Propylthiouracil-induced hypersensitivity syndrome

Zehra Aycan, Ebru Arhan, Ergun Çetinkaya, Sadi Vidinlisan, Nurcan Menekşe
Hüsniye Yücel, Nilgün Çakar
Department of Pediatric Endocrinology, Social Security Ankara Children's Hospital, Ankara, Turkey

SUMMARY: Aycan Z, Arhan E, Çetinkaya E, Vidinlisan S, Menekşe N, Yücel H, Çakar N. Propylthiouracil-induced hypersensitivity syndrome. Turk J Pediatr 2006; 48: 162-165.

Propylthiouracil (PTU) is usually the first choice for the treatment of hyperthyroidism, but it has serious side effects such as hepatitis, cholestatic jaundice, splenomegaly and lupus-like syndrome, in addition to mild and common side effects like granulocytopenia, pruritus, urticaria and maculopapular or papular eruption. Antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis is another serious side effect. A 14-year-old female receiving PTU treatment for hyperthyroidism was referred to our clinic with fever, cough and dyspnea. The PTU dosage was first decreased but pericardial, dermal and joint involvement ascribed to PTU developed later and the drug was discontinued. ANCA-positive vasculitis due to PTU was considered when tests revealed an ANCA-positive state. We suggest that severe multisystemic vasculitis due to PTU should be considered during PTU usage.

Key words: propylthiouracil, hypersensitivity, vasculitis.

Propylthiouracil (PTU) is a member of the thionamide group and is used frequently for the treatment of hyperthyroidism. An antineutrophil cytoplasmic antibody (ANCA)-positive state with or without clinical signs of vasculitis has been reported in Graves patients using PTU[1-4]. The vasculitis is multisystemic and consists of generalized maculopapular eruption, urticaria, angioedema, generalized pruritus, alopecia, acne-like pustules, hair depigmentation, photosensitivity, mucosal ulceration and cutaneous vasculitis[5].

We present a case who developed vasculitis with pleural, pericardial, cutaneous and joint involvement while being treated with PTU.

Case Report

A 14-year-old female presented to our hospital with symptoms of fever, cough, chest pain and leg swelling for the last week. She had been locally diagnosed as hyperthyroidism eight months ago and PTU and propranolol had been started. Family history revealed a cousin with hyperthyroidism. Physical examination findings were: body temperature 36.5°C, apical heart beat 120/min, respiration 20/min, blood pressure 100/60 mmHg, chronological age 14, body weight 48 kg (25-5Oth percentile), height 147.5 cm (3rd percentile), and puberty stage B3 P3. Bilateral exophthalmos was present, measured with the Hertel exophthalmometer at 21 mm right and 20 mm left. Respiratory sounds had decreased bilaterally and rough sounds were detected over the upper part of the left lung. The liver could be palpated below the costal margin. Pretibial edema was present. Laboratory findings were: hemoglobin: 9.2 g/dl, hematocrit: 29%, mean erythrocyte volume: 73.2 fl, red cell distribution width (RDW): 13, leukocytes: 12,900/mm^3, erythrocyte sedimentation rate (ESR) 98 mm/hr, and C-reactive protein (CRP) (+). Telecardiography revealed cardiomegaly; the echocardiography showed pericardial fluid and the pleural fluid was noted on thorax tomography. Pericardial tube was placed and 500 ml of hemorrhagic fluid drained. There were no bacteria on the Gram stain of the pericardial fluid smear and no growth in the cultures. A pericardial biopsy showed chronic inflammation. Pleural fluid taken with thoracentesis was hemorrhagic in character with no growth in cultures, and a polymerase chain reaction (PCR) for

tuberculosis was negative. The first thyroid function test (TFT) results were consistent with hyperthyroidism with a high free triiodothyronine (fT3) and free thyroxine (fT4) and suppressed thyroid stimulating hormone (TSH) (Table I). A mitral insufficiency due to papillary muscle dysfunction secondary to hypertrophy. Thyroid function test showed a high fT3 and suppressed TSH (Table I). The repeated ultrasonography revealed increased thyroid volume. The result

