

Case Report

Dapsone-induced pure red cell aplasia and cholestatic jaundice: A new experience for diagnosis and management

Kamal Kumar Sawlani¹, Shyam Chand Chaudhary¹, Jitendra Singh¹, Deep Chandh Raja¹, Sanjay Mishra², Madhu Mati Goel³

¹Department of Medicine, King George Medical University, Lucknow, Uttar Pradesh, India

²Department of Clinical Hematology and Oncology, King George Medical University, Lucknow, Uttar Pradesh, India

³Department of Pathology, King George Medical University, Lucknow, Uttar Pradesh, India

Received: January 2016

Accepted: March 2016

Corresponding author:
Dr. Jitendra Singh,
E-mail: drjitengsvm@gmail.com

ABSTRACT

Dapsone (4,4'-diaminodiphenylsulfone) is the parent compound of the sulfones, and it has potent antiparasitic, anti-inflammatory, and immunomodulatory effects. It is used in the treatment of leprosy, dermatitis herpetiformis, and prophylactically to prevent *Pneumocystis pneumonia* and toxoplasmosis in patients unable to tolerate trimethoprim with sulfamethoxazole. We hereby report a case of dapsone toxicity who developed pure red cell aplasia and cholestatic jaundice in a suspected case of dermatitis herpetiformis. Patient had an excellent response to corticosteroids after withdrawal of dapsone.

Keywords: Cholestatic jaundice; Dapsone; dermatitis herpetiformis; pure red cell aplasia

INTRODUCTION

Dapsone is generally well tolerated. The common side effects of dapsone include hemolysis, methemoglobinemia, hypersensitivity syndrome, and toxic hepatitis. Dapsone-induced cholestatic jaundice and pure red cell aplasia are rare entities but have been reported separately.^[1,2] To the best of our knowledge, it is the first case of dapsone therapy who developed these two dangerous adverse effects in the same case.

CASE REPORT

A 30-year-old female presented with generalized weakness, fever, jaundice, and pruritus all over the body for 7 days. On examination, she was

febrile (temperature, 102°F), blood pressure was 110/70 mm Hg, and pulse rate was 112/min. She had icterus and pallor. Pruritic papulovesicular rashes and urticarial plaques were present all over the body with predominantly involvement of lower extremities without mucosal involvement. On systemic examination, hepatomegaly was present. Patient had a history of on and off pruritic skin lesions for the last 2 years. A general practitioner diagnosed her as a case of suspected dermatitis herpetiformis, and dapsone therapy was started. She was taking tablet dapsone 100 mg/day for the last 3 months. On inquiry, we found a normal report of complete blood count prior dapsone therapy.

On the day of admission, her hemoglobin was 2.6 g/dl, total leukocyte count 12,480/mm³, platelet

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Sawlani KK, Chaudhary SC, Singh J, Raja DC, Mishra S, Goel MM. Dapsone-induced pure red cell aplasia and cholestatic jaundice: A new experience for diagnosis and management. *J Res Pharm Pract* 2016;5:215-8.

Access this article online



Website: www.jrpp.net

DOI: 10.4103/2279-042X.185743

count 310,000 cells/mm³, and reticulocyte count was 0.08%. Peripheral smear showed normocytic normochromic anemia. Liver function tests revealed bilirubin (total), 24.3 mg/dl (direct bilirubin - 17.7), aspartate aminotransferase - 365 U/L, alanine aminotransferase - 345 U/L, alkaline phosphatase - 2840 U/L, serum protein - 7.7 g/dl (serum albumin - 3.4 g/dl), and prothrombin time 13.0 s (INR 1.0). Her blood urea, creatinine, random blood sugar, uric acid, electrolytes, urine analysis, and stool examination were within normal limits. Significant complete blood counts and liver function tests are summarized in Table 1.

Serologic tests for hepatitis A, B, C, E viruses and HIV screening were negative. Coombs test and polymerase chain reaction for parvo B19 virus were negative. Autoimmune hepatitis was ruled out by the absence of antinuclear (ANA), anti-mitochondrial (AMA), and anti-lysosomal kidney mitochondrial antibodies (anti-LKM). Serum assays for C₃, C₄, haptoglobin, and glucose 6-phosphatase dehydrogenase were within normal limits. Urinary porphobilinogen excretion test was negative. Rapid malarial test was negative. X-ray chest was normal.

Repeated ultrasonography of abdomen showed hepatomegaly with normal echotexture without any evidence of extrahepatic biliary obstruction. Bone marrow aspiration showed cellular fragments with preponderance of myeloid cells with normal morphology and maturation [Figure 1]. Liver biopsy revealed ballooning of hepatocytes and canalicular cholestasis without any obvious inflammation suggestive of drug-induced cholestasis [Figure 2].

