Antineutrophilic Cytoplasmic Antibody - Positive Systemic Vasculitis Associated with Propylthiouracil Therapy : Report of 2 Children with Graves' Disease

PREAMRUDEE POOMTHAVORN, M.D.*, WIWAT TAPANEYA-OLARN, M.D.*, AMORNSRI CHUNHARAS, M.D.*

PAT MAHACHOKLERTWATTANA, M.D.*, AMPAIWAN CHUANSUMRIT, M.D.*,

Abstract

Systemic vasculitis is a rare complication of therapy with antithyroid medication. Antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis has been described in patients treated with propylthiouracil (PTU) and methimazole (MMI). The majority of cases have underlying Graves' disease. The authors report 2 children who developed ANCA-associated systemic vasculitis during PTU therapy of Graves' disease. One patient, after PTU treatment for 3 years, developed severe systemic vasculitis. After 3 weeks of arthritis, she abruptly presented with hematuria, proteinuria and edema concomitant with anemia. Her serum creatinine was elevated, to 6 mg/dl. Renal biopsy revealed crescentic glomerulonephritis. After admission, she developed intracerebral hemorrhage and pulmonary hemorrhage. She had positive perinuclear-ANCA (p-ANCA) with a titer of 1:160. Despite intensive therapy with immunosuppressive agents and plasmapheresis, as well as discontinuation of PTU, she died of the complications of severe systemic vasculitis. The other patient developed fever, arthralgia and leukocytoclastic vasculitis of the skin during treatment with PTU for about 2 years. Her symptoms and skin lesions disappeared after discontinuation of PTU. However, she has had a persistently high titer of p-ANCA 1:320 through 17 months follow-up time. Thus, patients who are treated with PTU can develop ANCA-positive vasculitis in a mild or severe form. Therefore, they should be carefully followed and monitored, not only for their thyroid status but also the serious complications of PTU.

Key word : Antineutrophilic Cytoplasmic Antibody, Propylthiouracil, Vasculitis, Graves' Disease, Thyrotoxicosis, Rapidly Progressive Glomerulonephritis

POOMTHAVORN P, MAHACHOKLERTWATTANA P, TAPANEYA-OLARN W, CHUANSUMRIT A, CHUNHARAS A
J Med Assoc Thai 2002; 85 (Suppl 4): S1295-S1301

* Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

Propylthiouracil (PTU) is a drug commonly used in the treatment of Graves' disease. It has a number of side effects including hepatitis, leukopenia, skin rash, fever, arthralgia, systemic lupus erythematosus-like syndrome and systemic vasculitis[1,2]. Antineutrophilic cytoplasmic antibodies (ANCA) represent the autoantibodies reactive with neutrophil granules which may be involved in a variety of vasculitis, such as Wegener's granulomatosis, microscopic polyarteritis, autoimmune hepatitis, primary sclerosing cholangitis and crescentic glomerulonephritis[3]. Indirect immunofluorescence using human peripheral blood neutrophils as the substrate is the technique used for detecting ANCA in serum. Two patterns of staining can be visualized which indicate reactivity with different antigens and relate to different clinical correlations. Cytoplasmic ANCA (c-ANCA) has a diffuse granular reactivity, whereas the perinuclear ANCA (p-ANCA) has staining around the nucleus. c-ANCA has been found to be a specific marker for Wegener's granulomatosis. p-ANCA is associated with crescentic glomerulonephritis, microscopic polyarteritis and non-vasculitic conditions such as autoimmune hepatitis and infection.

