Case Report

Ticlopidine-induced Hepatitis

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Key Words
hepatitis; ticlopidine; toxic

Ticlopidine is a commonly prescribed drug in cerebrovascular or cardiovascular diseases. Since the first introduction in 1970's, ticlopidine was shown to be a relatively safe drug. The adverse effects of ticlopidine were mainly bone marrow toxicity and elevation of liver function tests. Ticlopidine-induced hepatitis is rare and only 33 cases were reported in previous English literature. In Taiwan, a case of ticlopidine-induced cholestatic hepatitis was ever reported. Herein, we present another rare case of ticlopidine-induced hepatitis in Taiwan with nature of hepatocellular liver injury.

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Case Report

A 72-year-old male visited our out-patient department (OPD) because of the persistence of general malaise, tea-colored urine and jaundice for one week. The physical examinations were performed thoroughly without any particular abnormal findings except icteric sclera. A month before the discomfort, he underwent a physical check-up in a local hospital where normal liver function tests were disclosed and ticlopidine 100mg tid, loratadine 10mg qd, and tim epidium bromide 30mg tid were prescribed for him due to bilateral carotid atheroma. He took the medicines regularly for three weeks until he visited our OPD. Thereafter, he was admitted for further survey and management. Reviewing his disease course, there was no fever, no chills, no abdominal discomfort or recent body weight reduction and he denied any underlying liver diseases. He also denied habitual alcohol consumption or recent traveling history. The liver function tests showed elevated total bilirubin of 12.8 mg/dL, with a direct form of 9.3 mg/dL, alanine amino transferase (ALT) of 847 U/L (0-40 U/L), aspartate aminotransferase (AST) of 393 U/L (5-45 U/L), r-glutamyl transpeptidase (GGT) of 648 U/L (8-61 U/L). The complete blood cell (CBC) analysis showed no leukocytosis, leukopenia or other abnormalities. Serological tests for viral hepatitis A,

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B, and C in cluding antiHAV-IgM (Abbott, IL, USA), HBsAg (Abbott, Abbott Park, IL, USA), antiHBc-IgM (Abbott, Abbott Park, IL, USA), and anti-HCV (Ever-New, Tai pei, Tai wan) were all neg a tive. The se rum eosinophil count and im mu no glob ulin E were both within the nor mal ranges. Ab dom i nal sono graphy and endoscopic retrograde cholangiopancreato graphy (ERCP) showed no no ta ble le sions. Other rare vir al hep a ti tis mark ers as cy tome ga lovirus (CMV), her pes sim plex vi rus (HSV) and Ep stein-Barr vi rus (EBV) were neg a tive. Anti-nuclear an ti body and anti- mito chond rial an ti body were neg a tive also. Liver bi opsy was per formed and the pa thol ogy dis closed choles tasis in the hepatocytes and canaliculi around the centro lob ular ar eas (Fig. 1). Tiny foci of spotty ne cro sis were noted in fo cal centrilobular area. There was no bridging hepatic necrosis and drug-induced cholestasis was highly favored. The liver function

tests improved grad u ally af ter dis con tin u a tion of the pre vious medic a tion (Table 1).

**Discussion**

Re viewing the drug his tory of this pa tient, ticlo pidine was the only newly pre scribed agent 3 weeks before the hepatitis episode. Loratadine and time pidium were pre scribed and con tin u ously taken for 2 months be fore the dis com fort and there is no loratat dine or timepidium-induced hep a ti tis ever re ported in the lit er a tures re view. Ticlopidine is rel a tively a safe drug. Ticlopidine As pi rin Stroke Study (TASS) re ported no ad verse hepatotoxicity of ticlopidine.\(^5\) How ev er, the in ci dence of ab nor mal liver func tion tests was 4.4 % in CATS.\(^2\) To date, 33 cases of ticlopidine-induced hep a ti tis were re ported in major Eng lish liter-

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<thead>
<tr>
<th>Table 1. Evolutionary change of liver function tests of the patient with ticlopidine-induced hepatitis</th>
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<tr>
<td>Alanine aminotransferase (0-40 U/L)</td>
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<tr>
<td>Aspartate aminotransferase (5-45 U/L)</td>
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<tr>
<td>Alkaline phosphatase (10-100 U/L)</td>
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<td>γ-Glutamyltranspeptidase (8-61 U/L)</td>
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<tr>
<td>Total bilirubin (0.2-1.6 mg/dl)</td>
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Fig. 1. Liver bi opsy showed tiny foci of spotty ne cro sis (ar row) in fo cal cen tri lobular area (H&E stain, 400X).
The confirmation of drug-induced hepatitis relies mainly on re-challenge of the suspected agent, but re-challenge of the suspected agent is obviously not realistic nowadays. There is an alertative clinical scale for the diagnosis of drug-induced hepatitis. This patient we pre-sented falls in the category of probable drug-induced hepatitis that stands for the accuracy of 92%. The daily dose age of ticlopidine for this patient was 300 mg. It is compatible with the previous series of the 33 cases that reported the daily dose range from 250-500 mg. The average age of the reported cases ranged from 29 to 92 (me dian: 69.45) and this patient is 72-year-old. The latency period ranged from 1 to 16 weeks (me dian: 5.37 weeks) and this patient is 3 weeks. The clinical presentation of patients in previous reports is mainly jaundice and other non-specific ones as pruritus, abdominal discomfort, skin eruption, anorexia, fever, nausea, and weakness. This patient presented general malaise and jaundice on his visit of our OPD. The per iod of recovery of liver function tests ranged from 11 days to 1 year (median: 4.8 months) and this patient takes 10 weeks to recover. The characteristics of ticlopidine-induced hepatitis of this patient are very similar to those of the previous reports. All the acute viral hepatitis markers were checked during the course of illness. The appearance of anti-HCV antibody might be delayed for 1-2 months, some times 4 months following the acute phase of liver injury. How ever, this con-di-tion is ex cluded by the repeated negative surveys of anti-HCV in the following OPD visits. According to all the available information on the acute phase of this patient in cluding clinical course and liver biopsy, the mechanism of ticlopidine-induced hepatic injury is of this patient likely to be idiosyncratic and the classification of this liver injury is hepatocellular rather than cholestatic.

Despite the low in incidence of ticlopidine-induced hepatitis, periodic check-up of blood routine and liver function tests every 3 months are recommended for those who regularly take ticlopidine to early detect the possible neutropenia or liver function impairment.

**References**


