

Liver transplantation after DRESS syndrome: a case report and review of the literature

Igor Calil¹, FRANCISCO TUSTUMI², Rafael Pinheiro¹, Ryan Tanigawa², Jorge de Sousa¹, Ruy Cruz Junior², Luiz D’Albuquerque², and Rafael Pecora¹

¹Hospital Israelita Albert Einstein

²Universidade de Sao Paulo Hospital das Clinicas

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Abstract

Drug reaction with eosinophilia and systemic symptoms is a quite unusual condition related to drug reaction. A case report of sulfasalazine-induced liver failure is described. The patient was submitted to liver transplantation. Liver transplantation is an option when DRESS is associated with acute liver failure, but the prognosis remains poor.

KEY CLINICAL MESSAGE

This study describes a patient with drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), associated with liver failure.

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) is a quite unusual condition related to drug reaction.¹ Several drugs have been linked to DRESS. It is a severe idiosyncratic drug reaction characterised by erythematous or papulo-pustular skin eruption associated with lymphadenopathy, fever, and visceral involvement (hepatitis, nephritis pneumonitis, pericarditis, myocarditis, and colitis).²⁻⁶ Leucocytosis, eosinophilia (90%) and/or mononucleosis (40%) also may be seen.⁶ Severe acute hepatitis due to sulfasalazine or Trimethoprim-sulfamethoxazole is described in literature, but the occurrence of DRESS and liver failure is rare.

In this study, we report a patient with acute liver failure due to sulfasalazine-induced DRESS, treated with liver transplant.

CASE REPORT

An 18-year-old male patient was treated for toxoplasma retinochoroiditis with sulfasalazine, along one month. The patient had no past history of allergies or drug intolerance. He presented in a local hospital with fever, vomiting, cervical and inguinal nodules, abdominal pain, and macular rash on all body. The patient was transferred to our Transplant Center after onset of jaundice and encephalopathy. He was admitted in intensive care unit with facial edema, generalized scaling exanthema and acute hepatitis. Serological tests for viral hepatitis and all autoimmune antibodies were negative. Laboratory tests showed a total eosinophil count of 3220/mm³ (normal, <500 mm³), high level of transaminases (AST=1303 IU/L; ALT=1768 IU/L, lactate dehydrogenase level of 2274 IU/L (normal, 240 to 480 IU/L), total bilirubin level of 18.47mg/dL, direct bilirubin level of 14.81mg/dL, prothrombin time (PT) international normalized ratio (INR) of 5.18, and Factor V 17%. Abdominal ultrasound examination identified no cronical liver disease. The RegiSCAR⁷

system scored 5 points confirming the diagnosis of DRESS. Skin biopsy observed Interface and spongiotic dermatitis, consistent with drug eruption.

Therefore, the patient was worked up for urgent orthotopic liver transplantation (OLT), which was performed 24 hours after admission. At this time he was under corticosteroids and clinical support, including mechanic ventilation due progressive encephalopathy and dialysis due latic acydosis.

The orthotopic liver transplantation was uneventfull. Even though liver function improved in postoperative period, the patient developed sepsis requiring high doses of vasopressors. Broad-spectrum antibiotics were introduced but patient remained hemodynamic unstable. The patient died at 7th postoperative day. Blood cultures showed growth of a *Klebsiella pneumoniae* resistant to carbapenems.

Liver and Skin histology

The histology analysis demonstrated massive eosinophils infiltrate compatible with DRESS and the liver explant presented a massive necrosis associated with eosinophilic infiltration (Figure 1 and 2).

DISCUSSION

The present report describes an adult patient with DRESS syndrome and liver failure treated with OLT. Liver failure in the setting of DRESS syndrome is quite rare. Few case reports presented patients with DRESS syndrome and high level of hepatic injury (Table 1). In these studies, most of the patients were treated with corticosteroids⁸⁻²⁹.