In 1992, Strankus and Johnson reported PTU-induced ANCA-positive vasculitis presenting with respiratory failure[4]. Subsequently, Dolman et al reported 6 patients with PTU-induced ANCA-positive vasculitis in 1993[5]. Since then, PTU-induced ANCA-positive vasculitis has been reported in about 30 patients[4-14]. The majority of the reported cases were adults. Only 3 children have been reported[8, 14]. Vogt et al reported 2 cases of children who developed PTU-induced ANCA-positive vasculitis [8]. One patient, after PTU treatment for 34 months, presented with arthralgia and an ulcerated skin lesion. His symptoms subsided after PTU withdrawal and resumed 2 weeks later following PTU re-administration. With the second episode of symptoms, he also had crescentic glomerulonephritis and renal failure. Despite immunosuppressive therapy, his renal function did not improve. Finally, he required chronic hemodialysis to replace his renal function. The other patient developed arthralgia and crescentic glomerulonephritis after 2 weeks of PTU discontinuation. She was treated with prednisolone and cyclophosphamide for 1 year and remained clinically stable. Fujieda et al also reported a case of PTU-induced crescentic glomerulonephritis[14]. The patient had a good clinical response after decreasing the dose of PTU as well as glucocorticoid administration. All these three reported cases in children had severe renal involvement requiring immunosuppressive therapy.

The authors report 2 cases of children who presented with PTU-induced ANCA-positive systemic vasculitis. The first one had severe systemic vasculitis and did not respond to intensive therapy. The second one developed minor organ involvement and responded well to PTU discontinuation.

CASE REPORTS

Patient 1, a 9-year-old girl was diagnosed with Graves' disease. Her initial thyroid function tests revealed free thyroxine (FT_4) > 6 ng/dl, total thyroxine (T_4) 22.6 μg/dl, total tri-iodothyronine (T_3) 475 ng/dl and thyrotropin (TSH) < 0.005 mU/L. She had been treated with PTU and achieved euthyroid 1 month after treatment. Three years after treatment, she was euthyroid while receiving PTU 50 mg/day. Her last thyroid function tests revealed FT_4 1 ng/dl, T_4 6.3 μg/dl, and T_3 131 ng/dl. She developed arthritis of both knees and 3 weeks later she suffered from fever, anemia, edema and vesicular skin lesions. Her urine displayed 3+ protein, and more than 50 red blood cells/high power field. Laboratory data on admission showed anemia and renal failure (Table 1).

Renal biopsy was performed and revealed chronic glomerulonephritis with crescents and vasculitis of small blood vessels. Her serum displayed ANCA positivity, perinuclear pattern (p-ANCA), with a titer of 1:160. Thus, the clinical and histological diagnosis of rapidly progressive glomerulonephritis (RPGN) was made. She was immediately treated by methylprednisolone pulse regimen, and PTU was discontinued. Despite intensive therapy, renal function progressively deteriorated.

A skin biopsy specimen of one of the lesions on her right arm showed large subcorneal vesiculopustules filled with neutrophils.

On the 8th day after admission, she developed sudden headache, drowsiness and left hemiparesis. Her blood pressure was 130/80 mmHg (Fig. 1). Computed tomography scan of the brain revealed intracerebral hematoma of right frontal lobe 4.4 x 2.7 x 2.5 cm in size with a subdural hematoma 5 mm in thickness. Her platelet count was 420,000/μl. Coagulogram revealed activated partial thromboplastin time 36.4 seconds (normal 30-38 sec), pro-

Table 1. Laboratory data on admission of patient 1.

Variables	Value	Reference value
Hemoglobin (g/dl)/hematocrit (%)	6.2/19.2	11.5-15.5/35-45
Mean corpuscular volume (fl)	77.1	77-95
White cell count (/μl)	4,270	4,500-13,500
Neutrophil/lymphocyte/monocyte/eosinophil (%)	43/ 49/5/3	54-62/25-33/3-7/1-3
Platelet count (/μl)	337,000	150,000-400,000
Reticulocyte count (%)	0.8	0.5-1.5
Erythrocyte sedimentation rate (mm/h)	151	0-10
BUN (mg/dl) / Cr (mg/dl)	92/6	5-18/0.3-0.7
Coomb's test	Negative	Negative
LE cell	Negative	Negative
FANA/AntiDNA	Negative	Negative
p-ANCA	1:160	< 1:20
Activated partial thromboplastin time (sec)	36.2	30-38
Prothrombin time (sec)	13.2	12-14
Thrombin time (sec)	10.8	9-11
Urinalysis	3+ protein, marked positive blood, rbc > 50/hpf, granular casts	Negative for protein, blood, casts
24 h urine protein (mg)	2,160	50-80

thrombin time 12.5 seconds (normal 12-14 sec) and thrombin time 9.2 seconds (normal 9-11 sec). Bleeding time was 4 minutes 15 seconds (normal 2-7 min). After receiving treatment with intubation, hyperventilation and dexamethasone to decrease brain edema, she regained full consciousness.

