Hydroxychloroquine and Leflunomide Induced DRESS Syndrome: A Case Report

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ABSTRACT

Background: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a rare but potentially life-threatening hypersensitivity reaction characterized by fever, rash, eosinophilia, and internal organ involvement, typically emerging several weeks after exposure to certain medications. Its diagnosis and management pose significant clinical challenges, especially when compounded by overlapping autoimmune and infectious complications.

Case Presentation: This case report describes a 37-year-old female with rheumatoid arthritis who developed DRESS syndrome after initiating hydroxychloroquine and leflunomide therapy. Skin biopsy showed perivascular lymphocytic infiltrates with pigment incontinence, confirming drug-induced hypersensitivity. Laboratory tests revealed eosinophilia, elevated transaminases, and positive Leptospira IgM. The condition was complicated by autoimmune hepatitis (positive anti-smooth muscle antibody), recurrent DRESS episode, gastrointestinal and urinary tract infections (sepsis). Initial treatment with corticosteroids, cyclosporine and prompt withdrawal of the offending drugs led to temporary improvement, but rapid steroid tapering and HCQ re-challenge precipitated relapse. The patient required a multidisciplinary approach including immunosuppressants, IV immunoglobulin, hepatoprotective agents, antibiotics, electrolyte correction, and total parenteral nutrition. Gradual improvement was achieved with close monitoring and slow steroid tapering alongside multidisciplinary supportive measures resulted in clinical stabilization and discharge.

Conclusion: This case highlights the complexities of managing DRESS syndrome, particularly in patients with autoimmune comorbidities, and the potential for DRESS recurrence with autoimmune overlap. It underscores the essential role of clinical pharmacists in early recognition, allergy documentation, therapeutic optimization, monitoring for hepatic safety, long-term management to prevent recurrence and patient education, thereby enhancing safety and better therapeutic outcomes. They also had a role in adverse drug reaction detection, reporting and antimicrobial stewardship. Rapid steroid withdrawal and drug rechallenge precipitated relapse, emphasizes the necessity of slow tapering and avoidance of re-exposure. Further research is required to better understand the underlying mechanisms, long-term outcomes, and optimal therapeutic strategies for managing such complex and rare cases.

Keywords: DRESS syndrome, Hydroxychloroquine (HCQ), Leflunomide, Eosinophilia, Autoimmune hepatitis

INTRODUCTION

Drug Reaction with Eosinophilia and Systemic Symptoms syndrome also known as DRESS syndrome, a rare yet potentially life-threatening form of adverse drug reaction characterized by rash, fever, lymphadenopathy and eosinophilia with evidence of visceral involvement after drug initiation.[1]The earliest accounts of similar drug reaction were documented in 1937 with sulfanilamide by Myers et al.[2] and diphenylhydantoin (1938) by Meritt and Puttman.[3] In 1996, Bocquet et al. introduced the term “drug rash with eosinophilia and systemic symptoms.” Later, as the syndrome became more clearly defined, the R changed to “Reaction” due to multiple system involvement.[4] Currently, around 60 medications have been associated with DRESS syndrome including phenytoin, carbamazepine, sulphonamides, NSAIDs, beta lactam antibiotics, vancomycin,

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minocycline, allopurinol, sulfasalazine and antiretrovirals.[5] Reported mortality ranges from 3.8% to 10%.[1] The overall risk to the general population has been estimated to range from approximately 1 in 1,000 to 1 in 10,000 exposures to the drug.[12]

DRESS syndrome involves a multifactorial interplay between genetic predisposition, impaired drug metabolism and viral reactivation (HHV-6, EBV, CMV).[1,5] The clinical manifestations usually appear 2-6 weeks after the offending drug initiation and may recur upon re-exposure.[6] The earliest sign is fever, followed by erythematous pruritic morbilliform rash typically on face, upper trunk and extremities in over 90% of cases, rarely with concomitant mucosal lesions and vesicular, target or purpuric lesions.[1,8] Up to 75% of individuals have either localized or generalized lymphadenopathy followed by internal organ dysfunction, commonly affecting hematologic (eosinophilia is key diagnostic criterion) and hepatic system (seen in 80% of cases transaminitis, hyperbilirubinemia, fulminant liver failure, death) and less commonly renal, pulmonary, cardiac, GI or neurological system.[6,7,8] pancreatitis, new-onset type 1 diabetes, GI symptoms, GI bleeding, or perforation. [1]

