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REVIEW ARTICLE

Oral clindamycin causing acute cholestatic hepatitis without ductopenia: a brief review of idiosyncratic drug-induced liver injury and a case report

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Clindamycin is a lincosamide antibiotic active against most of the anaerobes, protozoans, and Gram-positive bacteria, including community-acquired methicillin-resistant *Staphylococcus aureus*. Its use has increased greatly in the recent past due to wide spectrum of activity and good bioavailability in oral form. Close to 20% of the patients taking clindamycin experience diarrhea as the most common side effect. Hepatotoxicity is a rare side effect. Systemic clindamycin therapy has been linked to two forms of hepatotoxicity: transient serum aminotransferase elevation and an acute idiosyncratic liver injury that occurs 1–3 weeks after starting therapy. This article is a case report of oral clindamycin induced acute symptomatic cholestatic hepatitis and a brief review of the topic.

Keywords: *drug-induced liver injury*; *clindamycin*; *acute cholestatic hepatitis*; *acute liver failure*; *hepatotoxicity*

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Clindamycin is a bacteriostatic lincosamide antibiotic. It works primarily by binding to the 50S ribosomal subunit of bacteria and inhibiting protein synthesis. It has a broad spectrum of activity against anaerobic bacteria (90% of *Bacteroides fragilis*), Streptococci, Staphylococci, certain protozoa, and *Chlamydia trachomatis*. It is used to treat bone, soft tissue, head and neck, abdominal, respiratory, and pelvic infections (1–6). It is metabolized and excreted by the liver. It has a half-life of 2–2.5 h. However, in patients with liver failure, the half-life is prolonged and dose modifications are recommended (3). Bioavailability of oral clindamycin is close to 50% (7).

Common side effects of systemic clindamycin therapy are diarrhea, nausea, vomiting, abdominal pain/cramps, and metallic taste. Hepatotoxicity is a rare side effect of clindamycin. When hepatotoxicity occurs, it is usually a transient elevation of transaminases. There are only a handful cases of acute idiosyncratic liver injury after receiving systemic clindamycin therapy. Clindamycin-induced liver injury is mediated by various apoptotic mechanisms that eventually result in cell death (8–19).

Herein, we present a case of acute cholestatic hepatitis in a patient who received oral clindamycin for a urinary tract infection.

Case report

A 75-year-old Caucasian female with a past medical history of type 2 diabetes presented with fatigue, jaundice, and pruritus for 7 days. Ten days prior to presentation, she had a urinary tract infection that was treated with oral clindamycin, 450 mg every 6 h. Her symptoms started 3 days after she started taking clindamycin. Her home medications include metformin 500 mg twice daily. She does not take any over-the-counter or herbal medications. On admission, physical examination was significant for scleral icterus, jaundice with no other sequelae of chronic liver disease. Initial labs showed a total bilirubin 14.2 mg/dl, direct bilirubin 9.2 mg/dl, aspartate transaminase (AST) 315 U/L, alanine transaminase (ALT) 227 U/L, alkaline phosphatase (ALP) 296 U/L, and international normalized ratio (INR) 1.5. Evaluation was negative for viral hepatitis (HSV, EBV, and CMV viral serology) or autoimmune etiology (ANA, ASMA, and IgG levels were normal). CT abdomen and right upper quadrant ultrasound showed no obstructive etiology or vascular abnormality. She denied alcohol use. As there was a temporal relationship with clindamycin, it was discontinued due to suspected drug-induced liver injury (DILI). She was empirically started on *N*-acetyl cysteine (NAC) 10,000 mg intravenously for

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3 days, and pentoxyphylline 400 mg thrice a day. In the next several days, transaminase levels started to trend down but total bilirubin and INR worsened to 25 mg/dl and 2.5, respectively. At this point, a liver biopsy was obtained (Figs 1–6) that showed moderate cholestasis (predominantly zone three), focal mild-to-moderate peri-portal chronic inflammation, mild sinusoidal mononuclear infiltrate, no ductopenia, and no significant fibrosis. She was started on solumedrol 125 mg intravenously twice a day. Over the next several days, the total bilirubin, INR, and transaminases trended down and her symptoms began to resolve. She was discharged home on prednisone taper over 4 weeks. At 4 weeks follow up, biochemical tests returned to baseline normal values.

In this patient, clindamycin was suspected as an etiology for DILI due to the following reasons:

1. There was a temporal association between clindamycin use and onset of symptoms. Fatigue, pruritus, and jaundice started 3 days after the patient started taking clindamycin.
2. Other causes of acute liver injury were ruled out.
3. There was no alternate etiology that would explain the liver injury.
4. Symptoms and labs improved after discontinuing the offending agent.
5. The pattern of liver injury and liver biopsy findings on histology also suggested a possible drug-induced injury, and no underlying liver disease.