On the basis of clinical and laboratory findings, she was diagnosed as a case of dapsone-induced pure red cell aplasia and cholestatic jaundice. We stopped dapsone immediately and prednisolone 40 mg/day was started. Four units of packed red blood cells were transfused. She was also given antipyretics and oral

antihistamines. Patient had fever and mild elevated leukocytes count which might be due to secondary infection, so broad spectrum antibiotics were given. Patient improved day by day and her laboratory parameters returned to normal after 3 weeks. During her 2-years follow-up, she was doing well.

DISCUSSION

Dapsone (4,4'-diaminodiphenylsulfone) has been in clinical use for almost 50 years. Dapsone is used in dermatology for its anti-inflammatory properties, particularly in sterile (noninfectious) pustular diseases of the skin. Dapsone is approved for the use in dermatitis herpetiformis and leprosy. It is particularly useful in the treatment of linear immunoglobulin A (IgA) dermatosis, bullous systemic lupus erythematosus, erythema elevatum diutinum, and subcorneal pustular dermatosis.

Potential side effects of dapsone are included in Table 2.^[3,4] Other adverse reactions of dapsone

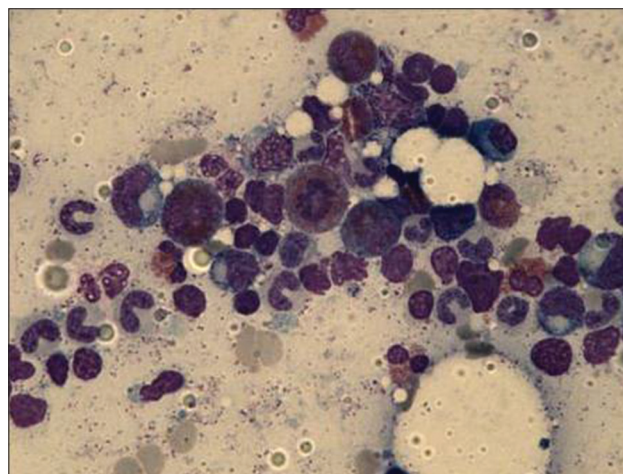


Figure 1: Bone marrow aspirate showing mainly myeloid precursors with very few erythroid precursors suggestive of pure red cell aplasia

Table 1: Significant laboratory parameters of patient

Parameter (unit)	During admission (days)						Follow-up
	D1	D4	D7	D12	D17	D22	D60
Hgb (g/dl)		4.6	5.8	7.0	8.1	9.2	13.2
TLC (10 ³ /μL)	12.48	12.2	11.80	8.61	9.22	8.6	7.6
DLC (%)	N56, L35, E4	N60, L32, E4	N56, L30, E6	N60, L32, E5	N56, L30, E6	N55, L34, E6	N58, L28, E8
PC (10 ³ /μL)	3.1	2.8	3.0	3.2	2.98	3.2	2.96
Bil. T (D) (mg/dl)	24.3 (17.7)	20.2 (15.1)	14.2 (8.2)	9.6 (5.2)	4.4 (2.8)	2.4 (1.9)	0.42 (0.14)
ALT (IU/L)	345	330	330	280	120	68	70
AST (IU/L)	365	302	270	186	102	73	66
ALP (IU/L)	2840	2780	2180	1604	768	218	118
Protein (g/dl)	7.7	7.8	7.0	7.6	6.8	6.6	7.8
Albumin (g/dl)	3.4	3.1	3.2	3.2	3.0	3.3	3.3

D=Day, Hgb=Hemoglobin, TLC=Total leucocyte count, DLC=Differential leucocyte count, N=Neutrophil, L=Lymphocyte, E=Eosinophil, PC=Platelets count, Bil. T (D)=Serum bilirubin total (direct), ALT=Alanine transaminase, AST=Aspartate transaminase, ALP=Alkaline phosphatase

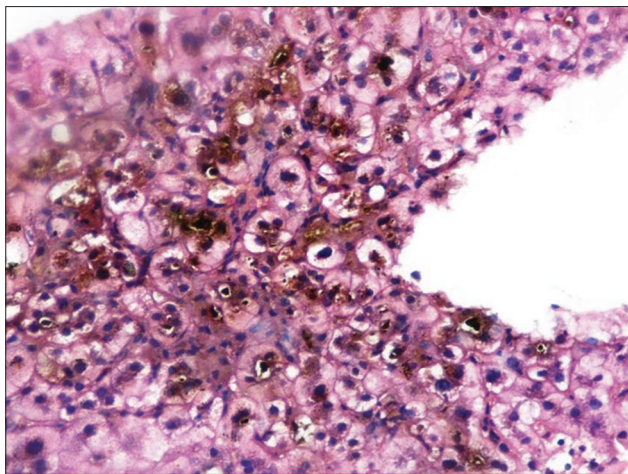


Figure 2: Liver parenchyma with ballooning of hepatocytes and canalicular cholestasis. No obvious inflammation. Findings suggestive of drug-induced cholestasis

