

## The Day Dapsone DRESSed as DILI

Lee B Sigmon<sup>\*</sup>, Tom De Roche and Herbert Bonkovsky

Wake Forest University School of Medicine, Winston Salem, USA

<sup>\*</sup>Corresponding author: Sigmon LB, Wake Forest University School of Medicine, Winston Salem, USA, Tel: 7047633896; E-mail: [lsigmon@wakehealth.edu](mailto:lsigmon@wakehealth.edu)

Received date: May 21, 2015; Accepted date: Jun 22, 2015; Published date: Jun 28, 2015

Copyright: © 2015, Sigmon LB, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

### Abstract

Dapsone is a diaminodiphenylsulfone drug approved to treat leprosy with off-label use in HIV. It is a rare cause of idiosyncratic liver injury and has been associated with hypersensitivity. The pattern of liver injury is typically cholestatic, and the development of cholestasis due to dapsone has been described in rats. Here we describe a case of intrahepatic cholestasis and hypersensitivity syndrome in a patient with AIDS after initiation of dapsone for *Pneumocystis* pneumonia. The patient was admitted from clinic for scleral icterus of 3 days duration. He was febrile, hypotensive, and tachycardic with scleral icterus, jaundice, and a patchy erythematous rash on the torso. Laboratory studies showed eosinophilia and cholestatic injury pattern with value of  $R^*=0.5$ . All anti-retroviral medications and dapsone were stopped. Given concern for immune reconstitution in this AIDS patient, a liver biopsy was performed which was consistent with drug induced liver injury. Anti-retroviral therapy was re-started and the patient's aminotransferases and bilirubin gradually improved over span of 8 weeks following discontinuation of dapsone.

**Keywords:** Drug induce liver injury; Hypersensitivity; Dapsone; Cholestasis

### Introduction

Dapsone is a diaminodiphenylsulfone drug approved to treat leprosy with off-label use in HIV for *Pneumocystis* treatment and prophylaxis in those patients unable to receive standard therapy. It is a rare cause of idiosyncratic liver injury and has been associated with hypersensitivity [1]. The pattern of liver injury is typically cholestatic, and the development of cholestasis due to dapsone has been described in rats [2]. Here we describe a case of intrahepatic cholestasis and hypersensitivity syndrome in a patient with AIDS who presented with scleral icterus after initiation of dapsone for *Pneumocystis* pneumonia.

### Case Report

A 27 year-old African American male with AIDS (CD4 count 70 cells/uL) receiving treatment for *Pneumocystis* pneumonia was admitted to the hospital with three days of scleral icterus. He had no prior history of icterus, no pre-existing liver disease, and denied abdominal pain, nausea or vomiting. He had been diagnosed with *Pneumocystis* pneumonia 5 weeks prior to presentation and, due to past history of sulfa allergy (rash and facial swelling), was prescribed a 3 week course of clindamycin, primaquine and prednisone and anti-retroviral therapy (ART- darunavir, raltegravir, ritonavir, and zidovudine). This regimen was used in lieu of traditional *Pneumocystis* treatment with trimethoprim/sulfamethoxazole given patient's sulfa allergy. A test for glucose-6-phosphate dehydrogenase (G6PD) activity in erythrocytes was normal. He completed the treatment course, after which ART therapy was continued and dapsone, 100 mg/day, was prescribed for *Pneumocystis* prophylaxis.

Two weeks later he presented with jaundice. He denied family history of liver disease. He drank 3 beers per month and did not use recreational drugs or dietary supplements. On physical exam, he was febrile, hypotensive, and tachycardic with scleral icterus, jaundice, and

a patchy erythematous rash on the torso. Laboratory studies showed eosinophilia (15%, absolute eosinophil count 1600 /ul), serum aspartate aminotransferase (AST) 68 U/L, alanine aminotransferase (ALT) 145 U/L, alkaline phosphatase (ALP) 909 U/L and total bilirubin 12.4 mg/dl (direct 8.1). The value of  $R^*=0.5$ , indicating cholestatic injury [3]. Urine drug screen was negative and there was no evidence of hemolysis. Viral hepatitis serologies and anti-mitochondrial antibodies were negative. Abdominal ultrasound did not demonstrate biliary obstruction.

Days onset	from	ALT (U/L)	AST (U/L)	ALP (U/L)	T bili (mg/dl)
-40		34	61	98	0.6
0		145	68	909	12.4
2	(dapsone and ART stopped)	99	55	813	8.3
6		93	105	769	9.5
17 (peak)		31	55	1290	19.3
22		33	59	1244	15.5
56		22	22	755	4.8

Table 1: Summary of transaminase, alkaline phosphatase and bilirubin levels over course of patient's illness.

Given concern for likely drug induced liver injury, dapsone and anti-retroviral drugs were stopped. After 2 weeks off of these medications, his total bilirubin and INR continued to rise to a peak of total bilirubin 19.3 mg/dl and INR 1.6, respectively (Table 1). Given concomitant AIDS and recent ART initiation, there was concern for immune reconstitution inflammatory syndrome, and liver biopsy was performed. The liver biopsy showed a cholestatic hepatitis pattern of injury (Figure 1), typified by a predominant component of cholestatic

injury with only mild lobular necroinflammatory activity. There was moderate hepatocellular and canalicular cholestasis; the parenchyma also showed foci of lobular inflammation with apoptotic hepatocytes and patchy hepatocyte dropout. Occasional loosely formed granulomas were identified in the hepatic lobules. The portal tracts were expanded by a mixed inflammatory infiltrate with readily identifiable eosinophils. While occasional interlobular bile ducts exhibited degenerative epithelial changes in keeping with bile duct injury, there was no evidence of bile duct loss. Special stains for acid-fast bacteria, fungi, cytomegalovirus, and Epstein-Barr virus were negative. The cholestatic hepatitis was favored to be drug-induced, most likely related to dapsone, especially in the context of portal eosinophil infiltrates and lobular granulomas. ART was re-started and symptoms and liver tests gradually improved to normal over a period of 8 weeks.