Discussion and review

DILI is the leading cause of acute liver failure (ALF) in the United States (20). Current epidemiologic data suggest that approximately 14–20 new cases of DILI per 100,000 persons occur each year. Idiosyncratic DILI accounts for about 11% of the cases of ALF in the United States (10, 21). However, the actual incidence is probably much higher due to the difficulty of diagnostic challenges and lack of reporting of suspected cases (8, 21–23).

DILI can be dose related (as seen with acetaminophen) or idiosyncratic (dose independent). Idiosyncratic DILI will be discussed here in detail. While prescription medications are largely responsible for DILI, dietary supplements and OTC drugs are an increasingly recognized cause (20). It develops independent of route of administration, dose of the medication, or duration of intake (9, 20, 21). It has a wide spectrum of clinical and histological presentations (9). Hepatocellular injury is usually manifested by significant elevations of serum aminotransferases, bilirubin, and ALP levels (8, 21).

DILI is typically a diagnosis of exclusion. Obtaining a thorough medical history is important: non-specific

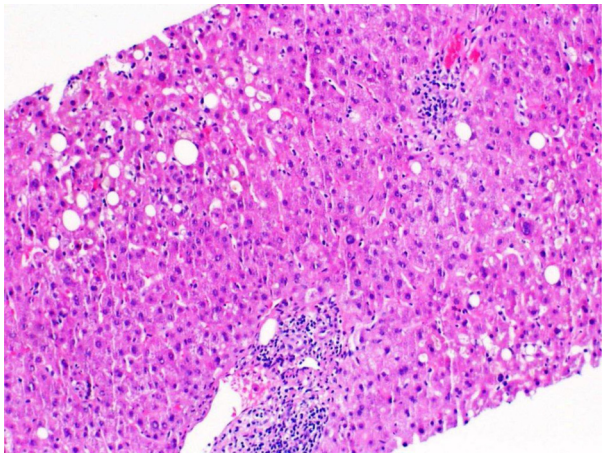

Fig. 2. Liver biopsy: medium power microscopic view showing mild-to-moderate peri-portal inflammation with mild steatosis and mild cholestasis.

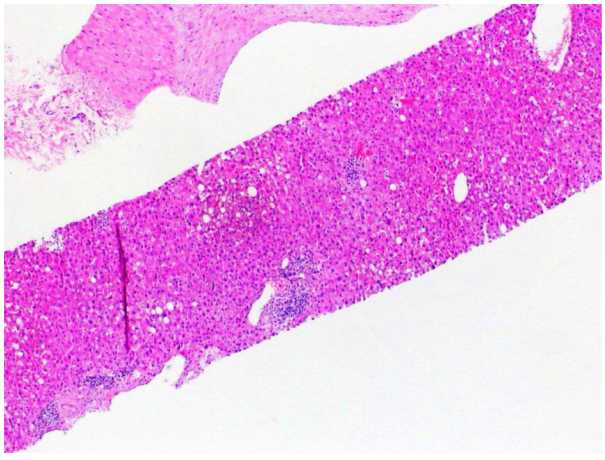

Fig. 1. Liver biopsy: low-power microscope view showing mild-to-moderate peri-portal inflammation with mild steatosis and mild cholestasis.

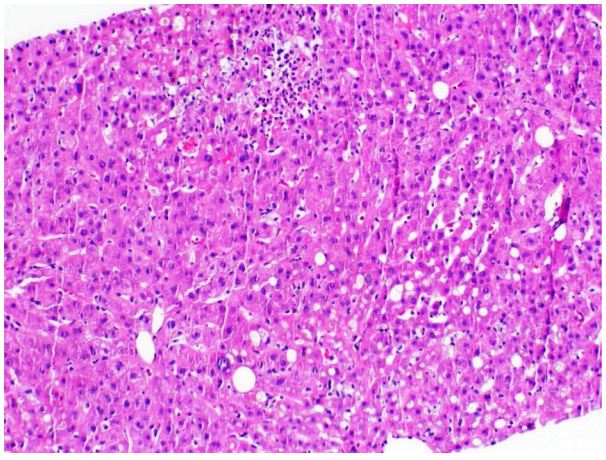

Fig. 3. Liver biopsy: medium power microscopic view showing mild-to-moderate peri-portal inflammation and mild cholestasis.