Table I. Clinical and Laboratory Findings of the Case at Admission and Follow-up

	At admission	3rd month	6th month	22nd month	27th month
Age (year)	14	14.3	14.6	15.9	16.3
Symptom	Fever, cough, chest pain	Palpitation, dyspnea chest pain		Fever, malaise, rash	
Goiter stage (I-IV)	III	III	IV	III	III
fT3 (pg/ml) (2.3-4.2)	11.6	4.9	2.0	3.9	3.8
fT4 (ng/dl) (0.8-1.8)	2.5	2.0	0.1	1.1	0.9
TSH (IU/L) (0.3-0.5)	0.02	0.3	54.4	2.8	3.7
Anti-M (IU/ml (0-20)	6500			178	
Anti-Tg (IU/ml) (0-50)	5950			594	
TRAb (IU/L) (10-14)	42			23.8	
Anti-MPOAb (0-20 RU/ml)		176			113
Anti PR3 Ab (0-20 RU/ml)		5.3			3.3
Skin biopsy				Leukocytoclastic vasculitis	
Therapy	PTU Propranolol	PTU Propranolol	PTU Propranolol L-T4	Methimazole Propranolol L-T4 Steroid	Methimazole Propranolol L-T4 Steroid

fT3: Free triiodothyronine. fT4: Free thyroxine. Anti-M: Anti-microsomal antibody. Anti-Tg: Anti- thyroglobulin antibody. TRAb: TSH receptor antibody. Anti-MPO Ab: Anti-myeloperoxidase antibody. Anti-PR3 Ab: Anti-proteinase antibody. PTU: Propylthiouracil. L-T4:L-thyroxine.

diagnosis of Hashitoxicosis was made with the following test results: antimicrosomal antibody (Anti M) 6500 IU/ml (0-20), antithyroglobulin antibody (Anti Tg) 5950 IU/ml (0-50), and TSH receptor antibody (TR ab) 42 U/L (10-14)[6]. A thyroid ultrasonography revealed increase in the thyroid volume (22.27 cm^3) and parenchyma heterogeneity. The daily PTU dose of the patient was increased to 5 mg/kg and the daily propranolol dose to 1 mg/kg. TFT results were euthyroid with no tachycardia 10 days later and the patient was discharged.

The patient presented again three months later with palpitations, dyspnea and chest pain. The physical examination findings were: temperature 37°C and apical heart beat 122/min. Laboratory findings were: ESR 60 mm/hr and CRP (++). Echocardiography showed minimal

of the fine needle aspiration biopsy of the thyroid was consistent with lymphocytic thyroiditis. Autoimmunity test results were: antinuclear antibody (ANA): negative, anti-double strand ANA (anti dsANA): negative, immunoglobulins: normal, and pANCA positive [antimyeloperoxidase antibody (anti MPO Ab): 176 RU/ml (0-20), antiproteinase antibody (anti PR3 Ab): 5.3 RU/ml (0-20)]. The results of the follow-up TFT six months later (on the 14th month of PTU treatment) were consistent with hypothyroidism, and L-thyroxine (LT4) was added to the drug regimen.

The patient was seen at the 22nd month of PTU treatment with fever, malaise and sore throat followed by a rash. The rash had started on the auricular helix and cheeks and spread to the chest and distal extremities and showed

irregular margins, crustiness in places, and necrotic centers; ecchymosis was present, with the biggest lesion measuring 12x8 cm. She also had bilateral arthritis of the ankles (Fig. 1). A skin biopsy from the rash site was consistent with leukocytoclastic vasculitis with no immune deposits. PTU was stopped and methimazole started. In addition, methyl prednisolone 60 mg/day was started for the vasculitis and arthritis. On follow-up a month later, the TFT results were euthyroid and the skin lesions and arthritis had resolved. She continues to take steroids on alternate days, now on the 27th day of follow-up, and the pANCA (anti MPO Ab: 113.9 RU/ml) is still positive.