One day after intracerebral hemorrhage, she developed active pulmonary hemorrhage. She was diagnosed as having PTU-induced ANCA positive systemic vasculitis from evidence of crescentic glomerulonephritis, intracerebral hemorrhage and pulmonary hemorrhage. Administration of cyclophosphamide was begun and plasmapheresis was performed thereafter but without response. Finally she died of uncontrolled infection with Pseudomonas septicemia on day 16 after admission.

Patient 2, an 11-year-old girl with Graves' disease, had been treated with PTU for 2 years when she developed fever, arthralgia and papulovesicular skin lesions on her face, extremities and buttock. She still had a goiter of 3 x 3 cm. She was clinically hyperthyroid. Her thyroid function tests revealed FT_4 3.5 ng/dl, T_3 356 ng/dl and TSH < 0.005 mU/L. She had positive antithyroglobulin antibody of 1:160 and antithyroperoxidase antibody of 1:400. Complete blood count revealed hemoglobin 10 g/dl, white cell count 5,700/μl (62% neutrophils) and reticulocyte count 0.9 per cent. Erythrocyte sedimentation rate was 75 mm/h. ANCA was positive with perinuclear staining of titer more than 1:320. Other immunologic testings which included fluorescence antinuclear antibodies (FANA) and antiDNA were negative. Urinalysis was normal. Skin biopsy showed leukocytoclastic vasculitis. The patient responded to supportive treatment which included discontinuation of PTU and analgesic. Thus, her hyperthyroidism was controlled with methimazole (MMI).

Graves' disease in this patient subsequently responded well to block-and-replace regimen, MMI and L-thyroxine. The patient achieved euthyroid soon after treatment. She has not had clinical signs and symptoms of vasculitis despite persistently high titer of p-ANCA more than 1:320 at 5, 10, 13 and 17 months after discontinuation of PTU.

DISCUSSION

Drug-induced vasculitis is a well-documented, but relatively rare side effect of certain drugs such as hydralazine, allopurinol, chlorpromazine, sulfasalazine and thionamides. MMI and PTU are thionamides which commonly are prescribed for the treatment of hyperthyroidism.

Antithyroid drug-induced ANCA-associated vasculitis was first reported in 1992[4], and more than 30 cases have since been reported. Almost all these cases have been related to the administration of PTU.