Clinicians rely on diagnostic criteria of the European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR widely used), Japanese group criteria, and Bouquet et al. criteria.[9] A comprehensive evaluation of complete blood count, liver and renal function tests, inflammatory markers, PCR for herpes and hepatotropic viruses, parvovirus testing, and antinuclear antibody assays is advised.[10] Additionally, to identify the causative drug, an invitro lymphocyte transformation test can be performed 6-12 months post reaction (specificity of 82%, sensitivity of 73%).[11]

Management of DRESS syndrome starts with immediate withdrawal of the offending drug along with hydration, electrolyte homeostasis and symptomatic care. High potency topical steroids can be used for one week in mild disease (with / without mild organ involvement). Systemic steroids are used in severe drug-induced liver injury with multidisciplinary care. It is recommended to use oral prednisone dose of 0.8-1 mg/kg/day up to 2-3 weeks or until clinically better and then tapered to 5-10 mg/week. Spanish guidelines suggest oral methylprednisolone (60–120 mg/day) or oral prednisone (40–60 mg/day) initially in severe liver injury, followed by slow steroid taper, typically requiring one-two months to discontinue.[6,10] If desired response is not seen, then cyclosporine (4-5 mg/kg/day for 5-7 days, tapered by 50 mg/week), intravenous immunoglobulin (2g/kg for 5 days), cyclophosphamide or plasmapheresis could be added. Liver transplantation remains the proven option for acute liver failure. [10]

Case Report

A 37-year female patient presented with complaints of fever (temperature-101°F) since morning associated with rashes on bilateral hands, cold, generalised weakness, myalgias for past one week. Her medical history illustrates that she is a known case of rheumatoid arthritis with RF IgM-165, initiated on hydroxychloroquine and leflunomide. After 20 days of hydroxychloroquine and leflunomide use, she developed fever, oral ulcer, joint pain, generalized rash, altered LFT, positive Leptospira IgM, leucocytosis, ANA, blood cultures and HBsAg were negative, skin biopsy revealed epidermal thickening with mild perivascular lymphocytic infiltrate and pigment incontinence confirmed the diagnosis as HCQ and leflunomide induced DRESS syndrome. Drugs were withdrawn and she responded well to corticosteroids and antibiotics initially and along with steroid tapering, HCQ was cautiously rechallenged under close monitoring. However, she developed recurrent fever, dyspnoea, worsening rash, severe transaminitis (SGOT- 1200 U/L, SGPT- >3000U/L), hyperbilirubinemia-5 mg/dL and eosinophilia-15%. Therefore, HCQ was discontinued, steroids escalated, and was initiated but later the patient experienced shortness of breath and hypertension due to cyclosporine so the dose of cyclosporine was reduced. She was clinically stabilized and discharged. The allergies to NSAID, HCQ and leflunomide was documented.

Initial symptoms improved with intravenous methyl prednisolone 60mg and cyclosporine 100mg for rash, antihistamines, and antipyretics, but she developed acidity, diarrhoea, vomiting and dehydration. Inflammatory markers (CRP- 108mm/hr, ESR-50mm/hr) elevated, respiratory bio-fire panel detected rhinovirus and enterovirus, while stool bio-fire panel showed the presence of norovirus indicating GI infection, and urine culture grew pan-sensitive Citrobacter freundii and Klebsiella pneumonia suggesting urinary tract infection (sepsis). Treatment was broadened with antibiotics (meropenem 1g, amoxicillin, clavulanate 625mg), antacids, anti-diarrheal medication, probiotics and antiemetics. Lab investigations showed elevated faecal calprotectin

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stool-144 mg/kg, anaemia (Hb-8.5g/dL), eosinophilia-25%, leucocytosis (WBC-15.15×$10^3$$mm^3$), thrombocytopenia-74×$10^3$$mm^3$, and persistently elevated liver enzymes (Table 1), anti-smooth muscle antibodies (ASMA) were positive indicating autoimmune hepatitis. Despite the treatment, rashes worsened characterized as erythematous blanchable, petechial and purpuric. The patient had intermittent fever spikes, worsening of rash on the back, face, extremities, and facial flushing. Thus, hepatoprotective agents were added, increased methylprednisolone dose to 125mg/day and cyclosporine was discontinued in view of deranged LFT. 6 units of RDP and 1 unit of SDP was transfused for thrombocytopenia. The diagnosis was confirmed as recurrent DRESS syndrome with autoimmune hepatitis and sepsis.