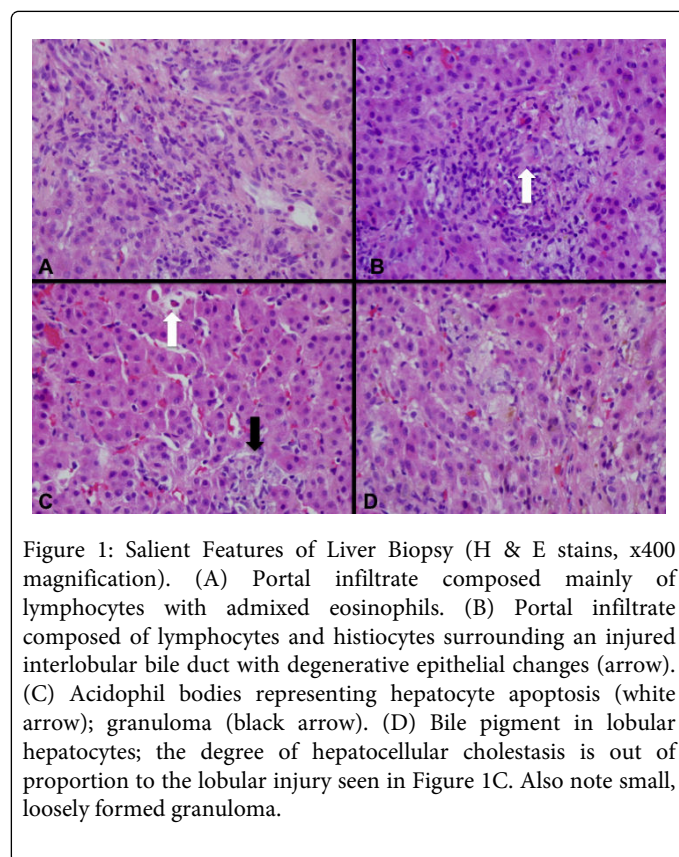


Figure 1: Salient Features of Liver Biopsy (H & E stains, x400 magnification). (A) Portal infiltrate composed mainly of lymphocytes with admixed eosinophils. (B) Portal infiltrate composed of lymphocytes and histiocytes surrounding an injured interlobular bile duct with degenerative epithelial changes (arrow). (C) Acidophil bodies representing hepatocyte apoptosis (white arrow); granuloma (black arrow). (D) Bile pigment in lobular hepatocytes; the degree of hepatocellular cholestasis is out of proportion to the lobular injury seen in Figure 1C. Also note small, loosely formed granuloma.

## Discussion

Dapsone has been linked to cases of idiosyncratic cholestatic liver injury and also hypersensitivity syndrome (a form of drug reaction

with eosinophilia and systemic symptoms also known as DRESS) [4]. Review of interactions among the patient's medications does show that ritonavir and darunavir in combination with dapsone can lead to a very minor increase in dapsone levels through decreased CYP3A4 metabolism- this is classified as a "non-significant" or "minor" interaction by Micromedex though it could have contributed to the injury seen in this case. The case reported here is a rare presentation that demonstrates both cholestatic liver injury ( $R=0.5$ ) and hypersensitivity syndrome (fever, rash, eosinophilia, hepatitis) with a time course, injury pattern, and resolution typical of dapsone [1,3].

Given the presence of a hypersensitivity component in this case, we considered administering corticosteroids, but the patient was already on a steroid taper for treatment of *P. carinii*. There are no randomized controlled data to support steroids in DILI, although there may be benefit in dapsone-related DILI when patients have hypersensitivity features of fever, rash, and eosinophilia [1,3]. The potential benefit from steroids is likely related to the proposed pathogenesis of dapsone-related injury as a hypersensitivity mechanism, perhaps through its metabolism to an antigenic metabolite [1,5]. In summary, there is a potential for idiosyncratic liver injury and hypersensitivity syndrome with dapsone exposure, especially in patients with prior history of hypersensitivity to other drugs. The pattern of liver injury is cholestatic ( $R<2$ ), and is likely mediated by the host's intrinsic and adaptive immune response. \*R is defined as serum ALT/upper limit of normal for ALT divided by serum alkaline phosphatase [AP]/upper limit of normal for AP. By convention,  $R<2$  denotes 'cholestatic' type liver injury.

## References

1. National Library of Medicine. LiverTox:Dapsone. Accessed 2/26/15.
2. Veggi LM, Crocenzi FA, Roma MG, Dawson PA, Pellegrino JM, et al. (2002) Dapsone-induced cholestasis and impairment of bile salt output in the rat. *Biochem Pharmacol* 63: 1553-1563.
3. Bonkovsky HL, Shedlofsky SI, Jones DP, Russo M (2012) Drug induced liver injury. In: Boyer TD, Manns MP, Sanyal A (eds.) *Zakim and Boyer's Hepatology Textbook of Liver Disease* (6th edn.) Saunders-Elsevier, Philadelphia, pp. 417-461.
4. Vinod KV, Arun K, Dutta TK (2013) Dapsone hypersensitivity syndrome: A rare life threatening complication of dapsone therapy. *J Pharmacol Pharmacother* 4: 158-160.
5. Foureau DM, Walling TL, Maddukuri V, Anderson W, Kleiner DE, et al. (2015). Comparative analysis of portal hepatic infiltrating leukocytes in acute drug-induced liver injury, idiopathic autoimmune, and viral hepatitis. *Clin Exp Immunol* 180: 40-51.