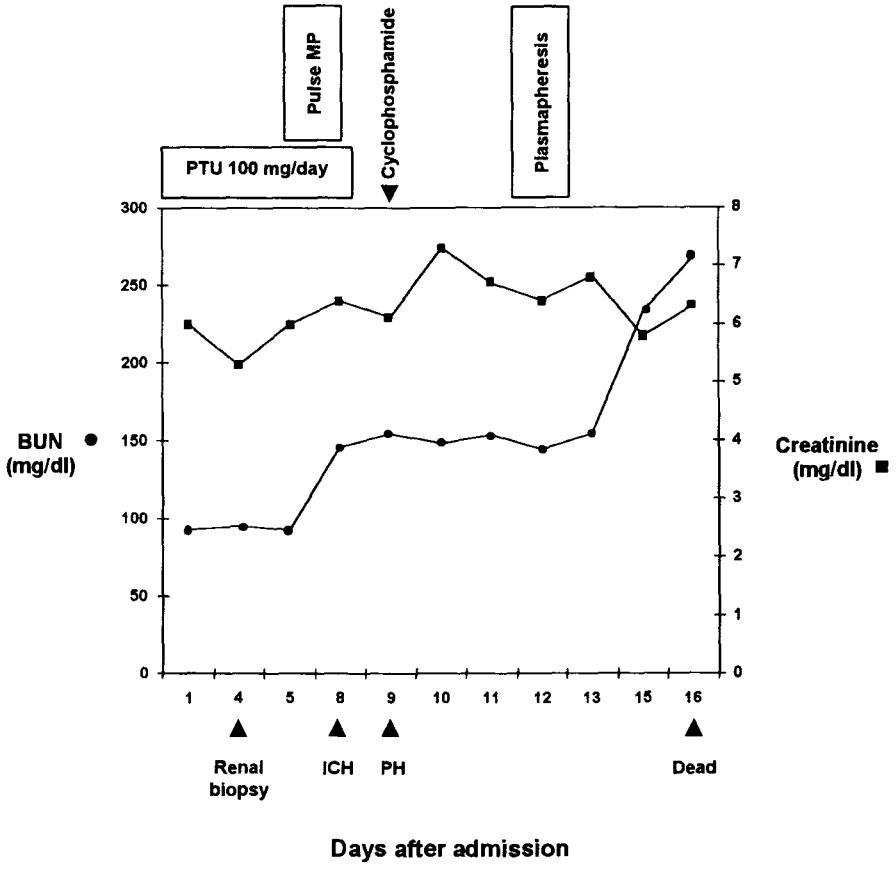

Fig. 1. Clinical course of Patient 1, a percutaneous renal biopsy was performed on day 4 of admission. Then, pulse methylprednisolone (MP) was started, but without improvement. Subsequently, intracerebral hemorrhage (ICH) and pulmonary hemorrhage (PH) developed and did not respond to treatment with cyclophosphamide and plasmapheresis.

Only 2 reported cases were related to MMI therapy [11,15]. Most of the cases were adults. Only 3 children have been reported[8,14].

PTU-induced ANCA-positive systemic vasculitis may cause a variety of constitutional symptoms including fever, myalgia, arthralgia and flu-like syndrome[5,6,8,10-13]. Blood vessels in various organs may be involved. Kidney is the most commonly affected organ in about 60 per cent[6]. The commonest renal lesion is necrotizing crescentic glomerulonephritis[6], but can vary from microscopic to gross hematuria or mild proteinuria to nephrotic range or pyuria. Skin involvement is also common. Leukocytoclastic vasculitis is the most common pathology found[16-18]. Pulmonary involvement, both upper and lower respiratory tract diseases, include epistaxis[19], rhinorrhea[19], nasal pain[20] and life-threatening pulmonary hemorrhage[10,11,21]. Moreover, anemia[12], leukopenia[15], scleritis[13], splenomegaly[5] and pachymeningitis[22] can be presented in this condition.

Crescentic glomerulonephritis developed in the first patient after 3 years of PTU therapy. Her serologic evaluations did not indicate any other causes of rapidly progressive glomerulonephritis. However, she had p-ANCA positive with a titer of 1:160, which is speculated to be involved in the pathogenesis of tissue injury[23].

The pathogenesis of PTU-induced ANCA positivity is not clearly understood. PTU has been shown to accumulate in neutrophils[24], bind to myeloperoxidase, change its structure[25] and allow

initiation of autoantibody formation. Myeloperoxidase, released from neutrophils, converted PTU to cytotoxic or immunogenic products has been proposed to be the other possible mechanism[26-28].

The first patient also developed presumably other severe vasculitic manifestations which included vesicular skin lesions consistent with subcorneal pustular dermatitis, intracerebral hemorrhage and pulmonary hemorrhage. Her intracerebral and pulmonary hemorrhage could not be explained by any other causes of bleeding such as hypertension, coagulopathy or thrombocytopenia. Extent of systemic vasculitis in this patient was very severe and could not be controlled despite treatment with immunosuppressive drugs and plasmapheresis.

The possibility of PTU-induced ANCA-positive vasculitis depends on duration of PTU treatment, however, it may occur as early as 2 weeks or as late as 6 years after receiving PTU[4,5]. Despite cessation of PTU, there have been reports of this condition 2 weeks, 1 month and 5 months after PTU discontinuation[8,10,29]. ANCA positivity may persist and gradually decline to a low titer for a year[5,12].