The management of DRESS syndrome is challenging. It is important to withdraw the suspected drug and the delay is associated with poorer outcomes.³⁰⁻³² Supportive therapy in intensive care unit should be provided to stabilize the patient. Early administration of systemic corticosteroid therapy is generally recommended.³³ Systemic corticosteroid helps to improve in both clinical symptoms and laboratory abnormalities within days.³³ Most of the cases reports of DRESS syndrome with liver dysfunction showed success with corticosteroids treatment (Table 1).

Liver transplantation is an option when DRESS is associated with acute fulminant hepatic failure, but the prognosis remains poor (Table 2)³⁴⁻³⁹. Besnard et al.³⁴ reported two pediatric Crohn's disease patients undergoing liver transplantation after DRESS syndrome induced by sulfasalazine. During follow-up, one of them developed acute rejection and fatal aspergilosis. Song et al.³⁷ reported living-donor liver transplantation in a 14-years old patient. Patient presented chronic rejection after 25-months follow-up. Amante et al.³⁵ and Roales-Gómez et al.³⁸ reported adult patients treated with OLT, with no information concerning long-term follow-up. Mennicke et al.³⁶ reported an adult patient treated with OLT, with mortality in postoperative period due to massive intrabdominal blood loss.

Recent studies support the use of Molecular Adsorbents Recirculation System (MARS) as a rescue for patients with liver failure. Roales-Gómez et al.³⁸ described MARS use, although patient did not respond well, and patient was eventually submitted to OLT. Ng et al.²³ reported a pediatric patient that underwent MARS in the intensive care unit, with satisfactory response.

The present study showed a patient with Sulfasalazine and Trimethoprim-sulfamethoxazole severe reaction. Sulfasalazine and Trimethoprim-sulfamethoxazole carries a significant risk of drug toxicity. Yusuf et al.²⁴ reported the first case of DRESS syndrome in a child treated for toxoplasma retinochoroiditis. Rare cases of immunologic reactions to sulfasalazine, including DRESS syndromes, have been reported, such as the classic "3-week sulfasalazine syndrome" occurring 3 weeks after the first administration.⁸

CONCLUSION

DRESS associated with acute liver failure is a life-threatening condition. Liver transplantation is an option for the management of these patients, although the prognosis remains poor.

AUTHORS CONTRIBUTIONS:

- Igor Lepski Calil³, PhD: (analysis and interpretation of data)
- Rafael Soares Nunes Pinheiro¹, PhD: (acquisition of data and drafting the article)
- Ryan Yukimatsu Tanigawa², MD: (paper drafting)
- Francisco Tustumi¹, PhD: (paper drafting)
- Rafael Antônio Arruda Pecora³, PhD: (revising the paper critically for relevant intellectual content)
- Ruy Jorge Cruz Junior¹, MD: (revising the paper critically for valuable intellectual content)
- Luiz Augusto Carneiro D’Albuquerque¹, PhD: (conception and design of the study)
- Orlando de Castro e Silva Júnior¹ PhD: (final approval of the version to be submitted)

