

Propylthiouracil Treatment may be Associated with Agranulocytosis and Hepatotoxicity

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Abstract

Agranulocytosis is a rare adverse effect of propylthiouracil. The usual duration of treatment prior to the onset of agranulocytosis is approximately 1 to 4 months, and can be as long as 1 year. Agranulocytosis together with hepatotoxicity is an extremely rare side effect of propylthiouracil treatment. We present an unprecedented case of a hyperthyroidism patient who showed a strong reaction to propylthiouracil with obvious agranulocytosis and hepatotoxicity which developed approximately one month after administration. The patient's symptoms and laboratory abnormalities resolved following withdrawal of offending drug. This case, along with a literature review, is aimed to increase the awareness of physicians of sudden onset of agranulocytosis and hepatotoxicity due to propylthiouracil.

Keywords: Agranulocytosis; Hepatotoxicity; Hyperthyroidism; Propylthiouracil

Introduction

Hyperthyroidism is characterized by elevated levels of thyroid hormones in the circulation [1,2]. The most common causes of hyperthyroidism are Graves' disease, multinodular toxic goiter, and autonomous hyperfunctioning thyroid nodules. While propylthiouracil (PTU) has been widely used for hyperthyroidism since 1947 [3], we are still in the process of understanding rare adverse effects of this medication. It is commonly used for Grave's disease [4] and inhibits thyroid hormone synthesis and conversion of thyroxine to triiodothyronine within the gland and peripheral tissues [5]. Antithyroid drug (ATD) therapy is associated with variety of adverse reactions. Urticaria (or skin rash), low-grade liver dysfunction, and arthralgia are common minor side effects, whereas agranulocytosis, myeloperoxidase-antineutrophil cytoplasmic antibody-related vasculitis, and severe hepatotoxicity are rare but serious complications [6]. Among them, agranulocytosis, defined as a granulocyte count below 500/L, is the most serious life threatening event. It can occur abruptly, and prediction and prevention are very difficult [5-8]. Methimazole (MMI) and PTU are ATD which their administration is associated with liver injury in humans [5,9]. The precise mechanism (s) of these ATD-induced hepatotoxicity is unknown so far [10,11]. In very few cases [12-14], these two situations (agranulocytosis and hepatotoxicity) can happen on the same patient. Here, a case of agranulocytosis and hepatotoxicity induced by PTU is presented; the duration of PTU therapy before the onset of these complications was approximately one month.

Case Report

In November 2016, A 52-year-old female patient visited the general surgery polyclinic of our hospital with weight loss, palpitation, sweating, tremor, irritability and nausea. The patient was a diagnosed case of hyperthyroidism [free T4 (FT4): 18 pg/mL, free T3 (FT3): 7.7 ng/dL, Thyroid stimulating hormone (TSH): 0.005 μ IU/ml]. At that time, her blood count and liver function test were within the normal range (Table 1). PTU (100 mg twice a day) and propranolol (20 mg twice a day) treatments were started. One month after these treatments she admitted to polyclinic again. There was no sign of infection. Laboratory analysis was as follows; Aspartate transaminase (AST): 50.3 U/L, Alanine transferase (ALT): 84 U/L, C reactive protein (CRP): 0.01

mg/dL, sedimentation: 28 mm/min, White blood cell (WBC): 4.18×10^9 /L, Granulocyte: 1.65×10^9 /L (Table 1). The patient was referred to the Internal Medicine polyclinic. She had fever, headache, nausea, vomiting, loss of appetite and sore throat. On physical examination: Fever: 38.5, Pulse rate: 116/min, respiratory rate 22/min, arterial blood pressure: 100/70 mmHg. The skin was warm, moist, and hand tremor was observed. A nodular goiter was found during neck palpation. Oropharynx was red and edematous, tonsils were hypertrophic and cryptic. Laboratory analysis was as follows; AST:52.3 U/L, ALT:104 U/L, CRP: 2.57 mg/dL, sedimentation:109 mm/dk, WBC: 650×10^9 /L, lymphocyte 600×10^9 /L, monocyte 30×10^9 /L, granulocyte 20×10^9 /L. Cholestatic enzymes ve other biochemical parameters were within the laboratory's reference ranges (Table 1). Peripheral blood smear showed normocytic normochromic red blood cell (RBC) series, reduced total leukocyte count with neutropenia (Figure 1). Lipid values were within normal limits. No serum perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) and cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) were detected. Viral hepatitis A, B, C and E and other viruses such as Epstein-Barr virus, cytomegalovirus, varicella zoster virus and simple herpes virus were excluded. Blood culture was performed before antibiotic use and gave negative results. Multinodular goiter was found in ultrasonographic examination of thyroid gland. Abdominal ultrasound showed no alterations in the liver and pancreatic areas and no distortion of the biliary ductal system. ECG showed sinus tachycardia. Chest X-ray showed no abnormality. In the light of these data, we detected agranulocytosis and hepatotoxicity due to PTU use in patient with toxic multinodular goiter disease. There was also tonsil infection secondary to concurrent agranulocytosis.

