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Case Report

Fulminant Hepatic Failure Associated With Propylthiouracil: A Case Report With Treatment Emphasis on the Use of Plasmapheresis

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Propylthiouracil is a commonly used medication for hyperthyroidism. Though propylthiouracil-induced hepatotoxicity is a rarely encountered problem, death due to fulminant hepatic failure may occur. In the English literature, only 34 cases have been described with severe hepatotoxicity secondary to this drug. Here we report a case of fulminant hepatic failure due to propylthiouracil and review the issues of treatment and management with special emphasis on the use of plasmapheresis in such situations. J. Clin. Apheresis 20:235–238, 2005. © 2005 Wiley-Liss, Inc.

Key words: propylthiouracil; hyperthyroidism; fulminant hepatic failure; plasmapheresis

INTRODUCTION

Propylthiouracil (PTU) induced hepatotoxicity is a rare but potentially life threatening situation [1–28]. High mortality in such settings may be observed [1–9]. Rather than direct toxicity, varied immune mechanisms have been postulated to explain severe PTU hepatotoxicity [2,13,14,18,20,22,29].

Few treatment options exist. Evidence for the benefits of plasmapheresis in the setting of PTU-induced severe hepatic failure is contradictory [2,5]; however, plasmapheresis has been shown to be of potential value in the management of various thyroid diseases, including hyperthyroidism, immune-mediated hepatic toxicity, coagulopathy, and encephalopathy [30–34]. Here we report a case of a patient with fulminant hepatic failure due to PTU who improved markedly after plasmapheresis with eventual recovery of hepatic function.

CASE REPORT

A 22-year-old female, previously diagnosed with Grave's disease, was admitted with confusion and signs of agitation. One and a half years prior to admission she began daily oral PTU therapy (400 mg). Within 20 days of admission, her PTU dose had been increased to 600 mg per day. At that time, liver function tests were completely normal. Three weeks later, she developed icterus and became anxious. There was no history of concurrent drug use, alcohol abuse, or any prior episodes of jaundice, hepatitis, or blood transfusions. Physical examination revealed a heart rate of 135 beats/min, blood pressure of 160/80 mmHg, and respiratory rate of 20 breaths per minute, and a temperature of 36.8°C, with generalized icterus, tremor, and bilateral exophthalmia. The thyroid gland was diffusely palpable. The patient's liver was not palpable and no splenomegaly and ascites were present. Laboratory evaluations were consistent with thyrotoxicosis and hepatotoxicity (Table I). Tests for hepatitis A, B, C, and E viruses and autoimmunity markers such as anti-nuclear antibody, anti-smooth muscle antibody, anti-mitochondrial antibody, anti-liver/kidney microsome antibody, anti-soluble liver antigen antibody, and perinuclear antineutrophil

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TABLE I. Thyroid and Liver Function Tests on Admission and After First Plasmapheresis Session

	Normal range	Admission	After first plasmapheresis
ALT (U/L)	3–42	1,350	898
AST (U/L)	3–37	990	554
GGT (U/L)	4–50	54	42
ALP (U/L)	40–125	266	218
Bilirubin, total (mg/dL)	0–1.2	26	20.4
Bilirubin, direct (mg/dL)	0–0.4	21.3	17
Prothrombin time (Sec)	8.8–11.6	69.7	37
Free T_3 (Ng/dL)	1.8–4.6	4.9	2.9
Free T_4 (Ng/dL)	0.9–1.7	3.7	2.8
TSH (IU/mL)	0.27–4.2	0.01	0.01

cytoplasmic antibodies were all negative. Antibodies to the thyrotropin receptor, thyroglobulin, and thyroid peroxidase were, however, all positive. Immunofluorescent assays for toxoplasmosis, cytomegalovirus, and Epstein-Barr viruses were negative. Serum levels of copper, ceruloplasmin, and alpha1-antitrypsin were within normal ranges, but the ammonia level was elevated. On abdominal sonography, the liver and biliary tract were normal. Liver biopsy was contraindicated at the time secondary to increased risk of bleeding due to severe coagulopathy. Tc-99m Sn scintigraphic evaluation of the liver was performed and was suggestive of the presence of submassive hepatic necrosis (Fig. 1). PTU was immediately withheld and the patient was given supportive treatment with parenteral fluids, propranolol and oxygen inhalation. On the same day of admission, plasmapheresis was performed using an intermittent flow device, MCS plus 9000 (Haemonetics), with 2,500 ml plasma volume removed during each plasmapheresis session. Fresh frozen plasma served as the replacement fluid. After the first plasmapheresis, 30 mCi of I^{131} was administered. Prednisone 40 mg/day was begun. Soon after completion of the first session of plasmapheresis, the patient's agitation and confusion abated and resolved completely. Clinical assessment one month after radioiodine treatment still revealed hyperthyroidism with a progressive deterioration of liver function tests. Plasmapheresis was therefore re-instituted and three more sessions were performed 20 days apart from each other as described above. These sessions were beneficial with respect to improvement of both clinical and laboratory parameters. Two and a half months after admission, all liver and thyroid function tests had returned to normal. Four months later, in a follow-up scintigraphic evaluation of the liver, increased scintigraphic uptake consistent with the disappearance of hepatic necrosis was noted.