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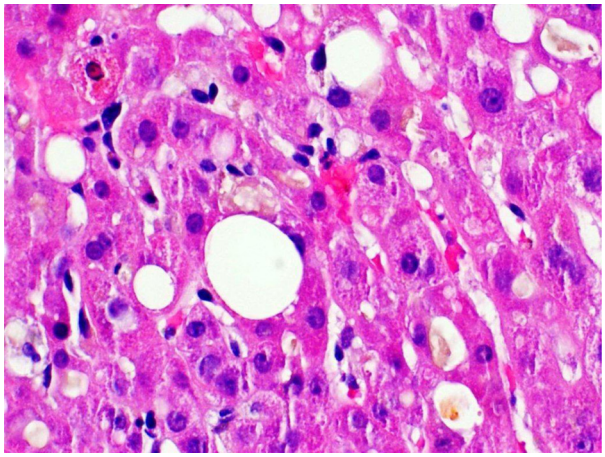

Fig. 4. Liver biopsy: high-power microscopic view showing cholestasis and feathery degeneration of hepatocytes.

symptoms including nausea, anorexia, fatigue; history of use of over-the-counter medications/prescription medications, herbal/dietary supplements; and jaundice (8, 20, 22). Acute viral hepatitis (hepatitis A/B/E infection and, sometimes acute hepatitis C infection), biliary tract disorders, alcoholic or autoimmune hepatitis, and hemodynamic problems must be excluded (8, 24). Liver biopsy usually does not provide a definitive diagnosis of DILI. A biopsy is primarily used to rule out other causes or support an alternative diagnosis (20, 25, 26). However, a biopsy is recommended if autoimmune hepatitis is a high on the differential and if immunosuppressive medications are to be given (27–29).

Once there is a strong suspicion for DILI, the suspected agent should be promptly discontinued, and supportive care should be provided along with timely consultation from a hepatologist or liver transplant center in severe cases (8, 20, 21). There are no definite therapies available

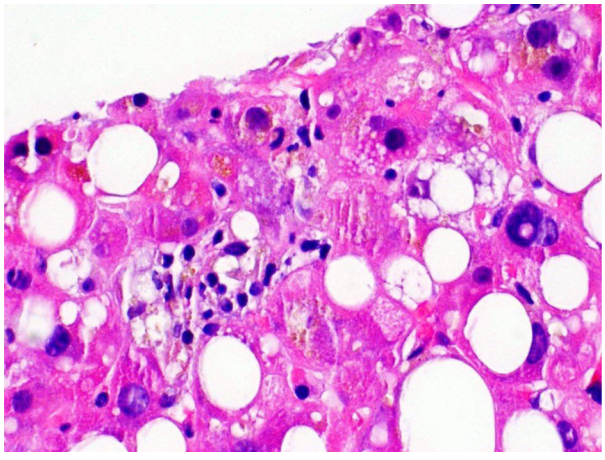

Fig. 5. Liver biopsy: high-power microscopic view showing cholestasis and feathery degeneration of hepatocytes.

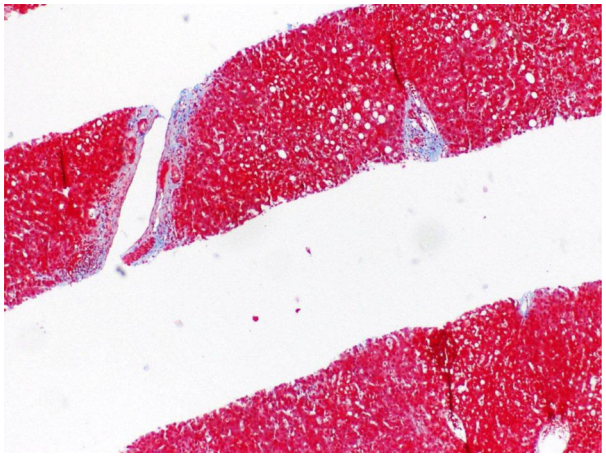

Fig. 6. Liver biopsy: trichrome stain showing no fibrosis.

for idiosyncratic DILI; however, NAC could be considered in early-stage ALF adults (30) It has a relatively safe side-effect profile and was found to be efficacious in DILI of any cause especially in patients with encephalopathy (8, 20, 30). Due to the risk of enhanced reaction of the body's immune system to an already exposed antigen, suspected hepatotoxic drug should not be re-challenged (8, 20, 21).