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Date	15.11.2016 ^a	17.12.2016 ^a	07.01.2017	08.01.2017	09.01.2017	05.04.2017	Reference range
AST	36.5	50.3	52.3	--	--	23.7	1-40 U/L
ALT	32	84.4	104	--	--	28.6	1-49 U/L
T.B	0.3	0.4	0.5	--	--	0.2	0.02-1.6 mg/dL
D.B	0.1	0.2	0.1	--	--	0.1	0-0.4 mg/dL
ALP	55	57	--	--	--	50	25-175 U/L
GGT	24	12	--	--	--	20	6-65 U/L
CRP	0.01	0.01	2.57	--	--	0.02	0-0.5 mg/dL
ESR	21	28	109	--	--	28	1-20 mm/h
WBC	6.32	4.18	0.65	1.09	2.51	6.78	4-10 × 10 ⁹ /L
Granulocyte	2.64	1.65	0.02	0.03	0.70	2.9	2-7 × 10 ⁹ /L
RBC	4.34	4.32	4	3.85	4.32	4.44	3.5-6 × 10 ¹² /L
HGB	12.1	12.4	11.2	10.8	12	12.8	11-16 g/dL
HCT	37.8	37.9	33.7	32.5	36.8	38.5	37-54%
PLT	290	282	280	320	434	326	150-400 × 10 ⁹ /L

^aWhen propylthiouracil was started.

^bWhen propylthiouracil was discontinued and methimazole started.

AST: Aspartate Transaminase; ALT: Alanine Transferase; TB: Total Bilirubin; DB: Direct Bilirubin; ALP: Alkaline Phosphatase; GGT: Gamma glutamyl transpherase; CRP: C reactive protein; WBC: White Blood Cell; RBC: Red Blood Cell; HGB: Hemoglobin; HCT: Hematocrit; PLT: Platelet

Table 1: Laboratory values.

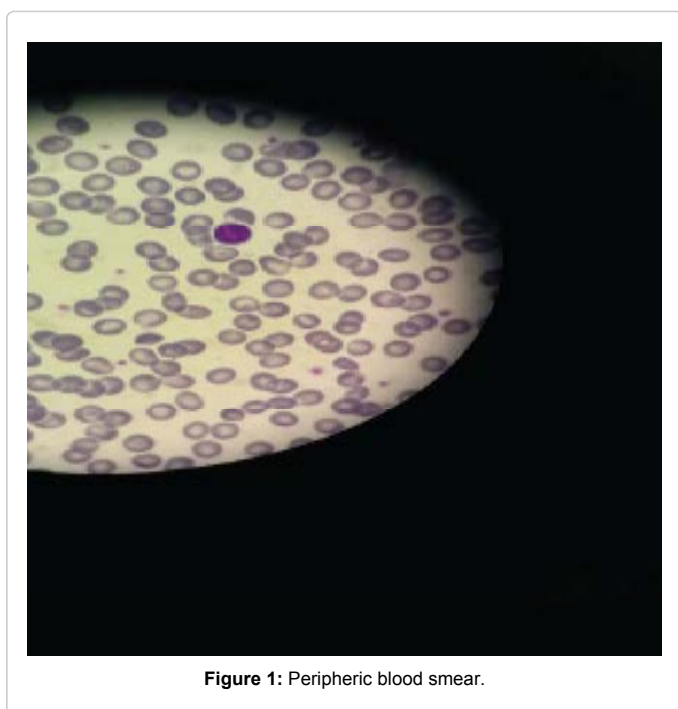


Figure 1: Peripheral blood smear.