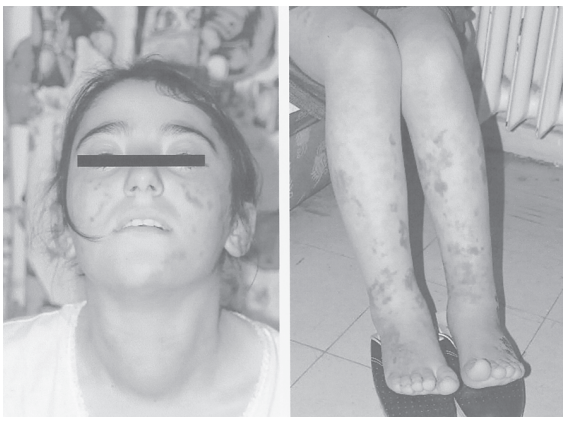

Fig. 1. Photographs of the patient demonstrating rash on the auricular helix and cheeks spreading to the distal extremities. The rash on the lower extremities was crusty in places and there were necrotic centers. Ecchymosis was present, with the biggest lesion measuring 12x8 cm.

Clinical and laboratory findings at admission and follow-up are given in Table I.

Discussion

Fever, arthralgia, sore throat and rash are the classical initial findings in vasculitis due to PTU hypersensitivity, with skin being the most commonly involved organ[7]. There may be accompanying myalgia, malaise and weight loss[5,8]. No relationship has been found between PTU vasculitis and the patient's age or the medication dosage. The increased prevalence in females has been ascribed to the increased prevalence of thyroid disease in females[9,10]. The condition may be limited to the skin[11] or cause a multiple-system clinical picture similar to polyarteritis nodosa (PAN) or Wegener's granulomatosis[12]. The dermal vasculitic lesions are more commonly found on the face, auricular helix, chest and distal extremities, and our case showed this pattern. Histopathology of the dermal lesions shows leukocytoclastic hypersensitivity vasculitis involving the superficial and deep dermal vessels[5,8,13]. Our case had similar biopsy findings. Direct immunofluorescent studies are usually negative, as in our case, but deposition of IgM, IgG, IgA, fibrinogen and complement around the dermal blood vessels has been reported[5,8].

Propylthiouracil-associated vasculitis frequently causes arthritis and this can sometimes be the initial finding. Joint involvement can vary from arthralgia of moderate intensity to severe synovitis and can take the form of a migratory polyarthritis of the small and large joints[13]. Our case had arthritis starting from the ankles and extending to the interphalangeal joints of both hands.

Extracutaneous findings of PTU-associated hypersensitivity vasculitis include conjunctivitis, pharyngitis, cholestatic jaundice, hepatitis, hepatosplenomegaly, pleural effusion, pneumonia, respiratory failure, cardiomegaly, arrhythmia, pericarditis, hematological findings (leukopenia, anemia, thrombocytopenia), glomerulonephritis, and renal failure[1,2,4,5,7-15]. The extracutaneous findings of our case were arthritis, pleural effusion, pericarditis, rash and anemia. Some ANCA-positive patients using PTU can develop vasculitis between the first week to the 13th year of treatment[7,16]. However, patients have been reported with the findings limited to the skin and no renal involvement. The ones who may develop ANCA-positive PTU vasculitis should be under close observation for possible nephritis[11,17].

Autoimmune thyroid disease patients not receiving thionamides have been studied for ANCA positivity, and rates of 28.5% for Graves disease and 9% for Hashimoto thyroiditis have been reported[18]. Another study looked at the ANCA positivity rate among the groups treated with PTU and methimazole and reported 37% among those receiving PTU, while the methimazole group was negative[19].

While an improvement is observed in the vasculitic skin lesions following PTU discontinuation in most cases, those with severe

renal failure or multiple organ involvement may require months of high-dose steroid treatment[20]. In our case, the skin lesions and arthritis resolved completely within 10 days once the PTU was stopped and steroid treatment started. In case of severe multisystem involvement accompanying PTU vasculitis, other treatment modalities used are cyclophosphamide, azathioprine and plasmaph eresis[7,13,17,21,22].

In conclusion, PTU is a rare cause of vasculitis and the hypersensitivity reaction, which typically consists of acral purpuric skin lesions and various degrees of internal organ involvement. We want to emphasize with this report that serious hypersensitivity vasculitis should be kept in mind and that PTU should be chosen with caution when children are treated for hyperthyroidism.