Only a handful cases of systemic clindamycin-related DILI have been reported in the literature (31):

1. A patient developed liver failure after getting treated with clindamycin for an aspiration pneumonia. Elevated liver enzymes and synthetic function improved during his hospital stay after removing the offending agent (32). Sepsis could have been a cofounding factor in this case.
2. Two patients developed cholestatic liver disease with bile duct paucity (ductopenia) after exposure to clindamycin and trimethoprim–sulfamethoxazole, respectively (33).
3. Middle-aged female with Stevens–Johnson syndrome and intrahepatic cholestasis caused by clindamycin versus chlorpheniramine (34).
4. A case of mixed-type (hepatocellular and cholestatic) hepatic injury after 6 days of oral clindamycin treatment for dental infection. Biliary ductopenia was not noticed in this patient (35).

Due to the increasing use of clindamycin and association of clindamycin to liver injury, efforts must be made to promptly identify the patients that develop signs and symptoms of liver injury. In these patients, it is necessary to have a low threshold to check liver functions if the patient has constitutional symptoms or scleral icterus develops (8, 20, 21, 24). While transient increases in transaminases (AST/ALT) may be seen when many medications are initiated, these typically resolve spontaneously.

When jaundice, coagulopathy, or encephalopathy develops, this portends a poor prognosis and the medication should be immediately discontinued. NAC therapy should be considered and there should be a low threshold for consultation or transfer to a liver transplant center should fulminant hepatic failure result (8, 20, 21). Close to 40% of patients with drug-induced fulminant liver failure eventually require liver transplantation (20, 32, 36–39). About 15–20% of DILI patients eventually develop chronic liver injury. Thus, close follow-up upon discharge is recommended (40).

Despite recent advances in our understanding of DILI, many aspects of its pathophysiology and clinical impact remain unclear. Genomic studies like micro-RNA proteomics are currently being studied to create new biomarkers for DILI (21, 23). Our understanding and management of DILI could further be improved with ongoing research and international multicenter collaborative efforts (22).

Conclusions

This report highlights a rare but important complication of clindamycin treatment and should be considered in patients with an acute change in clinical status especially if jaundice/scleral icterus develops in the appropriate setting. Prompt discontinuation of drug remains the most important intervention and supportive care, if recognized early will result in satisfactory outcomes.

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References

1. Smieja M. Current indications for the use of clindamycin: A critical review. Can J Infect Dis 1998; 9(1): 22–8.
2. Steigbigel NH. Macrolides and clindamycin. In: GL Mandell, JE Bennett, R Dolin (eds.), Douglas and Bennett's principles and practice of infectious diseases, p. 334–6. New York: Churchill Livingstone; 1995.
3. O'Hanley PD, Tam JY, Holodniy M. Infectious disorders. In: KL Melmon, HF Morrelli, BB Hoffman, DW Nierenberg (eds.), Melmon and Morrelli's clinical pharmacology: Basic principles in therapeutics. 3rd edn, p. 710. New York: McGraw-Hill; 1992.
4. Falagas ME, Gorbach SL. Clindamycin and metronidazole. Med Clin North Am 1995; 79: 845–67.
5. Klainer AS. Clindamycin. Med Clin North Am 1987; 71: 1169–75.
6. Nordbring F. Aspects of the clinical use of clindamycin. A summary. Scand J Infect Dis 1984; 43(Suppl): 89–90.
7. Gatti G, Flaherty J, Bubp J, White J, Borin M, Gambertoglio J, et al. Comparative study of bioavailabilities and pharmacokinetics of clindamycin in healthy volunteers and patients with AIDS. Antimicrob Agent Chemother 1993; 37: 1137–43.
8. Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med 2006; 354: 731–9.
9. Fontana RJ. Pathogenesis of idiosyncratic drug-induced liver injury and clinical perspectives. Gastroenterology 2014; 146(4): 914–28.
10. Daly AK. Drug-induced liver injury: Past, present and future. Pharmacogenomics 2010; 11(5): 607–11.
11. Beaune P, Dansette PM, Mansuy D, Kiffel L, Finck M, Amar C, et al. Human anti-endoplasmic reticulum autoantibodies appearing in a drug-induced hepatitis are directed against a human liver cytochrome P-450 that hydroxylates the drug. Proc Natl Acad Sci USA 1987; 84: 551–5.
12. Robin MA, Le Roy M, Descatoire V, Pessayre D. Plasma membrane cytochromes P450 as neoantigens and autoimmune targets in drug-induced hepatitis. J Hepatol 1997; 26(Suppl 1): 23–30.
13. Honig PK, Woosley RL, Zamani K, Conner DP, Cantilena LR Jr. Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. Clin Pharmacol Ther 1992; 52: 231–8.
14. Yun CH, Okerholm RA, Guengerich FP. Oxidation of the antihistaminic drug terfenadine in human liver microsomes: Role of cytochrome P-450 3A(4) in N-dealkylation and C-hydroxylation. Drug Metab Dispos 1993; 21: 403–9.
15. Trauner M, Meier PJ, Boyer JL. Molecular pathogenesis of cholestasis. N Engl J Med 1998; 339: 1217–27.
16. Reed JC. Apoptosis-regulating proteins as targets for drug discovery. Trends Mol Med 2001; 7: 314–19.
17. Pessayre D, Berson A, Fromenty B, Mansouri A. Mitochondria in steatohepatitis. Semin Liver Dis 2001; 21: 57–69.
18. Lee WM. Drug-induced hepatotoxicity. N Engl J Med 2003; 349: 474–85.
19. Kaplowitz N. Biochemical and cellular mechanisms of toxic liver injury. Semin Liver Dis 2002; 22: 137–44.
20. Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. Mayo Clin Proc 2014; 89(1): 95–106.
21. Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ, et al. ACG clinical guideline: The diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol 2014; 109: 950–966.
22. Bjornsson E. Review article: Drug-induced liver injury in clinical practice. Aliment Pharmacol Ther 2010; 32(1): 3–13.
23. Au JS, Navarro VJ, Rossi S. Review article: Drug-induced liver injury – Its pathophysiology and evolving diagnostic tools. Aliment Pharmacol Ther 2011; 34(1): 11–20.
24. Hussaini SH, Farrington EA. Idiosyncratic drug-induced liver injury: An update on the 2007 overview. Expert Opin Drug Saf 2014; 13(1): 67–81.
25. Kalb RE, Strober B, Weinstein G, Lebwohl M. Methotrexate and psoriasis: 2009 National Psoriasis Foundation Consensus Conference. J Am Acad Dermatol 2009; 60: 824–37.
26. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008; 59: 762–84.
27. Davern TJ, Chalasani N, Fontana RJ, Hayashi PH, Protiva P, Kleiner DE, et al. Acute hepatitis E infection accounts for some cases of suspected drug-induced liver injury. Gastroenterology 2011; 141: 1665–72, e1–9.