One month before, the patient was followed by the general surgery department. Then he admitted to the our Internal medicine policlinic. This is why patient at time of prescription could not be educated. We hospitalized the patient in internal medicine clinic. Patient needed rapid and definitive correction of hyperthyroidism. He was taken to a single ward with isolation measures. PTU immediately stopped. MMI started. In some studies, MMI was replaced by PTU in case of adverse events. We started using intravenous antibiotics (ampicillin and sulbactam) to control tonsilla infection, and hepatoprotective drug (Reduced glutathione) to lower transaminase levels. Hematopoietic growth factors were not given because the white cells increased. Three days after PTU discontinuation, the WBC count increased to 2.51 × 10⁹/L on day 3, the patient's symptoms of thyrotoxicosis remit, and it

took time to return the liver enzymes to the normal range (Table 1). The patient was discharged on the 7th day and treatment was continued with MMI, and in the following months she entered the euthyroid status (Table 2). General surgery clinic performed thyroidectomy.

Discussion

Antithyroid drug -induced agranulocytosis tends to occur within 2 or 3 months after starting treatment, some cases were reported to develop after several months or after 1-2 years of MMI treatment [15]. However, sudden onset agranulocytosis cases, especially those complicated with other fatal side effects, are rare and often require a multidisciplinary approach. This case report shows the complexity of these situations, in which multiple and rare hematological and nonhematological complications are often present together. To our knowledge, this is one of the rare cases of agranulocytosis along with hepatotoxicity onset within approximately one month in a hyperthyroidism patient who was treated with PTU. Vilchez et al. presented a 37-year-old woman diagnosed with severe hyperthyroidism resulting from Graves' disease. Treatment with carbimazole 30 mg/day was initiated. Within 15 days following the start of therapy, both minor (eg, pruritus, rash, urticaria, fever, arthralgias) and potentially life-threatening (eg, agranulocytosis, severe mixed hepatotoxicity with severe cholestatic jaundice) adverse effects developed. The patient's symptoms and laboratory abnormalities resolved following withdrawal of carbimazole. Treatment with other antithyroid drugs was not attempted, and radioactive iodine (¹³¹I) ablation of the thyroid was successfully performed. Thyroid function was maintained with standard follow-up care. Agranulocytosis, identified following bone marrow biopsy, was treated with granulocyte colony-stimulating factor administration [12].

Date	15.11.2016 ^y	17.12.2016 ^z	05.01.2017	05.04.2017	Reference range
FT3	18	14.65	10.2	3.37	2.02-4.43 pg/mL
FT4	7.7	3.39	1.73	1.07	0.7-1.8 ng/dL
TSH	<0.005	<0.005	<0.005	3.35	0.34-5.6 mIU/mL

^yThyroid hormone analysis at the time of patient admission.

^zWhen propylthiouracil was stopped and methimazole was started.

FT3: Free T3; FT4: Free T4; TSH: Thyroid Stimulating Hormone.

Table 2: Thyroid hormone analysis.

Jain et al. presented a 45-year-old female diagnosed with severe hyperthyroidism. Treatment with carbimazole 30 mg/day was initiated. Within 6 weeks following the start of therapy, patient developed potentially life-threatening acute cholestatic hepatitis and agranulocytosis as adverse effects to carbimazole. The patient's symptoms and laboratory abnormalities resolved following withdrawal of offending drug [13]. Yang et al. present an unprecedented case of a Grave's disease patient who showed a strong reaction to methimazole with obvious agranulocytosis and hepatotoxicity which developed only 6 days after administration. Granulocyte-colony stimulating factor (G-CSF) was prescribed to raise neutrophils. The patient was discharged on the 15th day and received I₁₃₁ treatment on the same day [14].