REFERENCES

1. Newell BD, Moinfar M, Mancini AJ, Nopper AJ. Retrospective analysis of 32 pediatric patients with anticonvulsant hypersensitivity syndrome (ACHSS). *Pediatr Dermatol* 2009;26:536-46.
2. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms: DRESS). *Semin Cutan Med Surg* 1996;15:250-7.
3. Naisbitt DJ, Britschgi M, Wong G et al. Hypersensitivity reactions to carbamazepine: characterisation of the specificity, phenotype and cytokine profile of drug-specific T-cell clones. *Mol Pharmacol* 2003; 63: 732-41.
4. Naisbitt DJ, Farrell J, Wong G et al. Characterisation of drug-specific T cells in lamotrigine hypersensitivity. *J Allergy Clin Immunol* 2003 ; 111: 1393-403.
5. Eland IA, Dofferhoff AS, Vink R, Zondervan PE, Stricker BH. Colitis may be part of the antiepileptic drug hypersensitivity syndrome. *Epilepsia* 1999; 40: 1780-83.
6. Callot V, Roujeau JC, Bagot M et al. Drug induced pseudolymphoma and hypersensitivity syndrome. Two different clinical entities. *Arch Dermatol* 1996; 132: 1315-21.
7. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* . 2007;156:609-611.
8. Brooks H, Taylor HG, Nichol FE (1992) The three week sulphasalazine syndrome. *Clin Rheumatol* 11:566-568
9. Queyrel V, Catteau B, Michon-Pasturel U, Fauchais AL, Delcey V, Launay D, Legout L, Hachulla E, Hatron PY, Devulder B. DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) syndrome after sulfasalazine and carbamazepine: report of two cases. *Rev Med Interne*. 2001 Jun;22(6):582-6.
10. Mainra, RR, Card, SE. Trimethoprim-sulfamethoxazole-associated hepatotoxicity - part of a hypersensitivity syndrome. *Can J Clin Pharmacol*. 2003 Winter;10(4):175-8.
11. Descloux E, Argaud L, Dumortier J, Scoazec JY, Boillot O, Robert D. Favourable issue of a fulminant hepatitis associated with sulfasalazine DRESS syndrome without liver transplantation. *Intensive Care Med*. 2005 Dec;31(12):1727-8
12. Michel, F, Navellou, JC, Ferraud, D, Toussiro, E, Wendling, D. DRESS syndrome in a patient on sulfasalazine for rheumatoid arthritis. *Joint Bone Spine*. 2005 Jan;72(1):82-5.
13. Teo L, Tan E. Sulphasalazine-induced DRESS. *Singapore Med J* 2006; 47(3):237-239
14. Bejia I, Ben Hammouda S, Riahi K, Zinelabidine F, Mediouni B, Touzi M, Bergaoui N. DRESS syndrome induced by sulphasalazine in rheumatoid arthritis. *Joint Bone Spine* . 2006 Dec;73(6):764-5.
15. Aquino RT, Vergueiro CS, Magliari ME, de Freitas TH. Sulfasalazine-induced DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms). *Sao Paulo Med J*. 2008 Jul;126(4):225-6.
16. Augusto JF, Sayegh J, Simon A, Croue A, Chennebault JM, Cousin M, Subra JF. A case of sulphasalazine-induced DRESS syndrome with delayed acute interstitial nephritis. *Nephrol Dial Transplant*. 2009 Sep;24(9):2940-2.
17. Yeşilova, Z, Kantarcioğlu, M, Erçin, CN, Safalioğlu, M, Kilciler, G, Koç, E, Atli, M, Uygün, A. Sulfasalazine-induced hypersensitivity: a case report of DRESS syndrome. *Turk J Gastroenterol*. 2009 Dec;20(4):298-9
18. Rosenbaum J, Alex G, Roberts H, Orchard D. Drug rash with eosinophilia and systemic symptoms secondary to sulfasalazine. *J Paediatr Child Health* . 2010 Apr;46(4):193-6.
19. van der Mark SC¹, Segers D, Bakker RC, van Wijngaarden, P. DRESS syndrome as a result of sulfasa-

