

Propylthiouracil-induced liver failure and artificial liver support systems: a case report and review of the literature

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Background: Antithyroid drugs carry a potential risk of hepatotoxicity. Propylthiouracil (PTU) is commonly prescribed for patients with hyperthyroidism. PTU, however, can induce liver injury, ranging from mild asymptomatic elevation of aminotransferases to acute liver failure (ALF).

Case presentation: This case reports on a 16-year-old Chinese girl with hyperthyroidism, who was admitted to our hospital for jaundice, nausea, and fatigue associated with severe hyperbilirubinemia and coagulopathy. She had been prescribed PTU 5 months earlier. There was no history of hypersensitivity to drugs, viral liver diseases, blood transfusion, or surgery. On the basis of her symptoms and the clinical data, she was diagnosed with PTU-induced ALF. Due to the limited number of available donor organs for liver transplantation, she was started on treatment with artificial liver support system (ALSS). After four sessions of ALSS, her clinical signs and symptoms were found to be markedly improved, and she was discharged 25 days after admission. Four months later, her liver function normalized.

Conclusion: Although PTU-induced liver failure is rare in clinical practice, liver function should be appropriately monitored during treatment with PTU. PTU-induced ALF in this patient was successfully managed with an ALSS, suggesting that the latter may be an alternative to liver transplantation.

Keywords: propylthiouracil, liver injury, acute liver failure, artificial liver support systems

Introduction

Antithyroid drugs (ATDs), including propylthiouracil (PTU), methimazole (MMI), and carbimazole (CBM), are the primary medical agents used to treat hyperthyroidism.¹ PTU is commonly prescribed for patients with hyperthyroidism, especially for pregnant women during their first trimester.¹ Drug-induced liver injury (DILI), ranging from mild asymptomatic elevation of aminotransferases to acute liver failure (ALF),² however, has been observed in some patients treated with ATDs. This case report describes a patient with PTU-induced ALF, who was successfully managed with an artificial liver support system (ALSS), suggesting that the latter may be an alternative to liver transplantation.

Case presentation

A 16-year-old Chinese girl was admitted to West China Hospital of Sichuan University for the treatment of liver failure on 15 January 2015. A written informed consent was obtained from the patient's parent for the publication of this case report. Five months earlier, she had been diagnosed with hyperthyroidism (Grave's disease) at a local hospital

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and was prescribed PTU 50 mg every 12 hours. Two weeks before admission to our hospital, after treatment with PTU for 4 months, she began to experience a change in urine color, decreased appetite, and increasing icterus of the sclera and skin. At admission to our hospital, her thyroid-stimulating hormone concentration was 0.025 mU/L (normal range, 0.27–4.2 mU/L), free triiodothyronine was 13.68 pmol/L (normal range, 3.6–7.5 pmol/L), free thyroxine was 92.33 pmol/L (normal range, 12.0–22.0 pmol/L), thyrotrophin receptor antibody was 19.98 IU/L (normal range, <3 IU/L), and ammonia concentration was 136 μ mol/L (normal range, 9.0–33.0 μ mol/L). Her hepatic function tests revealed a total bilirubin of 408.9 μ mol/L (normal range, 5.0–28.0 μ mol/L), direct bilirubin of 298.7 μ mol/L (normal range, <8.8 μ mol/L), alanine aminotransferase (ALT) of 130 IU/L (normal range, <40 IU/L), aspartate aminotransferase (AST) of 100 IU/L (normal range, <35 IU/L), alkaline phosphatase of 389 IU/L (normal range, 105–560 IU/L), gamma-glutamyl transpeptidase of 79 IU/L (normal range, <45 IU/L), total protein of 54.9 g/L (normal range, 65.0–85.0 g/L), and albumin of 32.9 g/L (normal range, 40.0–55.0 g/L). Coagulation tests showed a prothrombin time of 27.0 seconds (normal range, 9.6–12.8 seconds) and prothrombin time international normalized ratio of 2.35 (normal range, 0.88–1.15). She was negative for serum markers of hepatitis A, B, C, D, and E; human immunodeficiency virus; Epstein–Barr virus; cytomegalovirus; and for antibodies indicative of autoimmune hepatitis (antinuclear antibody, smooth muscle antibody, liver/kidney microsome type 1, liver cytosol type 1, soluble liver antigen, and antineutrophil cytoplasmic antibody) and primary biliary cirrhosis (antimitochondrial antibody). She had no history of drug hypersensitivity, liver diseases, blood transfusion, or surgery. She denied using over-the-counter

