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Case Report

Indomethacin Induced Toxic Hepatitis: A Case Report

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ABSTRACT

Nonsteroidal anti-inflammatory drugs deare widely used worldwide for analgesic, antipyretic and anti-inflammatory purposes. Indomethacin is a potent nonsteroidal anti-inflammatory drug and can cause severe liver damage. Few cases of idiosyncratic toxic hepatitis have been reported. Here, we present a case of indomethacin-induced toxic hepatitis that improved with methylprednisolone treatment.

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Introduction

Indomethacin is a potent nonsteroidal anti-inflammatory drug typically used for chronic inflammatory arthritis.[1] Fewer than a dozen cases of indomethacin related toxic hepatitis have been reported in the literatüre.[2-7] In this report, we discussed a case of indomethacin related toxic hepatitis, which recovered with palliative care and methylprednisolone treatment.

Case Report

A 23-year-old female patient, who had been well except for a history of hypothyroidism and levothyroxine 100 mcg/day use for 14 years, was referred to our centre with jaundice, dark urine, pale stool and itching. Due to low back pain, the patient received 25 mg/day for five days. The patient was admitted to the clinic to investigate the aetiology. The patient had liver damage in the hepatocellular pattern (R index: 11.5). The course of laboratory values was shown in Table 1.

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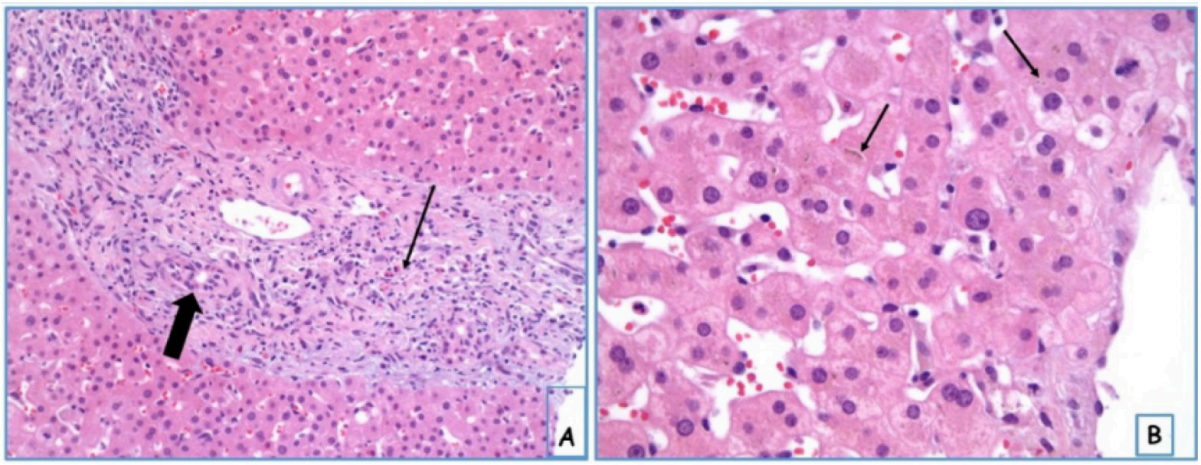
Table 1. The course of the patient's laboratory values.

Time after the onset of indomethacin	Event	AST (U/L)	ALT (U/L)	Bilirubin (mg/dL)	ALP (U/L)	GGT (U/L)	INR	Albumin (g/L)
Day 5		79	237	5.78	-	-	0.9	-
Day 10		86	230	7.69	-	67	1	47
Day 14		208	336	10.25	-	48	1	45
Day 18	Liver biopsy Methylprednisolone 1 mg/kg	296	473	9.86	220	45	1.1	42
Day 21		923	1,571	10.12	208	43	1	42
Day 24		1,533	3,019	7.54	180	68	1	44
Day 28		681	2.695	4.44	184	176	0.95	48
Day 38	Methylprednisolone 0.75 mg/kg	162	1.027	2.33	130	297	0.97	48
Day 48		88	358	1.48	109	305	0.9	47
Day 60	Methylprednisolone 0.5 mg/kg	64	157	0.6	82	250	1	47
Day 75		44	103	0.47	78	200	1	49
Day 90		34	55	0.67	84	113	1.1	45
Day 100	Discontinuation of methylprednisolone	33	49	0.41	83	83	0.94	44
Day 120		22	27	0.47	74	61	1	49

AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, INR: the international normalized ratio.