The second patient who experienced fever, arthralgia and leukocytoclastic vasculitis from PTU-induced ANCA-associated vasculitis, had positive p-ANCA titer more than 1:320 for at least 17 months after changing from PTU to MMI.

Graves' disease per se may attribute to the occurrence of ANCA positivity because the disorder is among the autoimmune diseases and probably because antithyroperoxidase antibody may cross react with leukocyte myeloperoxidase[7,30]. For these 2 patients, the authors did not obtain serum p-ANCA before initiation of PTU treatment.

Overall, prognosis of this condition is good after withdrawal of PTU[6] except for life-threatening conditions for which immunosuppressive therapy such as glucocorticoids and/or cyclophosphamide and plasmapheresis should be considered.

In conclusion, the authors reported 2 childhood cases of ANCA-associated systemic vasculitis, the first case presented as having severe systemic vasculitis leading to death despite intensive treatment. The second case had mild vasculitis of skin and joints and had a good response to PTU discontinuation, but she has had persistent ANCA positivity in a high titer for at least 17 months of follow-up period. Thus, patients who are treated with PTU can develop ANCA-positive vasculitis either a mild or severe form. Therefore, they should be carefully followed and monitored, not only their thyroid status but also the serious complications of PTU.

(Received for publication on September 16, 2002)

REFERENCES

1. Cooper DS. Antithyroid drugs. N Engl J Med 1984; 311: 1353-62.
2. Amrhein JA, Kenny FM, Ross D. Granulocytopenia, lupus-like syndrome, and other complications of propylthiouracil therapy. J Pediatr 1970; 76: 54-63.
3. Tucker LB, Miller LC, Schaller JG. Rheumatic disorders. In: Stiehm ER, ed. Immunologic disorders in infants & children. Philadelphia: WB Saunders, 1996: 742-93.
4. Stankus SJ, Johnson NT. Propylthiouracil-induced hypersensitivity vasculitis presenting as respiratory failure. Chest 1992; 102: 1595-6.
5. Dolman KM, Gans ROB, Vervaat TJ, et al. Vasculitis and antineutrophil cytoplasmic autoantibodies associated with propylthiouracil therapy. Lancet 1993; 342: 651-2.
6. Gunton JE, Stiel J, Caterson RJ, Mc Elduff A. Anti-thyroid drugs and antineutrophil cytoplasmic antibody positive vasculitis. A case report and review of the literature. J Clin Endocrinol Metab 1999; 84: 13-6.
7. 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: 4270-3.
8. Vogt BA, Kim Y, Jennette JC, Falk R, Burke BA, Sinaiko A. Antineutrophil cytoplasmic autoantibody-positive crescentic glomerulonephritis as a complication of treatment with propylthiouracil in children. J Pediatr 1994; 124: 986-8.
9. Yuasa S, Hashimoto M, Yura T, et al. Antineutrophil cytoplasmic antibodies (ANCA) associated crescentic glomerulonephritis and propylthiouracil therapy. Nephron 1996; 73: 701-3.
10. D'Cruz D, Chesser AMS, Lightowler C, et al.