REFERENCES

1. Cooper DS. Antithyroid drugs. N Engl J Med 1984; 311: 1353-1362.
2. Stankus SJ, Johnson NT. Propylthiouracil-induced hypersensitivity vasculitis presenting as respiratory failure. Chest 1992; 102: 1595-1596.
3. Sato H, Hattori M, Fujieda M, et al. High prevalence of antineutrophil cytoplasmic antibody positivity in childhood onset Graves' disease treated with propylthiouracil. J Clin Endocrinol Metab 2000; 85 (11): 4270-4273.
4. Dolman KM, Gans R, Vervaat TJ, et al. Vasculitis and antineutrophil cytoplasmic autoantibodies associated with propylthiouracil therapy. Lancet 1993; 342: 651-652.
5. Vasily DB, Tyler WB. Propylthiouracil-induced cutaneous vasculitis. JAMA 1980; 243: 458-461.
6. Fisher DA. Thyroid disorders in childhood and adolescence. In: Sperling MA (ed). Pediatric Endocrinology, 2nd ed. New York: Elsevier Science; 2002.
7. Harper L, Cockwell P, Savage CO. Case of proylthiouracil-induced ANCA associated small vessel vasculitis. Nephrol Dial Transplant 1998; 13: 455-458.
8. Griswold WR, Mendosa SA, Johnson W, Nichols S. Vasculitis associated with propylthiouracil: evidence for immune complex pathogenesis and response to therapy. West J Med 1978; 128: 543-546.
9. Kitahara T, Hiromura K, Maezawa A, et al. Case of propylthiouracil induced vasculitis associated with anti-neutrocytoplasmic antibody (ANCA): review of literature. Clin Nephrol 1997; 47: 336-340.
10. Wing SS, Fantus IG. Adverse immunologic effects of antithyroid drugs. Can Med Assoc J 1987; 136: 121-126.
11. Wolf D, Ben-Yehuda A, Okon E, Naparstek Y. Nodular vasculitis associated with propylthiouracil therapy. Cutis 1992; 49: 253-255.
12. Miller RM, Savige J, Nassis L, Cominos BI. Antineutrophil cytoplasmic antibody (ANCA)-positive cutaneous leucocytoclastic vasculitis associated with antithyroid therapy in Graves disease. Australas J Dermatol 1998; 39: 96-99.
13. Oh BK, von Overveld GP, Macfarlane JD. Polyarthritis induced by propylthiouracil. Br J Rheumatol 1983; 22: 106-108.
14. Ohtsuka M, Yamashita Y, Doi M, Hasewaga S. Propylthiouracil induced alveolar haemorrhage associated with antineutrophil cytoplasmic antibody. Eur Respir J 1997; 10: 1405-1407.
15. Yuasa S, Hashimoto M, Yura T, et al. Antineutrophil cytoplasmic antibodies (ANCA)- associated crescentic glomerulonephritis and propylthiouracil therapy. Nephron 1996; 73: 701-703.
16. Yarman S, Sandalci O, Tanakol R, Azizerli H, Oğuz H, Alagol F. Propylthiouracil-induced cutaneous vasculitis. Int J Clin Pharmacol Ther 1997; 35: 282-286.
17. Carrasco MD, Riera C, Clotet S, Grifol M, Foz M. Cutaneous vasculitis associated with propylthiouracil therapy. Arch Intern Med 1987; 147: 1677.
18. Alfetra A, Paggi A, De Rosa FG, Manfredini P, Addessi MA, Amorosso A. Antineutrophil cytoplasmic antibodies in autoimmune thyroid disorders. Endocr Res 1998; 24: 185-194.
19. Sera N, Ashiwaza K, Ando T, et al. Treatment with propylthiouracil is associated with appearance of antineutrophil cytoplasmic antibodies in some patients with Graves disease. Thyroid 2000; 10: 595-599.
20. Chastain MA, Russo GG, Boh EE, Chastain JB, Falabella A, Millikan LE. Propylthiouracil hypersensitivity: report of two patients with vasculitis and review of the literature. J Am Acad Dermatol 1999; 41: 757-764.
21. Vogt BA, Kim Y, Jennette C, Falk RJ, Burke BA, Sinaiko A. Antineutrophil cytoplasmic autoantibody-positive crescentic glomerulonephritis as a complication of treatment in children. J Pediatr 1994; 124: 986-988.
22. Kudoh Y, Kuroda S, Shimamoto K, Limura O. Propylthiouracil induced rapidly progressive glomerulonephritis and propylthiouracil therapy. Nephron 1996; 73: 701-703.