DISCUSSION

Drug-induced hepatitis may be a difficult diagnosis to make. It is usually made by excluding other causes of hepatitis. Hyperthyroidism can induce abnormal liver function especially in the setting of congestive heart failure or thyroid crisis, since liver perfusion decreases and relative hypoxemia occurs [2,7,17]. These conditions were not present in our patient even though she had laboratory evidence of hyperthyroidism, thus making PTU-related hepatotoxicity the most reasonable diagnosis. In addition, fulminant liver injury was not observed. We also excluded other acquired or inherited causes of liver injury including viral hepatitis, autoimmunity, alcohol, other drug-induced hepatotoxicity, Wilson's disease, hemochromatosis, and alpha 1 antitrypsin deficiency.

To date, serious PTU-related hepatotoxicity has been reported in 34 cases in the literature (in English) [1–28]. This condition is potentially fatal since in 29.4% of cases patients have died due to fulminant hepatic failure. Symptom onset has ranged from one day to 15 months after the institution of PTU therapy [2,19]. The clinical course of patients with severe PTU hepatotoxicity may be unpredictable, with either early full recovery or death being reported.

Liver biopsy is the most reliable and sensitive method for documentation of liver damage in PTU-induced hepatic injury. Based on the severity of the disease process, the pathological findings may range from early signs of hepatocellular inflammation to submassive hepatic necrosis [2,5,6,8,18]. Liver scintigraphy may be utilized instead of liver biopsy especially in conditions where biopsy procedures are contraindicated [26]. Because our patient had coagulopathy, we performed liver scintigraphy and demonstrated submassive hepatic necrosis. Resolution of submassive hepatic necrosis was noted after four months by liver scintigraphy also.

In patients with fulminant hepatic failure, plasmapheresis may improve survival of patients who have sufficient residual hepatic capacity for regeneration. It appears effective in restoring homeostasis, improving neurological function, and prolonging biochemical stability of patients with fulminant hepatic failure [32–37].

Plasmapheresis has been used successfully to treat patients with hyperthyroidism in the past [30,31,38]. Since a significant proportion of thyroid hormones bind to serum proteins, removal via plasmapheresis provides an alternative and effective therapeutic strategy in situations where immediate restoration of euthyroidism has the utmost importance [31].

Plasmapheresis removes pathogenic antibodies and immune complexes out of the blood [39]. Although the mechanism of hepatic injury secondary

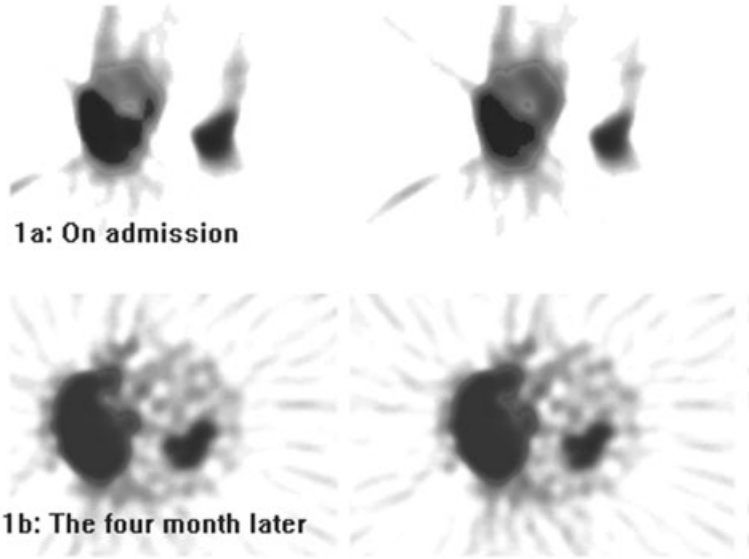

Fig. 1. **a:** Liver scintigraphy with Tc 99m Sn colloid showing decreased scintigraphic uptake on admission of the patient. **b:** Follow-up scintigraphic study revealing an increased scintigraphic uptake of Tc 99m Sn colloid material after 4 months of treatment.

to PTU remains obscure, positive lymphocyte sensitization studies in some patients who developed PTU hepatotoxicity suggest a potential immune reaction to PTU [2,13,14,18,20,22,29]. In our patient, there was a coincident relationship between plasmapheresis and clinical improvement, including clinical response as manifested by improvement in clinical symptoms, liver function, and thyroid function. Possible mechanisms accounting for this may include interruption of the immune-mediated liver damage and/or removal of T_4, T_3, and TSH receptor antibodies. It is surprising that the literature regarding the use of plasmapheresis in such settings is scant [2,5]. Only one case study involving a pediatric patient with severe PTU hepatotoxicity who underwent two sessions of plasmapheresis reported lack of efficacy with eventual death of the patient occurring [5]. In contrast, our patient showed dramatic improvement in both liver and thyroid function and clinical status.

After the first plasmapheresis session, I^{131} treatment was administered. As indicated in the literature, radioactive iodine therapy can also improve survival in patients with PTU-induced hepatotoxicity [2]. We also administered moderate doses of prednisone as in four cases in the literature [2,14,16,29] to control the possible PTU-induced immune effects, and to decrease the peripheral conversion of T_4 to T_3 [40].

In conclusion, PTU-induced hepatotoxicity is a rare, potentially life-threatening event and TPE may serve a valuable and immediate therapeutic option in the management of patients with such drug-induced fulminant hepatic failure.

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