Table 2: Potential adverse effects of dapsone

Systems	Adverse effects
Skin disorders	Bullous and exfoliative dermatitis, urticaria, phototoxicity, Steven Johnson syndrome
Endocrine	Hypoalbuminemia, male infertility
Gastrointestinal	Nausea, vomiting, abdominal pain, cholestatic jaundice, hepatitis
Renal	Albuminuria, renal papillary necrosis
Hematologic	Hemolytic anemia, agranulocytosis, methemoglobinemia
Central nervous system	Headache, insomnia, vertigo, psychosis
Cardiac	Tachycardia
Constitutional	Fever

include dramatic generalized hypersensitivity syndrome termed as “dapsone syndrome.” This syndrome has a frequency of 0.2–0.5% in patients on dapsone therapy. The constellation of features included in this syndrome is fever, exfoliative dermatitis, lymphadenopathy, lymphocytosis, methemoglobinemia, hemolytic anemia, and hepatotoxicity. Hyperbilirubinemia present in dapsone syndrome may partly be due to hemolysis in addition to hepatotoxicity. Both hepatocellular and cholestatic injury have been described. Cholestatic pattern may have less severe course and is characterized by high alkaline phosphatase level and modest increase of transaminases level. Rarely, dapsone can cause cholangitic liver injury.^[1] The mechanism of injury, including hepatotoxicity in dapsone syndrome, seems to be hypersensitivity reaction.^[5]

Pure red cell aplasia is the term now widely applied to isolated anemia secondary to failure of erythropoiesis. The cardinal findings are a low hemoglobin level, reticulocytopenia, and absent or extremely infrequent

erythroid precursor cells in the marrow. Like other marrow failure syndromes, pure red cell aplasia can be inherited or acquired, and its pathophysiology is heterogeneous. Idiosyncratic drug reactions account for a far smaller proportion of red cell aplasia than for agranulocytosis.^[6] The acquired form of pure red cell aplasia presents either as an acute self-limiting disease, predominantly seen in children or as a chronic illness that is more frequently seen in adults. It may present as a primary hematologic disorder in the absence of any other disease, or secondary to parvovirus infection, collagen vascular disease, leukemia, lymphoma, solid tumors, and treatment with recombinant human erythropoietin or other drugs.^[7] Case reports have implicated various agents such as diphenylhydantoin, sulfa and sulfonamide drugs, azathioprine, allopurinol, isoniazid, procainamide, ticlopidine, ribavirin, and D-penicillamine.^[6]

Pure red cell aplasia and cholestatic liver injury associated with dapsone therapy are life-threatening adverse reactions. Therefore, it is necessary for clinicians to confirm the diagnosis by histopathologic tests including skin biopsy before starting therapy. Furthermore, early diagnosis and aggressive management are necessary for a good outcome.

This case highlights an unusual and potentially fatal toxicity of dapsone therapy. Hence, treating physicians should have clear justification for diagnosis and use of dapsone therapy. Patient must also be counseled for any adverse reaction before starting dapsone therapy and should be advised to visit a respective doctor immediately.

AUTHORS' CONTRIBUTION

This manuscript is designed, studied, prepared and reviewed by all contributors. Beside this, Dr. Sanjay Mishra examined the bone Marrow and histopathological study was done by Dr. Madhu Mati Goel.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Itha S, Kumar A, Dhingra S, Choudhuri G. Dapsone induced cholangitis as a part of dapsone syndrome: A case report. *BMC Gastroenterol* 2003;3:21.
2. Borrás-Blasco J, Conesa-García V, Navarro-Ruiz A, Devesa P, Matarredona J, Marín-Jiménez F. Pure red cell aplasia

Sawlani, *et al.*: Dapsone-induced pure red cell aplasia

- associated with dapsone therapy. *Ann Pharmacother* 2005;39:1137-8.
3. Fox LP, Merk HF, Bickers DR. Dermatological pharmacology. In: Brunton LL, Lazo JS, Parker KL, editors. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 11th ed. New York: McGraw-Hill; 2006. p. 1679-706.
 4. Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: Overview and update. *J Am Acad Dermatol* 2001;45:420-34.
 5. Johnson DA, Cattau EL Jr., Kuritsky JN, Zimmerman HJ. Liver involvement in the sulfone syndrome. *Arch Intern Med* 1986;146:875-7.
 6. Young NS. Pure red cell aplasia. In: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT, editors. *Williams Hematology*. 8th ed. New York: McGraw-Hill; 2010. p. 485-95.
 7. Sawada K, Fujishima N, Hirokawa M. Acquired pure red cell aplasia: Updated review of treatment. *Br J Haematol* 2008;142:505-14.