In the history of our case, there were no hematologic or liver diseases, alcohol dependence, blood transfusion, drug usage, surgical operation. There was no other condition or disease that would cause hepatotoxicity (as indicated by the significant elevation of ALT and AST to 84.4 and 50.3 U/L, respectively) (Table 1) and agranulocytosis. Our case had several different aspects than others. She had toxic multinodular goiter, after using accusing drug PTU liver enzymes and whole blood cell counts deteriorated and healed over time after stopping PTU without need of G-CSF and I₁₃₁. The second case mentioned above had acute cholestatic hepatitis however our case had toxic hepatitis. Agranulocytosis is a serious, potentially fatal complication that affects 0.2-0.5% of patients taking thionamides-usually older patients who may be receiving high doses of drugs in this class. In the largest drug monitoring study conducted to date on the use of thionamides in the UK, 117 cases of neutropenia (96 with carbimazole and 21 with propylthiouracil) were noted; 6 of these were fatal [16]. The average doses were 40 mg/day of carbimazole and 300 mg/day of propylthiouracil. The average treatment duration was 31 and 33 days respectively, with one patient having the treatment for only 14 days. As has been documented in previous studies, age continues to be the most significant risk factor for neutropenia [17-19]. In our patient, age (52 y), dose (200 mg/day of propylthiouracil), and duration of exposure to the drug (approximately one month) were same those of other patients who have developed adverse effects [16,18].

To date, pathogenic mechanisms of this adverse reactions can not be fully explained. There are two major explanations of agranulocytosis, including direct toxic effects and immunological reactions [19]. Antithyroid drug can readily penetrate the marrow affecting oxygen and glucose utilization of leukocytes through the oxidized metabolites [5]. Toxic effects require 20 to 40 days of exposure, and the onset is insidious. It is dose and concentration dependent [20]. The bone marrow exposure time of our case is approximately one month. This may be due to toxic effects. Hepatotoxicity is another serious reaction to antithyroid agents. It occurs with a frequency of 0.1-0.2% of treated cases [9] and can also be fatal. A transient increase in aminotransferase levels with PTU treatment can develop in 30% of patients, usually within 3 months of treatment initiation. The effect is similar to allergy-related hepatitis, with a significant elevation in ALT. Fulminant hepatic failure associated with antithyroid drugs can be fatal in 25-50% of cases [21,22]. PTU-induced liver dysfunction is more common than MMI-induced liver dysfunction [23]. MMI-associated hepatic abnormalities are typical of cholestatic process [24]. Treatment involves withdrawal of the drug, support measures for liver dysfunction, and in some severe cases liver transplantation [25]. The mechanisms of hepatotoxicity for the two antithyroid drugs have not been clarified in detail. Immune injury may also act as an important role in the process [5,12].

Of note in our patient is the coexistence of several symptoms attributable to the use of thionamides. Because white blood cells tended to rise 3 days after the PTU was released. In our case G-CSF was not required. The upper respiratory tract infection due to agranulocytosis clinic also regressed. With respect to the effect of PTU on the liver, we believe that the occurrence of hepatotoxicity, with significant elevations in moderate elevations in aminotransferases, points to PTU as the cause of this adverse effect. However, it took some time (4 months) for the liver enzymes to return to normal course. Significant improvement was observed in the patient without the need for liver and bone marrow biopsy. In our case, since only PTU had been administered, the undesirable effects on the liver could be attributable to hepatocellular damage. In our opinion, there was no interaction between PTU and propranolol since granulocyte counts and liver enzyme values returned to baseline levels without propranolol being discontinued [26].

Conclusion

Finally, no case similar to ours was identified in our literature search: in some cases, the adverse effects were of greater or lesser severity than in our patient, and few cases showed all of these adverse effects present simultaneously. Use of the Naranjo probability scale indicated that the adverse effects were probably related to the PTU therapy. Our patient developed agranulocytosis and hepatotoxicity following the administration of the thionamide drug propylthiouracil, which had been administered for the treatment of hyperthyroidism. Following the withdrawal of the drug without I₁₃₁ and G-CSF treatment, we were able to achieve a favorable outcome. Clinicians need to be made aware of these potentially fatal adverse effects associated with this drug.