Antineutrophil cytoplasmic antibody positive crescentic glomerulonephritis associated with antithyroid drug treatment. Br J Rheumatol 1995; 34: 1090-1.
11. Hori Y, Arizono K, Hara S, Kawai R, Hara A, Yamada A. Antineutrophil cytoplasmic autoantibody positive crescentic glomerulonephritis associated with thiamazole therapy. Nephron 1996; 74: 734-5.
12. Tanemoto M, Miyakawa H, Hanai J, Yago M, Kitaoka M, Uchida S. Myeloperoxidase-antineutrophil cytoplasmic antibody-positive crescentic glomerulonephritis complicating the course of Graves' disease: Report of three adult cases. Am J Kidney Dis 1995; 26: 774-80.
13. Kitahara T, Hiromura K, Maezawa A, Yago M, Kitaoka M, Uchida S. Case of propylthiouracil-induced vasculitis associated with anti-neutrophil cytoplasmic antibody (ANCA); review of literature. Clin Nephrol 1997; 47: 336-40.
14. Fujieda M, Nagata M, Akioka Y, Hattori M, Kawaguchi H, Ito K. Antineutrophil cytoplasmic antibody-positive crescentic glomerulonephritis associated with propylthiouracil therapy. Acta Pediatr Jpn 1998; 40: 286-9.
15. Kawachi Y, Nukaga H, Hoshino M, Iwata M, Otsuka F. ANCA-associated vasculitis and lupus-like syndrome caused by methimazole. Clin Exp Dermatol 1995; 20: 345-7.
16. Jennette JC, Falk RJ. Small vessel vasculitis. N Engl J Med 1997; 337: 1512-23.
17. Ekenstam E, Callen JP. Cutaneous leukocytoclastic vasculitis: Clinical and laboratory features of 82 patients seen in private practice. Arch Dermatol 1984; 120: 484-9.
18. Sanchez NP, Van Hale HM, Su WPD. Clinical and histopathologic spectrum of necrotizing vasculitis: Report of findings in 101 cases. Arch Dermatol 1985; 121: 220-4.
19. Darben T, Savige J, Prentice R, Paspaliaris B, Chick J. Pyoderma gangrenosum with secondary pyarthrosis following propylthiouracil. Australas J Dermatol 1999; 40: 144-6.
20. Elkayam O, Yaron M, Caspi D. Minocycline induced arthritis associated with fever, livido reticularis and p-ANCA. Ann Rheum Dis 1996; 55: 769-71.
21. Evangelos R, David RF, Bruce WK. Propylthiouracil therapy: An unusual cause of antineutrophil cytoplasmic antibody associated alveolar hemorrhage. J Rheumatol 1995; 22: 803.
22. Ito K. PTU-induced vasculitis. Jpn J Nephrol 1994; 36: 1354.
23. Jennette JC, Falk RJ. Antineutrophil cytoplasmic autoantibodies and associated diseases: A review. Am J Kidney Dis 1990; 15: 517-29.
24. Lam DCC, Lindsay RH. Accumulation of 2-(14C) propylthiouracil in human polymorphonuclear leukocytes. Biochem Pharmacol 1979; 28: 2289-96.
25. Lee H, Hirouchi M, Hosokawa M, Sayo H, Kohno M, Kariya K. Inactivation of peroxidase of rat bone marrow by repeated administration of propylthiouracil is accompanied by a change in the heme structure. Biochem Pharmacol 1988; 37: 2151-3.
26. Jiang X, Khursigara G, Rubin RL. Transformation of lupus-inducing drugs to cytotoxic products by activated neutrophils. Science 1994; 266: 810-3.
27. Von Schmiedeberg S, Goebel C, Gleichmann E, Uetrecht J. Neutrophils and drug metabolism. Science 1995; 268: 585-6.
28. Lee E, Katsura H, Miki Y, Kariya K. Mechanism of inactivation of myeloperoxidase by propylthiouracil. Biochem Pharmacol 1990; 39: 1467-71.
29. Harris NL, McNeely WF, Shepard JO, Ebeling SH, Ellender SM, Peters CC. Case records of the Massachusetts general hospital: Case 21-2002. N Engl J Med 2002; 347: 122-30.
30. Haapala AM, Hyoty H, Soppi E, Parkkonen P, Mustonen J, Pasternack A. Cross-reactivity between antibodies to thyroid microsomal antigens and myeloperoxidase. Adv Exp Med Biol 1993; 336: 81-5.

