Indomethacin Induced Toxic Hepatitis: A Case Report

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A B S T R A C T

Nonsteroidal anti-inflammatory drugs are 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.

Keywords: Nonsteroidal anti-inflammatory drugs, adverse effect, indomethacin, liver damage, idiosyncratic toxic hepatitis, methylprednisolone treatment.

Introduction

Indomethacin is a potent nonsteroidal anti-inflammatory drug typically used for chronic inflammatory arthritis. Fewer than a dozen cases of indomethacin related toxic hepatitis have been reported in the literature. 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.
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 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. A liver biopsy was performed. The biopsy result 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.

### Table 1. The course of the patient’s laboratory values.

<table>
<thead>
<tr>
<th>Time after the onset of indomethacin</th>
<th>Event</th>
<th>AST (U/L)</th>
<th>ALT (U/L)</th>
<th>Bilirubin (mg/dL)</th>
<th>ALP (U/L)</th>
<th>GGT (U/L)</th>
<th>INR</th>
<th>Albumin (g/L)</th>
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</thead>
<tbody>
<tr>
<td>Day 5</td>
<td></td>
<td>79</td>
<td>237</td>
<td>5.78</td>
<td>-</td>
<td>-</td>
<td>0.9</td>
<td>-</td>
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<tr>
<td>Day 10</td>
<td>Liver biopsy</td>
<td>86</td>
<td>230</td>
<td>7.69</td>
<td>-</td>
<td>67</td>
<td>1</td>
<td>47</td>
</tr>
<tr>
<td>Day 14</td>
<td></td>
<td>208</td>
<td>336</td>
<td>10.25</td>
<td>-</td>
<td>48</td>
<td>1</td>
<td>45</td>
</tr>
<tr>
<td>Day 18</td>
<td></td>
<td>208</td>
<td>336</td>
<td>10.25</td>
<td>-</td>
<td>48</td>
<td>1</td>
<td>45</td>
</tr>
<tr>
<td>Day 21</td>
<td>Methylprednisolone 1 mg/kg</td>
<td>296</td>
<td>473</td>
<td>9.86</td>
<td>220</td>
<td>45</td>
<td>1.1</td>
<td>42</td>
</tr>
<tr>
<td>Day 21</td>
<td></td>
<td>923</td>
<td>1,571</td>
<td>10.12</td>
<td>208</td>
<td>43</td>
<td>1</td>
<td>42</td>
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<tr>
<td>Day 24</td>
<td></td>
<td>1,533</td>
<td>3,019</td>
<td>7.54</td>
<td>180</td>
<td>68</td>
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<td>44</td>
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<td>Day 28</td>
<td></td>
<td>681</td>
<td>2,695</td>
<td>4.44</td>
<td>184</td>
<td>176</td>
<td>0.95</td>
<td>48</td>
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<td>Day 38</td>
<td>Methylprednisolone 0.75 mg/kg</td>
<td>162</td>
<td>1,027</td>
<td>2.33</td>
<td>130</td>
<td>297</td>
<td>0.97</td>
<td>48</td>
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<tr>
<td>Day 48</td>
<td></td>
<td>88</td>
<td>358</td>
<td>1.48</td>
<td>109</td>
<td>305</td>
<td>0.9</td>
<td>47</td>
</tr>
<tr>
<td>Day 60</td>
<td>Methylprednisolone 0.5 mg/kg</td>
<td>64</td>
<td>157</td>
<td>0.6</td>
<td>82</td>
<td>250</td>
<td>1</td>
<td>47</td>
</tr>
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<td>Day 75</td>
<td></td>
<td>44</td>
<td>103</td>
<td>0.47</td>
<td>78</td>
<td>200</td>
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<td>49</td>
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<td>Day 90</td>
<td></td>
<td>34</td>
<td>55</td>
<td>0.67</td>
<td>84</td>
<td>113</td>
<td>1.1</td>
<td>45</td>
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<tr>
<td>Day 100</td>
<td>Discontinuation of methylprednisolone</td>
<td>33</td>
<td>49</td>
<td>0.41</td>
<td>83</td>
<td>83</td>
<td>0.94</td>
<td>44</td>
</tr>
<tr>
<td>Day 120</td>
<td></td>
<td>22</td>
<td>27</td>
<td>0.47</td>
<td>74</td>
<td>61</td>
<td>1</td>
<td>49</td>
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</tbody>
</table>

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. 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. Serum bilirubin values two times higher than normal and aminotransferases three times higher than normal are associated with poor prognosis. Studies show that corticosteroid therapy may be beneficial.

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.

Acknowledgment

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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.

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).
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