and traditional Chinese medicines. She did not drink alcohol and did not use recreational drugs. Her medical history and family history were not contributory. Physical examination revealed that her temperature was 37°C, blood pressure was 116/76 mmHg, pulse rate was 110 beats per minute, and breathing rate was 20 times per minute. She presented with severe icterus of the sclera and skin, but had experienced no disturbances in consciousness. Her thyroid was diffusely enlarged. Cardiovascular, respiratory, and abdominal examinations were normal. Ultrasound examination and computed tomography showed no obvious changes in her liver, pancreas, and spleen and no ascites. On the basis of these findings, she was diagnosed with PTU-induced ALF, without hepatic encephalopathy. PTU was discontinued, and medical treatment was started.

After 4 days of hepatoprotective treatment, she showed progressive worsening of itching, jaundice, and nausea, as well as deterioration in liver function, including total bilirubin 442.8 μ mol/L, direct bilirubin 350.7 μ mol/L, ALT 103 IU/L, AST 186 IU/L, total protein 49.7 g/L, and albumin 30.5 g/L. Owing to the limited number of donor organs available for liver transplantation, she was started treatment with ALSS. After four sessions of ALSS treatment, her clinical signs and symptoms were found to be improved, as the laboratory parameters showed (Table 1). Her total bilirubin level gradually improved to 122.1 μ mol/L, followed by improvements in symptoms by the time she was discharged 25 days after admission. Her liver function normalized after 4 months.

Discussion

More than 1100 drugs, herbal medicines, minerals, natural products, vitamins, dietary supplements, and recreational drugs have been found to cause DILI.^{3–5} In the USA,

Table 1 Biochemical parameters in the patient after each ALSS session

ALSS session	Total bilirubin (μ mol/L)	Direct bilirubin (μ mol/L)	ALT (IU/L)	AST (IU/L)	Bile acid (μ mol/L)	Ammonia (μ mol/L)
1 (Day 5)						
Before	442.8	350.7	103	186	346.6	128
After	205.9	158	53	100	277.5	55
2 (Day 7)						
Before	343.6	254.2	82	187	321.4	56
After	186.2	133	49	107	251	40
3 (Day 9)						
Before	250.1	189.2	40	49	295.4	42
After	129.8	97.5	23	30	236.6	58
4 (Day 12)						
Before	224	163	24	39	229.6	60
After	126.4	90.5	17	29	201.9	25

Note: Normal range was <10 μ mol/L for bile acid.

Abbreviations: AST, aspartate aminotransferase; ALSS, artificial liver support system; ALT, alanine aminotransferase.

DILI is the major cause of ALF, which can lead to liver transplantation and even death.³ The estimated incidence of ATD-associated hepatotoxicity ranges from 0.1% to 0.2%.⁶ PTU-induced hepatitis was first reported in 1947 in a patient who successfully recovered following drug discontinuation and supportive care.⁷ Six years later, the first case of PTU-induced liver failure was reported.⁸ Since then, these severe adverse events (AEs) have been observed in an extremely small number of patients receiving PTU.⁸ PTU-related AEs include rashes, leukopenia, arthritis, vasculitis, liver injury, and death, whereas MMI-related AEs include rashes, urticaria, arthralgias, vasculitis, and liver injury.^{9,10} PTU is able to inhibit the enzyme thyroperoxidase and block iodine organification. It also inhibits the enzyme 5'-deiodinase which converts thyroxine (T4) into the active triiodothyronine (T3).¹⁰