ภาวะหลอดเลือดอักเสบทั่วร่างกายที่สัมพันธ์กับ antineutrophilic cytoplasmic antibody จากยา propylthiouracil : รายงานผู้ป่วยไทรอยด์เป็นพิษในเด็ก 2 ราย

เปรมฤดี ภูมิถาวร, พ.บ., พัฒน์ มหาโชคเลิศวัฒนา, พ.บ.*,*
วิวัฒน์ ตปนียโอฬาร, พ.บ., อำไพวรรณ จวนสัมฤทธิ์, พ.บ.*, อมรศรี ชุณหรัศมิ์, พ.บ.**

หลอดเลือดอักเสบเป็นภาวะแทรกซ้อนที่พบได้น้อยมากจากการรักษาด้วยยาต้านไทรอยด์ มีรายงานการเกิดหลอดเลือดอักเสบที่สัมพันธ์กับ antineutrophilic cytoplasmic antibody (ANCA) ในผู้ป่วยที่ได้รับการรักษาด้วย propylthiouracil (PTU) และ methimazole ซึ่งโรคพื้นฐานในผู้ป่วยเหล่านี้ส่วนใหญ่ คือ Graves' disease ผู้วิจัยรายงานผู้ป่วยเด็กที่เป็น Graves' disease จำนวน 2 ราย ที่มีปัญหาหลอดเลือดอักเสบที่สัมพันธ์กับ ANCA ในช่วงที่กำลังได้รับการรักษาด้วย PTU ผู้ป่วยรายแรก หลังจากได้รับการรักษาด้วย PTU เป็นเวลา 3 ปี มีอาการข้ออักเสบ และหลังจากนั้น 3 สัปดาห์ มีปัสสาวะเป็นเลือด มีโปรตีนในปัสสาวะ บวมและซีด มีการเพิ่มขึ้นของ creatinine เป็น 6 mg/dl พยาธิสภาพของไตเข้าได้กับ crescentic glomerulonephritis ประมาณ 8 วันหลังจากรับผู้ป่วยไว้ในโรงพยาบาลด้วยปัญหาไตวาย ผู้ป่วยมีปัญหาเลือดออกในสมองและหลังจากนั้น 1 วันมีเลือดออกในปอด ผลการตรวจพบ perinuclear-ANCA (p-ANCA) titer 1:160 ผู้ป่วยได้รับการรักษาอย่างเต็มที่ด้วย immunosuppressive drugs และ plasmapheresis ร่วมกับหยุด PTU แต่ในที่สุดผู้ป่วยก็เสียชีวิตด้วยภาวะแทรกซ้อนจากหลอดเลือดอักเสบรุนแรงทั่วร่างกาย ผู้ป่วยรายที่ 2 มีอาการไข้ ปวดข้อ และตุ่มที่ผิวหนัง ซึ่งผลชิ้นเนื้อมีพยาธิสภาพเข้ากับ leukocytoclastic vasculitis หลังจากรักษาด้วย PTU ประมาณ 2 ปี อาการต่าง ๆ ของผู้ป่วยดีขึ้นหลังจากหยุด PTU แต่ยังคงมี titer ของ p-ANCA มากกว่า 1:320 ตลอดช่วงการติดตามรักษาเป็นเวลา 17 เดือน ดังนั้นผู้ป่วยที่ได้รับการรักษาด้วย PTU มีความเสี่ยงที่จะเกิดภาวะหลอดเลือดอักเสบที่สัมพันธ์กับ ANCA โดยอาการจากหลอดเลือดอักเสบอาจมีความรุนแรงน้อยหรือมากก็ได้ ดังนั้นจึงควรติดตามผู้ป่วยอย่างใกล้ชิด

คำสำคัญ : antineutrophilic cytoplasmic antibody, propylthiouracil, หลอดเลือดอักเสบ, ไทรอยด์เป็นพิษ, ภาวะไตเสียหน้าที่อย่างรวดเร็ว

เปรมฤดี ภูมิถาวร, พัฒน์ มหาโชคเลิศวัฒนา,
วิวัฒน์ ตปนียโอฬาร, อำไพวรรณ จวนสัมฤทธิ์, อมรศรี ชุณหรัศมิ์
จดหมายเหตุทางแพทย์ ฯ 2545; 85 (ฉบับพิเศษ 4): S1295-S1301

* ภาควิชากุมารเวชศาสตร์, คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400