

Acute Liver Failure Associated with Propylthiouracil in a Pregnant 26-Year-Old Woman

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Key Words

Acute liver failure · First trimester · Immune tolerance · Pregnancy · Propylthiouracil

Abstract

It seems appropriate to use propylthiouracil to treat maternal hyperthyroidism during the first trimester of pregnancy. We present the case of a 26-year-old woman with acute liver failure associated with propylthiouracil during the first trimester of pregnancy. She was successfully treated without liver transplantation. Attention should be paid to the possible occurrence of propylthiouracil-induced hepatotoxicity even during the first trimester of pregnancy.

Introduction

Based on a re-analysis of medical files reported to the US Food and Drug Administration (FDA) (1982–2008) for acute liver failure associated with propylthiouracil (PTU), it has been recommended that attention should be paid to the use of this drug [1]. Previous studies showed that the effect of PTU was significantly less than that of radioiodine treatment, and also that the effect of methimazole (MMI) was the same as that of radioiodine [2]. As the relative risk of MMI-induced choanal atresia and MMI causing a specific pattern of rare teratogenic effects after first-trimester exposure were reported, it has been considered appropriate to use PTU to treat maternal hyperthyroidism during the first trimester of pregnancy [3]. On the other hand, it has been reported that PTU can induce severe hepatotoxicity

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[3–6]. We report a rare case of acute liver failure in the first trimester during pregnancy, in PTU treatment following MMI for hyperthyroidism.

Case Report

A 26-year-old Japanese woman was referred to Chiba University Hospital for the treatment of acute liver failure. Blood tests showed serum alanine aminotransferase (ALT) 399 IU/l, aspartate aminotransferase (AST) 590 IU/l, alkaline phosphatase 677 IU/l, total bilirubin 15.9 mg/dl and prothrombin time international normalized ratio 1.78. She was diagnosed with hyperthyroidism (Graves' disease) at age 14, and she was treated with MMI 1 year before admission to our hospital. Five months before admission, she started taking PTU instead of MMI in consideration of her upcoming childbirth. Three months before admission (at 4 weeks gestation), mild liver dysfunction appeared (AST 76 IU/l, ALT 88 IU/l and total bilirubin 1.8 mg/dl). At 8 weeks gestation, her liver function test had not improved (AST 72 IU/l, ALT 104 IU/l and total bilirubin 1.6 mg/dl). One week before admission (at 11 weeks gestation), she underwent surgery for miscarriage at the first clinic. Three days before admission, she had developed fatigue and jaundice and was referred to our hospital. The clinical data at admission to our hospital are shown in [table 1](#). She had no drug hypersensitivities, liver diseases, blood transfusion or history of surgery other than the above. She did not drink alcohol and had no family history of liver disease. Physical examination revealed jaundice but no consciousness disturbance. Ultrasound examination and computed tomography showed a non-atrophic liver and no ascites. There were no positivities for any viral markers ([table 1](#)). A drug lymphocyte stimulation test for PTU was positive (stimulation index 234%; 100% for control) [7]. We diagnosed her as acute liver failure associated with PTU, without presenting hepatic encephalopathy. We started medical treatment such as glycyrrhizin, vitamin K and gabexate mesilate administration and made preparations for urgent liver transplantation [6, 7]. She improved and was discharged 26 days after admission ([fig. 1](#)).

During her hospitalization, 20 days after admission, liver biopsy was performed ([fig. 2](#)), and the specimen showed preserved architecture of the liver, with centrilobular necrosis and ceroid granules also being observed, findings compatible with drug-related liver injury.

Discussion

In the present case, the total dose of PTU was 5,700 mg, but until the onset of liver dysfunction, the dose of PTU was 1,400 mg. Unlike MMI, the side effects of PTU are not dose-related [6]. We diagnosed her as acute liver failure associated with PTU, as other causes could be ruled out. PTU-induced hepatotoxicity is rare but potentially lethal, with a spectrum of liver injury ranging from asymptomatic elevation of ALT levels to acute liver failure and death [6, 8–13]. Over the past 60 years of PTU and MMI use, reports of PTU-related liver failure and death have accumulated [13].

The FDA reported that of 32 patients taking PTU who developed serious liver injury, 13 died and 11 required a liver transplant, and that of 5 adults taking MMI who developed serious liver injury, 3 died [14]. A multicenter study from Korea reported that the risk of hepatic adverse drug events evaluated by the reported odds ratio values was high with PTU [15]. Current PTU use in children should be stopped in favor of alternate therapies [16]. PTU may be the treatment of choice during, and just before, the first trimester of pregnancy [5]

because it is believed that MMI has a relative risk of choanal atresia in the first trimester of pregnancy [3].

Sequeira et al. [6] reported a case with severe PTU-induced hepatotoxicity in the second trimester of pregnancy. Acute liver failure during pregnancy occurs more frequently in the third trimester of gestation, and its etiology is usually related to acute fatty liver of pregnancy and infectious diseases [17, 18]. Of interest in our case was the fact that severe PTU-associated acute liver failure occurred in the first trimester.

In the present case, the patient's liver function transiently worsened after surgery due to miscarriage. Pregnancy induces a state of immune tolerance with improvement of liver tests, and a flare-up often occurs after delivery as in autoimmune hepatitis [19]. It is possible that an immune mechanism of hepatotoxicity is involved in PTU-associated liver injury. In conclusion, clinicians should pay attention to the possible occurrence of PTU-induced hepatotoxicity even during the first trimester of pregnancy.