There was no alcohol or herbal medicine use and mushroom eating in the patient's history. Hepatitis A, B, C, and E, Epstein-Barr IgM, cytomegalovirus IgM, herpes simplex virus IgM and brucella agglutination tests were negative. Ceruloplasmin, 24-hour urine copper, ferritin, transferrin saturation and alpha-1-antitrypsin, IgM and IgG levels were within normal ranges. Kayser-Fleischer ring was not found in the ophthalmic examination. ANA, AMA, ASMA, LC-1, SLA/LP, LKM-1, c-ANCA, p-ANCA, PR3, MPO were negative. Anti-tissue transglutaminase IgA was negative. Abdominal ultrasonographic imaging revealed normal liver parenchyma and echogenicity. The bile ducts and gall bladder were normal.

Drug-induced toxic hepatitis was considered due to the emergence of hepatitis in the patient after taking the drug. There was no liver transplantation indication according to King's College criteria[8] in the patient who did not have an elevated INR and did not develop encephalopathy. The RUCAM (Roussel Uclaf Causality Assessment Method) score was calculated as fifteen.[9] A liver biopsy was performed. The biopsy result (*Picture 1*) was compatible with toxic cholangiopathy or hepatitis, and we started methylprednisolone 1x60 mg/day. The patient, who was followed up in the clinic for ten days, was discharged because there was no prolongation in the INR value and no development of encephalopathy. The patient's INR did not increase in the outpatient clinic controls, and bilirubin and transaminase levels returned normal. The methylprednisolone treatment was tapered and discontinued within three months.



Picture 1. Morphological evaluation of liver biopsy material; A: enlargement in the portal area, mixed inflammatory infiltration containing polymorphic nuclei and eosinophil leukocytes (thin arrow) and degenerative changes in bile duct epithelial cells (thick arrow) (HEx200), B: hepatocanalicular bilirubinocytosis (thin arrow) in the lobular area and hydropic degeneration of hepatocytes (HEx200).

Discussion

Toxic hepatitis is a disease that often occurs due to drugs and herbal substances. It encompasses a broad spectrum of clinical illnesses ranging from mild biochemical abnormalities to acute liver failure.[10] Mild and transient elevations in serum aminotransferase levels are found in up to 15% of patients taking indomethacin. Frank liver injury with jaundice from indomethacin is rare. The latency to onset symptoms or jaundice is variable but is usually within eight weeks of starting. Patients present with anorexia, nausea and vomiting followed by jaundice. Hepatocellular patterns of enzyme elevations are most common, but cholestatic and mixed patterns have been reported. The injury is usually self-limited, resolving in 1 to 3 months, but several fatal cases have been reported. Rechallenge may lead to recurrence and should be avoided.[11] Serum bilirubin values two times higher than normal and aminotransferases three times higher than normal are associated with poor prognosis.[12-14] Studies show that corticosteroid therapy may be beneficial.[15]

In the case presented, there was liver damage in the hepatocellular pattern. Her symptoms started one week after starting the drug. With the discontinuation of the drug and corticosteroid therapy, the patient's liver enzymes returned to normal within two months. Although indomethacin is known to cause liver damage, severe damage is rare. Therefore, in patients using indomethacin; If symptoms such as jaundice and dark urine colour develop, drug-related toxic hepatitis should be considered.