References

1. Ezer A, Caliskan K, Parlakgumus A, Belli S, Kozanoglu I, et al. (2009) Pre-operative therapeutic plasma exchange in patients with thyrotoxicosis. J Clin Apher 24: 111-114.
2. Keklik M, Kaynar L, Yilmaz M, Sivgin S, Solmaz M, et al. (2013) The results of therapeutic plasma exchange in patients with severe hyperthyroidism: A retrospective multicenter study. Transfus Apher Sci 48: 327-330.
3. Rivkees SA, Mattison DR (2009) Propylthiouracil (PTU) hepatotoxicity in children and recommendations for discontinuation of use. Int J Pediatr Endocrinol 132041.
4. Astwood EB (1984) Landmark article May 8, 1943: Treatment of hyperthyroidism with thiourea and thiouracil. JAMA 251: 1743-1746.
5. Cooper DS (2005) Antithyroid drugs. N Engl J Med 352: 905-917.
6. Pochin EE (1960) Leukaemia following radioiodine treatment of thyrotoxicosis. British Med J 2: 1545.
7. Brent GA (2008) Clinical practice: Graves' disease. N Engl J Med 358: 2594-2605.
8. Franklyn JA, Boelaert K (2012) Thyrotoxicosis. Lancet 379: 1155-1166.
9. Cooper DS (1999) The side effects of antithyroid drugs. Endocrinol 9: 457-478.
10. Heidari R, Babaei H, Eghbal M (2012) Mechanisms of methimazole cytotoxicity in isolated rat hepatocytes. Drug Chem Toxicol 36: 403-411.
11. Heidari R (2015) An overview on the proposed mechanisms of antithyroid drugs-induced liver injury. Advan Pharmaceut Bulletin 5: 1-11.
12. Vilchez FJ, Torres I, Garcia-Valero A, Lopez-Tinoco C, Aguilar-Diosdado M (2006) Concomitant agranulocytosis and hepatotoxicity after treatment with carbimazole. Ann Pharmacother 40: 2059-2063.
13. Jain K, Chakrapani M, Smitha K (2010) Acute cholestatic hepatitis along with agranulocytosis: A rare side effect of carbimazole. Ann Afr Med 9: 102-104.
14. Yang J, Zhong J, Zhou LZ, Hong T, Xiao XH, et al. (2012) Sudden onset agranulocytosis and hepatotoxicity after taking methimazole. Intern Med 51: 2189-2192.

15. Takata K, Kubota S, Fukata S (2009) Methimazole-induced agranulocytosis in patients with Graves' disease is more frequent with an initial dose of 30 mg daily than with 15 mg daily. *Thyroid* 19: 559-563.
16. Pearce SHS (2004) Spontaneous reporting of adverse reactions to carbimazole and propylthiouracil in the UK. *Clin Endocrinol* 61: 589-594.
17. Tajiri J, Noguchi S, Murakami Y, Murakami N (1990) Antithyroid drug-induced agranulocytosis. The usefulness of routine white blood cell count monitoring. *Ann Intern Med* 150: 621-624.
18. Cooper DS, Goldminz D, Levin AA (1983) Agranulocytosis associated with antithyroid drugs. *Ann Intern Med* 98: 26-29.
19. Meyer-Gessner M, Benker S, Lederbogen S, Olbicht T, Reinwein D (1994) Antithyroid drug-induced agranulocytosis: Clinical experience with ten patients treated at one institution and review of the literature. *J Endocr Invest* 17: 29-36.
20. Waldhauser L, Uetrecht J (1991) Oxidation of propylthiouracil to reactive metabolites by activated neutrophils: Implications for agranulocytosis. *Drug Metab Dispos* 19: 354-359.
21. Williams KV, Natak S, Becker D, Reyes J, Burmeister LA (1997) Fifty years of experience with propylthiouracil-associated hepatotoxicity: What have we learned? *J Clin Endocrinol Metab* 82: 1727-1733.
22. Ruiz JK, Rossi GV, Vallejos HA, Brenet RW, Lopez IB, et al. (2003) Fulminant hepatic failure associated with propylthiouracil. *Ann Pharmacother* 37: 224-228.
23. Livadas S, Xyrafis X, Economou F (2010) Liver failure due to antithyroid drugs: Report of a case and literature review. *Endocrine* 38: 24-28.
24. Arab DM, Malatjalian DA, Rittmaster RS (1995) Severe cholestatic jaundice in uncomplicated hyperthyroidism treated with methimazole. *J Clin Endocrinol Metab* 80: 1083-1085.
25. Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P (2004) Liver transplantation for acute liver failure from drug induced liver injury in the United States. *Liver Transpl* 10: 1018-1023.
26. Naranjo CA, Busto U, Sellers EM (1981) A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 30: 239-245.