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Table 1. Laboratory data on admission to Chiba University Hospital

White blood cells	6,700/ μ l	HBsAg	–
Eosinophils	7.1%	IgM-HBc	–
Red blood cells	493×10^4 / μ l	HBV DNA	–
Hemoglobin	11.0 g/dl	IgM-HA	–
Platelets	23.7×10^4 / μ l	Anti-HCV	–
PT%	29%	HCV RNA	–
PT-INR	1.78	HEV RNA	–
Total cholesterol	163 mg/dl	IgG	1,456 mg/dl
Total protein	6.0 g/dl	IgA	294 mg/dl
Albumin	3.1 g/dl	IgM	176 mg/dl
AST	590 IU/l	HGF	0.60 ng/ml
ALT	399 IU/l	IgM-EBV VCA	–
LDH	213 IU/l	IgM-CMV	–
γ -GTP	68 IU/l	IgM-HSV	–
ALP	677 IU/l	Anti-HIV	–
Total bilirubin	15.9 mg/dl	Antinuclear antibody	–
Ammonia	107 μ g/dl	ASMA	–
TSH	0.01 μ IU/ml	AMA	–
Free T3	2.28 pg/ml	Ceruloplasmin	26 mg/dl
Free T4	0.87 ng/ml	AFP	35.3 ng/ml

AFP = Alpha-fetoprotein; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AMA = anti-mitochondrial antibody; anti-HCV = HCV antibody; ASMA = anti-smooth muscle antibody; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; free T3 = free triiodothyronine; free T4 = free thyroxine; γ -GTP = gamma-glutamyl transpeptidase; HBsAg = hepatitis B (HB) surface antigen; HGF = hepatocyte growth factor; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; IgM-HA = hepatitis A antibody IgM; IgM-HBc = HB core IgM antibody; PT-INR = prothrombin time international normalized ratio; TSH = thyroid-stimulating hormone; – = negative.

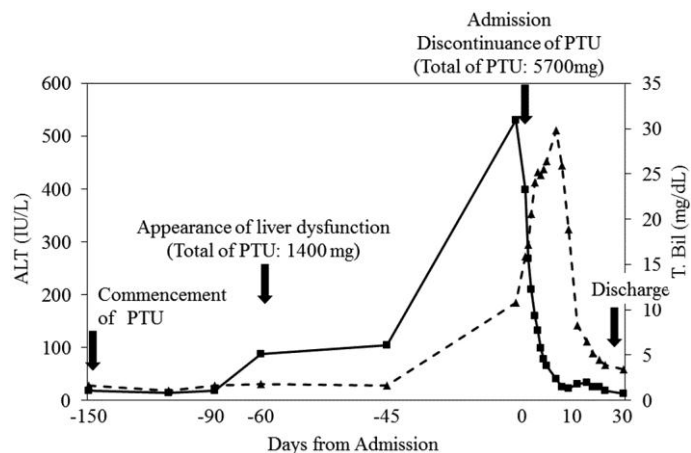


Fig. 1. Chart describing the course of ALT (black squares) and total bilirubin (black triangles) from the commencement of PTU administration until 1 week after discharge. ALT levels peaked at 531 IU/l. The total dose of PTU was 5,700 mg before admission. The patient improved after stopping PTU.

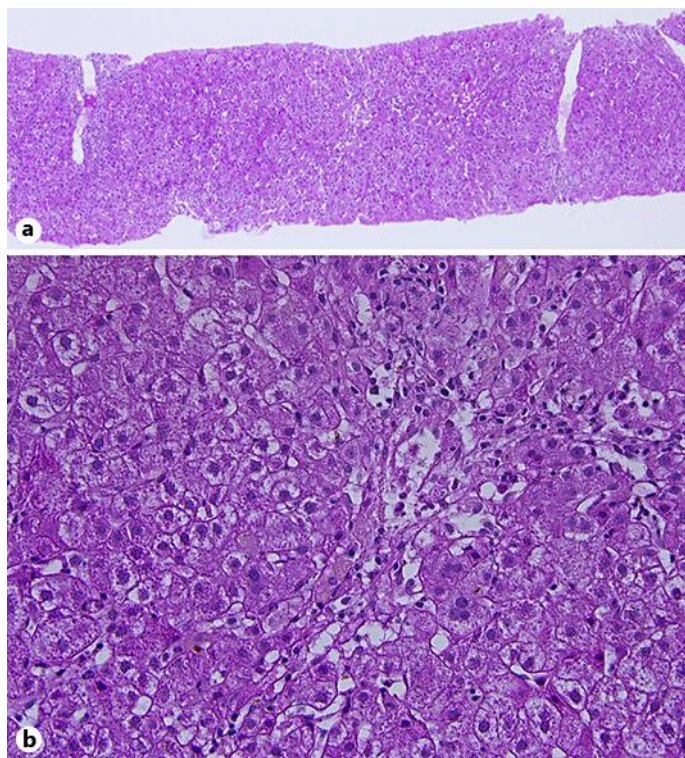


Fig. 2. Liver biopsy showed normal architecture of the liver and no cirrhosis (hematoxylin and eosin; original magnification 40×) (a). Centrilobular necrosis was also found (hematoxylin and eosin; original magnification 200×) (b). We diagnosed the patient as drug-induced liver injury associated with PTU.