lazine use. *Ned Tijdschr Geneeskd.* 2010;154(18):A2161

20. Piñana E, Lei SH, Merino R, Melgosa M, De La Vega R, Gonzales-Obeso E, Ramirez E, Borobia A, Carcas A. DRESS-syndrome on sulfasalazine and naproxen treatment for juvenile idiopathic arthritis and reactivation of human herpesvirus 6 in an 11-year-old Caucasian boy. *J Clin Pharm Ther.* 2010 Jun;35(3):365-70
21. Lau G, Kwan C, Meng Chong S (2001) The 3-week sulphasalazine syndrome strikes again. *Forensic Sci Int* 122:79–84.
22. Daoulah A, Alqahtani AA, Ocheltree SR, Alhabib A, Ocheltree AR. Acute myocardial infarction in a 56-year-old female patient treated with sulfasalazine. *Am. J Emerg Med.* 2012 May;30(4):638.e1-3.
23. Ng CT, Tan CK, Oh CC, Chang JP. Successful extracorporeal liver dialysis for the treatment of trimethoprim-sulfamethoxazole-induced fulminant hepatic failure. *Singapore Med J.* 2013 May 1;54(5):e113-6.
24. Yusuf IH, Sahare P, Hildebrand GD. DRESS Syndrome in a child treated toxoplasma retinochoroiditis. *J AAPOS.* 2013 Oct;17(5):521-3
25. Girelli,F, Bernardi,S, Gardelli,L, Bassi,B, Parente,G, Dubini,A, Serra,L, Nizzoli,MA New Case of DRESS Syndrome Induced by Sulfasalazine and Triggered by Amoxicillin. *Case Rep Rheumatol.* 2013;2013:409152.
26. Hernández,N, Borrego,L, Soler,E, Hernández,J. Sulfasalazine-induced linear immunoglobulin A bullous dermatosis with DRESS. *Actas Dermosifiliogr.* 2013 May;104(4):343-6.
27. Zaiem A, Aouinti I, Lakhoua G, Sahnoun R, Daghfous R, Lakhali M, El Aïdli S. Sulfasalazine-induced DRESS syndrome associated with Epstein Barr virus reactivation. *Therapie .* 2013 Sep-Oct;68(5):321-3.
28. Ferrero, NA, Pearson KC, Zedek DC, Morrell DS. Case report of drug rash with eosinophilia and systemic symptoms demonstrating human herpesvirus-6 reactivation. *Pediatr Dermatol.* 2013 Sep-Oct;30(5):608-13.
29. Pirklbauer,M, Gruber,J. DRESS syndrome following sulfasalazine treatment. *Z. Rheumatol.* 2014 Mar;73(2):180-3.
30. Bachot N, Roujeau JC. Differential diagnosis of severe cutaneous drug eruptions. *Am J Clin Dermatol* 2003;4:561-72.
31. Tas S, Simonart T. Drug rash with eosinophilia and systemic symptoms (DRESS syndrome). *Acta Clinica Belgica* 1999;54: 197-200.
32. Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. *Dermatology*2003;206:353-6.
33. Chiou CC, Yang LC, Hung SI, Chang YC, Kuo TT, Ho HC, et al. Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. *J Eur Acad Dermatol Venereol* 2008;22: 1044-9.
34. Besnard M, Debray D, Durand P, Cezard JP, Navarro J (1998) Sulfasalazine-induced fulminant hepatitis in pediatric Crohn's disease: report of two cases. *J Pediatr Gastroenterol Nutr*26:119–120.
35. Amante MF, Filippini AV, Cejas N, Lendoire J, Inventarza O, Parisi C. Dress syndrome and fulminant hepatic failure induced by lamotrigine. *Ann Hepatol.* 2009 Jan-Mar;8(1):75-7.
36. Mennicke M, Zawodniak A, Keller M, Wilkens L, Yawalkar N, Stickel F, Keogh A, Inderbitzin D, Candinas D, Pichler WJ. Fulminant liver failure after vancomycin in a sulfasalazine-induced DRESS syndrome: fatal recurrence after liver transplantation. *American journal of transplantation.* 2009 Sep;9(9):2197-202.
37. Song SM, Cho MS, Oh SH, Kim KM, Park YS, Kim DY, Lee SG. Liver transplantation in a child with acute liver failure resulting from drug rash with eosinophilia and systemic symptoms syndrome. *Korean J Pediatr* 2012;56(5):224-226
38. Roales-Gomez V, Molero AI, Perez-Amarilla I, Casabona-Frances S, Rey-Diaz-Rubio E, Catalan M, Vanaclocha F, Colina F DRESS syndrome secondary to ibuprofen as a cause of hyperacute liver failure. *Rev Esp Enferm Dig.* 2014 Aug;106(7):482-6.