Table 1: Liver function test results day wise

Liver enzymes	Day 1	Day 7	Day 14	Day 21	Day 28	Day 32
Bilirubin (mg/dL)	0.6	0.7	**1.4**	**1.2**	**1.2**	0.8
ALP (U/L)	99	**134**	**129**	**128**	113	76
SGPT (U/L)	**40**	**285**	**399**	**376**	**146**	**45**
SGOT (U/L)	14	**151**	**238**	**109**	**40**	28
GGTP (U/L)	**76**	**228**	**218**	**228**	**199**	**146**
Albumin (g/dL)	**3.2**	**2.0**	**2.7**	**2.4**	**1.2**	**1.5**

Liver biopsy revealed chronic hepatitis changes, drug induced liver injury, lymphocyte infiltration, and interface hepatitis. Liver enzymes were regularly monitored. Severe persistent diarrhoea resulted in hypokalaemia (2.5 mmol/L) and hypomagnesemia (1.2 mg/dL), which were corrected with supplemental IV magnesium sulphate and potassium chloride. Vitamin K was administered for elevated INR of 1.41. Mycophenolate mofetil 360mg twice daily, before meals was introduced as steroid sparing agent for DRESS syndrome, prednisolone 40mg, OD, levocarnitine with vitamin E was given for proximal muscle weakness. Hydrocortisone 100mg, IV, BD was administered for autoimmune hepatitis and DRESS. Mycophenolate mofetil was discontinued due to persistent diarrhoea and later mesalamine 400 mg twice daily was administered for diarrhoea, TPN at 50 ml/hr for nutrition and vancomycin 250 mg four times a day was given empirically for 8 days. Intravenous immunoglobulin (30g) was given for 4 days. While diarrhea, rashes, and liver enzymes showed some improvement, SGPT-45U/L remained elevated. Clostridium difficile toxin and stool bio-fire also turned negative. Maculopapular rash over limbs and skin lesion progressed towards exfoliative dermatitis, prompting re-initiation of cyclosporine 100mg, IV, BD. After administering amitriptyline 25mg, her rashes subsided. Hypoalbuminemia (Serum albumin 1.2 g/dL) was corrected with IV human albumin 20%, 100ml. The patient showed gradual improvement and hemodynamic stability. Steroids were tapered slowly, and she was discharged on a regimen including corticosteroids, antibiotics, antidiarrheals, hepatoprotective agents, probiotics, and antacids.

Table 2: RegiSCAR score: <2 no DRESS, 2-3 Possible DRESS, 4-5 Probable DRESS, >5 Definite DRESS

Clinical Features		**Score**			**Patient's Score**
		No	**Yes**	**Unknown**	
Fever >38.5°C		-1	0	-1	0
Lymphadenopathy		0	1	0	0
Atypical lymphocytes		0	1	0	0
Eosinophilia	10%-19.9%	0	1		2
	≥ 20%		2		
Skin rashes- Extent >50%		0	1		1
Atleast 2 of edema/ infiltration/ purpuric		-1	1		1

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/scaling					
Biopsy suggestive of DRESS		-1	0		1
Internal organ involvement	One	0	1	0	2
	Two		2		
Resolving in ≥ 15 days		-1	0	-1	0
Exclusion of other causes		0	1	0	1
Total					**8 (Definite)**