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: OS, TT, SGN, NU; Study Design: OS, TT, SGN, NU; Supervision: OS, TT, SGN, NU; Materials: OS, TT, SGN, NU; Data Collection and/or Processing: OS, TT, SGN, NU; Statistical Analysis and/or Data Interpretation: OS, TT, SGN, NU; Literature Review: OS, TT, SGN; Manuscript Preparation: OS, TT, SGN, ; Critical Review: OS, TT, SGN.

References

1. Huskisson EC, Taylor RT, Burston D, Chuter PJ, Hart FD. Evening indomethacin in the treatment of rheumatoid arthritis. Ann Rheum Dis. 1970 Jul;29(4):393-6. doi: 10.1136/ard.29.4.393.
2. Carson JL, Strom BL, Duff A, Gupta A, Das K. Safety of nonsteroidal anti-inflammatory drugs with respect to acute liver disease. Arch Intern Med. 1993 Jun 14;153(11):1331-6.
3. Cappell MS, Kozicky O, Competiello LS. Indomethacin-associated cholestasis. J Clin Gastroenterol. 1988 Aug;10(4):445-7. doi: 10.1097/00004836-198808000-00019.
4. Kelsey WM, Scharyj M. Fatal hepatitis probably due to indomethacin. JAMA. 1967 Feb 20;199(8):586-7.
5. Fenech FF, Bannister WH, Grech JL. Hepatitis with biliverdinaemia in association with indomethacin therapy. Br Med J. 1967 Jul 15;3(5558):155-6. doi: 10.1136/bmj.3.5558.155.
6. de Kraker-Sangster M, Bronkhorst FB, Brandt KH, Boersma JW. Massive liver cell necrosis following administration of indomethacin in combination with aminophenzone. Ned Tijdschr Geneeskd. 1981 Nov 7;125(45):1828-31 (in Dutch).
7. Opolon P, Cartron J, Chicot D, Caroli J. Application of the lymphoblastic transformation test (LTT) to the diagnosis of drug-induced hepatitis. Presse Med. 1969 Dec 20;77(54):2041-4 (in French).
8. Arıcı S. Toksik Hepatit. Pamukkale Tıp Dergisi. 2008;1(2):113-9.
9. Castaldo ET, Chari RS. Liver transplantation for acute hepatic failure. HPB (Oxford). 2006;8(1):29-34. doi: 10.1080/13651820500465741.
10. Danan G, Teschke R. RUCAM in drug and herb ınduced liver injury: The update. Int J Mol Sci. 2016;17(1):14. doi: 10.3390/ijms17010014.
11. Indomethacin. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012. 2018 Mar 23.
12. Andrade RJ, Lucena MI, Fernández MC, Pelaez G, Pachkoria K, García-Ruiz E, García-Muñoz B, González-Grande R, Pizarro A, Durán JA, Jiménez M, Rodrigo L, Romero-Gomez M, Navarro JM, Planas R, Costa J, Borras A, Soler A, Salmerón J, Martin-Vivaldi R; Spanish Group for the Study of Drug-Induced Liver Disease. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. Gastroenterology. 2005 Aug;129(2):512-21. doi: 10.1016/j.gastro.2005.05.006.
13. Björnsson E. Drug-induced liver injury: Hy's rule revisited. Clin Pharmacol Ther. 2006 Jun;79(6):521-8. doi: 10.1016/j.clpt.2006.02.012.
14. Reuben A. Hy's law. Hepatology. 2004 Feb;39(2):574-8. doi: 10.1002/hep.20081.
15. Andrade RJ, Chalasani N, Björnsson ES, Suzuki A, Kullak-Ublick GA, Watkins PB, Devarbhavi H, Merz M, Lucena MI, Kaplowitz N, Aithal GP. Drug-induced liver injury. Nat Rev Dis Primers. 2019 Aug 22;5(1):58. doi: 10.1038/s41572-019-0105-0.