Case Report	Patient	Drug	Treatment	Follow up
Brooks H et al ¹⁶	53-year-old man	Sulfasalazine	corticosteroids	Alive

Case Report	Patient	Drug	Treatment	Follow up
Queyrel V et al ³⁵	15-year-old woman	Sulphasalazine	corticosteroids	Alive
Mainra RR et al ³⁶	24-year-old woman	Trimethoprim-sulfamethoxazole	corticosteroids	Alive
Descloux E et al ³⁷	45-year-old woman	Sulphasalazine	corticosteroids	Alive
Michel F et al. ³⁸	63-year-old woman	sulfasalazine	corticosteroids	Alive
Teo L et al ¹⁴	49-year-old woman	Sulphasalazine	corticosteroids	Alive
Bejia I et al ³⁹	46-year-old woman	Sulphasalazine	corticosteroids	Alive
de Aquino RT et al ⁴⁰	47-year-old woman	Sulphasalazine	corticosteroids	Alive
Augusto JF et al ⁴¹	77-year-old woman	Sulphasalazine	corticosteroids	Alive
Yeşilova Z et al ⁴³	38-year-old man	Sulphasalazine	corticosteroids	Alive
Rosenbaum, J et al. ⁴⁴	11-year-old woman	Sulphasalazine	corticosteroids	Alive
van der Mark SC et al ⁴⁵	24-year-old woman	Sulphasalazine	corticosteroids	Alive
Piñana E et al ⁴⁶	11-year-old boy	Sulphasalazine /Naproxen	corticosteroids	Alive
Lau G et al ¹⁷	34-year-old woman	Sulphasalazine	corticosteroids	Died
Daoulah A et al ⁴⁷	56-year-old woman	Sulphasalazine	corticosteroids	Died
Ng CT et al ⁴⁸	17 year-old male	Trimethoprim-sulfamethoxazole	MARS	Alive
Yusuf IH et al ¹⁵	15-year-old girl	Sulphasalazine	corticosteroids	Alive
Girelli F et al ⁴⁹	53-year-old woman	Sulfasalazine/Amoxicillin	corticosteroids	Alive
Hernández N et al ⁵⁰	60-year-old woman	Sulphasalazine	corticosteroids	Alive
Zaiem A et al ⁵¹	45-year-old woman	Sulphasalazine	corticosteroids	Alive
Ferrero NA et al ⁵²	15-year-old boy	Sulphasalazine	corticosteroids	Alive
Pirklbauer M et al ⁵³	A 53-year-old woman	Sulphasalazine	corticosteroids	Alive

Table 1. Reported cases who had diagnosis of DRESS caused by associated Sulfasalazine and Trimethoprim-sulfamethoxazole

Case Report	Patient	Drug	Follow up
Besnard M et al ¹⁸	10-year-old male	Sulfasalazine	Died
Besnard M et al ¹⁸	10-year-old female	Sulfasalazine	Alive
Amante MF et al ⁵⁴	21-year old female	lamotrigine	Unknown
Mennicke M et al ⁴²	60-year-old male	Sulfasalazine/vancomycin	Died

Case Report	Patient	Drug	Follow up
Song S et al ⁵⁵	14-year-old female	Vancomycin	Alive
Roales-Gómez V et al ⁵⁶	22-year-old male	Ibuprofen	Alive
Present study	18-year-old male	Sulfamethoxazole	Died

Table 2. Patient diagnosed with DRESS undergoing liver transplantation.

Caption

Figure 1. Liver Histology. H&E stain. Massive eosinophils infiltrate with extensive necrosis of the liver compatible with fulminant hepatitis.

Figure 2. Skin Histology. H&E stain. Massive eosinophils infiltrate compatible with DRESS