DISCUSSION

This case illustrates the multifaceted challenges of reoccurrence of DRESS syndrome overlapping with autoimmune hepatitis and sepsis. The initial presentation of fever, rash, eosinophilia and systemic involvement following HCQ and leflunomide exposure suggests a hypersensitivity reaction. DRESS is believed to be a T-cell-mediated hypersensitivity reaction, though the exact mechanism remains unclear. Two main theories suggest either a drug-induced activation of CD4+ and CD8+ T cells or herpesvirus reactivation triggered by drug-induced immunosuppression.[13] There is a possibility of recurrent DRESS, despite drug withdrawal and treatment. While the exact causes of recurrence and relapse remain unclear, viral reactivation is considered a potential contributing factor. Additionally, prolonged use of glucocorticoids may induce immune dysregulation due to sustained immunosuppressive effects.[14] Recurrences are more frequently observed in patients receiving systemic corticosteroids, particularly when the tapering process is carried out too quickly which is likely possible in this case.[15] The significant liver enzymes elevation and positive ASMA confirmed a diagnosis of autoimmune hepatitis complicated by drug-induced liver injury, persistent diarrhoea probably due to GI involvement and gastrointestinal infection causing electrolyte disturbances, UTI and progressive dermatologic manifestations.

Based on the RegiSCAR scoring system for DRESS, the diagnostic criteria in this case aligned with a classification of “Definite DRESS” (Table 2)[1], thereby supporting the clinical diagnosis using standardized criteria. Management required a dynamic, multidisciplinary approach: high-dose corticosteroids as first-line therapy to control systemic inflammation; cyclosporine, mycophenolate mofetil as steroid-sparing agents in long-term steroid exposure, intravenous immunoglobulin therapy, hepatoprotective agents, antibiotics and supportive care. The resolution of symptoms allowed for a gradual tapering of steroids before discharge.

Clinical pharmacists play a crucial role in the identifying, preventing, and managing drug-induced adverse effects, especially in complex cases like DRESS syndrome. In this case, the clinical pharmacist contributed in the following ways: Early identification of drug reaction, withdrawal of offending drugs, causality assessment and timely reporting, medication review and allergy documentation helped prevent future exposure. Furthermore, optimization of immunosuppressive regimens, tapering of steroids slowly to prevent the risk of reoccurrence, and close monitoring of LFTs enabled dose adjustments if needed. By implementing antimicrobial stewardship pharmacist ensured appropriate antimicrobial therapy while minimizing the risk of antibiotic resistance. The pharmacist educated the patient and caregivers on medication benefits which included corticosteroids to reduce inflammation, hepatoprotective agents to protect liver, amitriptyline for symptomatic relief from reaction, antidiarrheals and probiotics to manage GI symptoms and restore gut flora. Medication adherence and the consequences of stopping medications (especially steroids and immunosuppressants) without physician’s advice, potential side effects, and the importance of regular follow-ups all aligns with American Society of Health-System Pharmacists (ASHP), European Society of Clinical Pharmacy, American college of clinical pharmacy and Infectious Diseases Society for America (IDSA) guidelines. Literature supports the role of pharmacists in reducing ADR-related morbidity through proactive interventions. Hence, clinical pharmacist in collaboration with multidisciplinary team are pivotal in improving patient’s outcomes. This case reinforces the need for integrated clinical pharmacy services in managing severe drug reactions.

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CONCLUSION

This case underscores the importance of vigilant monitoring in patients on immunosuppressive therapy, particularly those with autoimmune conditions predisposed to drug hypersensitivity reactions. The timely recognition and management of DRESS syndrome, along with comprehensive supportive care, were crucial in stabilizing the patient. Prompt identification of the suspected drugs, judicious use of immunosuppression with slow tapering of steroids and vigilant supportive care are essential to minimize morbidity. The patient's documented allergies emphasize the necessity of careful drug selection in future treatments. This case demonstrates how the clinical pharmacist, as an integral part of the healthcare team, plays a significant role in enhancing patient safety, optimizing therapeutic outcomes, monitoring and preventing medication-related complications. Further research is needed to better understand the immunopathogenesis of recurrent DRESS and its overlap with autoimmune hepatitis. Studies focusing on predictive biomarkers for early diagnosis and recurrence, developing standardized treatment regimens including steroid tapering schedule, evaluating long-term outcomes and sequalae, and roles of pharmacogenomics screening to prevent drug hypersensitivity may guide individualized treatment.

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