28. Czaja AJ. Corticosteroids or not in severe acute or fulminant autoimmune hepatitis: Therapeutic brinksmanship and the point beyond salvation. Liver Transpl 2007; 13: 953–5.
29. Ichai P, Duclos-Vallee JC, Guettier C, Hamida SB, Antonini T, Delvart V, et al. Usefulness of corticosteroids for the treatment of severe and fulminant forms of autoimmune hepatitis. Liver Transpl 2007; 13: 996–1003.
30. Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology 2009; 137(3): 856–64.e1.
31. Bawany MZ, Bhutto B, Youssef WI, Nawras A, Sodeman T. Acute liver failure: An uncommon complication of commonly used medication. Am J Ther 2013; 20(5): 566–8.
32. LiverTox, Clinical and Research Information on Drug-Induced Liver Injury. Clindamycin drug record. Available from: http://livertox.nih.gov/Clindamycin.htm [cited 10 January 2012].
33. Altraif I, Lilly L, Wanless IR, Heathcote J. Cholestatic liver disease with ductopenia (vanishing bile duct syndrome) after administration of clindamycin and trimethoprim-sulfamethoxazole. Am J Gastroenterol 1994; 89(8): 1230–4.
34. Sahagún Flores JE, Soto Ortiz JA, Tovar Méndez CE, Cárdenas Ochoa EC, Hernández Flores G. Stevens-Johnson syndrome plus intrahepatic cholestasis caused by clindamycin or chlorpheniramine. Dermatol Online J 2009; 15(5): 12.
35. Aygun C, Kocaman O, Gurbuz Y, Senturk O, Hulagu S. Clindamycin-induced acute cholestatic hepatitis. World J Gastroenterol 2007; 13(40): 5408–10.
36. Rangnekar AS, Fontana RJ. An update on drug induced liver injury. Minerva Gastroenterol Dietol 2011; 57(2): 213–29.
37. Sgro C, Clinard F, Ouazir K, Chanay H, Allard C, Guilleminet C, et al. Incidence of drug-induced hepatic injuries: A French population-based study. Hepatology 2002; 36: 451–5.
38. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989; 97: 439–45.
39. Lidofsky SD. Liver transplantation for fulminant hepatic failure. Gastroenterol Clin North Am 1993; 22: 257–69.
40. Bjornsson E, Davidsdottir L. The long-term follow-up after idiosyncratic drug-induced liver injury with jaundice. J Hepatol 2009; 50: 511–17.