85 u/l	83 u/l	135 u/l
GGT	447 u/l	445 u/l	536 u/l	-

Reevaluating her recent clinical and pharmacological history, it was decided to suspend sulfasalazine, and she evolved with disappearance of the skin lesions and no new febrile peaks, modulation of eosinophils and acute phase reactants and normalization of the hepatic profile. See table 1. Due to the persistence of joint symptoms, management was continued with Leflunomide and close monitoring of liver function.

II. DISCUSSION

Sulfasalazine is an anti-inflammatory drug used in the treatment of inflammatory bowel disease, rheumatoid arthritis, spondyloarthropathies, psoriasis and psoriatic arthritis (1). It is a prodrug composed of sulfapyridine (antibacterial action) joined by a covalent bond to 5-aminosalicyclic acid (5-ASA) (anti-inflammatory action), which in rheumatoid arthritis acts

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as a disease-modifying drug (DMARD), reducing inflammation and joint pain while preventing joint damage.

It is a drug that is absorbed in the intestinal lumen where it acts locally to hydroxylate initially at the hepatic level (phase 1 reaction) and subsequently acetylate (phase 2 reaction), to allow its excretion at the renal level (2). The speed with which sulfapyridine is acetylated at the hepatic level is genetically determined; patients can be classified as slow or fast acetylator phenotypes. This is of great importance in its adverse effects since the slow acetylation phenotype has been associated with a higher risk of DRESS (6).

DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) is a severe systemic adverse reaction, rare (1/1,000-10,000 exposures) (8) and potentially fatal, induced mainly by anticonvulsants, antibiotics and sulfonamides, including sulfasalazine, which produces "week three sulfasalazine syndrome". It is also related to predisposing factors such as reactivation of viral infections (14,15). See Table 2.

Its time of presentation is 4 to 8 weeks after exposure to the drug (4,10) and it has been found that the main cells involved in the systemic and cutaneous inflammation generated by this syndrome are activated lymphocytes in 30% of the cases (CD4+ T and cytotoxic T) and eosinophils in 95%. (8)

Table 2. Predisposing Factors

Virus relacionados con Síndrome de DRESS
Virus herpes humano [VHH] 6 y 7,epstein Barr, citomegalovirus
Fármacos asociados con Síndrome de DRESS
- Anticonvulsivantes: Carbamazepina, fenobarbital, fenitoína, ácido valproico, lamotrigina - Sulfonamidas: Sulfasalazina, sulfadiazina, dapsona. - Antibióticos: Amoxicilina, vancomicina, minociclina, trimetoprim-sulfametoxazol, ampicilina/sulbactam - Alopurinol

We present and discuss a clinical case of the development of DRESS syndrome in relation to sulfasalazine use.

DRESS syndrome has a heterogeneous clinical presentation, which typically presents with diffuse maculopapular rash >50% of the body surface and may be associated with facial and periorbital edema, fever, pruritus, cervical lymphadenopathy, axillary or inguinal lymphadenopathy, and multiorgan involvement, mainly hepatitis (50%), nephritis (10%) and pneumonitis (10%) (9,10), while it can generate peripheral eosinophilia (≥700/mm3) and/or atypical lymphocytosis (30%)(4,9). In the case of our patient, approximately 3 weeks after starting sulfasalazine, she developed morbilliform exanthema and febrile peaks, and laboratory studies showed eosinophilia, alteration of the hepatic profile of inflammatory type and elevation of C-reactive protein and erythrocyte sedimentation rate, which led to suspect the relationship of the symptoms with hypersensitivity to the drug.

The cutaneous involvement in DRESS syndrome is very variable; therefore, the differential diagnoses are very broad, including viral infections (infectious mononucleosis, HIV), Steven-Johnson syndrome, toxic epidermal necrolysis, toxic shock syndrome, Kawasaki disease and Still's disease (10). In our patient, obstructive biliary involvement was ruled out in parallel due to the presence of cholestatic pattern, without finding obstruction of the biliary tract, hepatosplenomegaly or active infectious processes.