Approximately 15,000 adults per year are treated with PTU in the USA, with ~0.1% experiencing PTU-induced severe liver injury.¹¹ Another study evaluating 71,379 patients with hyperthyroidism in Taiwan found that the incidence of ATD-induced hepatitis was high, being 1.19/1000 person-years and 3.17/1000 person-years in patients treated with PTU and MMI/CBM, respectively.¹² Moreover, treatment with high-dose MMI/CBM was found to be associated with a 5.08-fold increased risk of hepatitis compared with any use of PTU.¹² However, the risk of ALF was significantly higher in patients treated with PTU than MMI/CBM, with 1 of 17,688 patients requiring liver transplantation.¹² The US Food and Drug Administration (FDA) has reported that of 32 patients (22 adults and 10 children) taking PTU who developed to ALF, 13 (12 adults and 1 child) died and 11 (5 adults and 6 children) required liver transplantation, whereas, of 5 adult patients taking MMI who developed to ALF, 3 died.¹³ It has been indicated that children appeared to be at higher risk for PTU-induced liver injury than adults.^{1,10} Although PTU has been recommended to women with hyperthyroidism during their first trimester of pregnancy,¹ the FDA has described two pregnant women who experienced adverse effects of PTU treatment,¹⁴ and another case report described a 26-year-old woman with PTU-associated ALF during her first trimester of pregnancy.¹⁵ Treatment with MMI, which is also frequently prescribed for patients with hyperthyroidism, can induce cholestatic hepatitis after drug exposure ranging from 2 days to 3 months.⁹

Although liver failure is associated with high morbidity and mortality rates, treatment options are limited. Orthotopic liver transplantation is the only ultimate treatment for patients with liver failure and end-stage liver disease, improving their overall survival rate.¹⁶ Owing to the limited number of donor

organs available for liver transplantation, many patients die while on the waiting list. ALSS is developed to remove the water-soluble substances, lipophilic, and albumin-bound substances, thereby reducing recovery time from liver injury and serving as the bridge to liver transplantation.^{17,18} ALSS could significantly improve clinical manifestations, liver function, and 30-day survival rates in patients with acute-on-chronic liver failure.¹⁹ A case report described a patient with PTU-associated fulminant hepatic failure who was successfully managed with plasmapheresis.²⁰ The ALSS used in this case was a plasma exchange (PE)-centered ALSS, which is widely applied in clinical practice across China according to the guidelines for artificial liver therapy.²¹ Our patient received four sessions of ALSS (including PE and plasma bilirubin adsorption) and conventional medical treatment. Her clinical parameters were markedly improved after each ALSS session, accompanied by decreased serum concentration of total bilirubin, direct bilirubin, ALT, AST, bile acid, and ammonia. However, a liver biopsy sample was not obtained owing to her parents' refusal. The classic histologic changes associated with PTU-induced hepatic injury include preserved liver architecture without evidence of advanced fibrosis and cirrhosis, chronic lobular hepatitis with cholestasis, and centrilobular necrosis.^{15,22} In summary, ATDs carry a potential risk of hepatotoxicity. Although PTU-induced liver failure is rare in clinical practice, liver function should be appropriately monitored during treatment with PTU, especially in the first 6 months of therapy, the period during which most cases of PTU-induced liver injury occur. Drug-induced ALF can be severe and even life-threatening, which may call for liver transplantation. Owing to the limited number of donor organs in China, ALSS may provide an alternative to liver transplantation for the treatment of PTU-induced liver failure.

Conclusion

Although propylthiouracil (PTU)-induced liver failure is rare in clinical practice, liver function should be appropriately monitored during treatment with PTU. PTU-induced acute liver failure in this patient was successfully managed with an ALSS, suggesting that the latter may be an alternative to liver transplantation.

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Disclosure

The authors report no conflicts of interest in this work.

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