There is currently no Gold standard for the diagnosis of DRESS syndrome, but Kardaun and collaborators proposed a diagnostic tool based on the most frequent clinical manifestations and laboratory parameters, establishing whether the syndrome is an absent, possible, probable or definitive diagnosis (Table 3); however, this score is not designed to exclude other diseases with similar manifestations, so it must be applied in patients with high suspicion (10).

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Table 3. The RegiSCAR scoring system for diagnosing DRESS syndrome

Criterios diagnósticos RegiSCAR para síndrome de DRESS			
Característica	**Presente**	**Ausente**	**Desconocido**
Fiebre (> 38,5°C)	0	-1	-1
Aumento tamaño lindadenopatias (≥ 2 sitios, > 1 cm)	1	0	0
Linfocitos atípicos	1	0	0
Eosinofilia			
• 700 - 1.499 o 10% - 19,9% del recuento de glóbulos blancos	1		
• > 1.500 o > 20% del recuento de glóbulos blancos	2		
Eritema cutáneo		0	0
• Extensión > 50%	1	0	0
• Eritema sugerente de DRESS (≥ 2 de edema, infiltración, púrpura o descamación)	1	-1	0
• Biopsia sugerente de DRESS	0	-1	0
Compromiso de órganos internos		0	0
• Uno	1		
• Dos o más	2		
Resolución del exantema > 15 días	0	-1	-1
Evaluación negativa de otras potenciales causas: (ANA; hemocultivos; virus hepatitis A,B,C; Chlamydia, Micoplasma)	1	0	0
Puntaje final: < 2 = no; 2 – 3 = posible; 4 – 5 = probable; > 5= definitivo			
Tomado y modificado de Kardaun y cols, Registro Europeo de Reacciones Adversas Cutáneas Graves (RegiSCAR) (10)			

Comparing our findings with the validated diagnostic criteria Project/RegiSCAR score (Table 3), a probable diagnosis of drug reaction syndrome with eosinophilia and systemic symptoms (DRESS) related to sulfasalazine therapy was established, with a RegiSCAR score of 4 (fever = 1, rash = 1, eosinophilia = 1, organ involvement = 1), and the associated drug was immediately discontinued.

During the patient's follow-up, the disappearance of her skin lesions, modulation of the febrile peaks on the second day of sulfasalazine withdrawal and the modulation of the inflammatory response and eosinophilia on the third day of withdrawal of the drug, as well as the normalization of the hepatic profile, were evidenced.

The treatment of Dress's syndrome is not standardized at present; the first measure should be immediate discontinuation of the drug suspected of inducing the reaction. Glucocorticoids remain the most commonly used agents, although doses vary widely among case reports; better response has been seen in moderate and severe cases, mainly associated with organ dysfunction, usually administered at high doses of prednisolone and methylprednisolone (0. 5 to 1 mg/kg/day). Second-line treatment in refractory cases includes cyclosporine, cyclophosphamide, mycophenolate mofetil, intravenous immunoglobulin or plasmapheresis, depending on the clinical manifestations of the patient. However, the use of these measures is controversial, is not validated by controlled studies and is based on case series and expert opinions (11, 12).

III. CONCLUSION

DRESS syndrome is a condition associated with the use of some drugs and viral infections, which although rare, should be considered as a differential diagnosis in adults with mild to severe fever and exanthema. It has a varied clinical spectrum, but knowledge of the patient's drug history and clinical suspicion is essential to improve detection. Once infectious causes are ruled out, systemic corticosteroids appear to modulate the reaction, reducing duration and severity. However, as evidenced in our patient, the inflammatory modulation was progressive once sulfasalazine was discontinued and corticosteroids were not required.

ETHICAL CONSIDERATIONS

The patient signed a written informed consent in which he agreed to the use of his clinical data for the publication of this clinical case. Data anonymity was assured at all times.

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CONFLICT OF INTEREST

None declared by the authors.

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