# Clinical Features and Outcomes in Patient with Antineutrophil Cytoplasmic Autoantibody–Positive Glomerulonephritis Associated with Propylthiouracil Treatment in Siriraj Hospital

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***Background:*** *ANCA is detected in several vasculitic diseases, including drug-induced systemic vasculitis : propylthiouracil (PTU), hydralazine, minocycline, penicillamine, allopurinol, procainamide, carbimazole, thiamazole, clozapine and phenytoin. All have been known to induce ANCA positive vasculitis in adult patients.*
***Objective:*** *To study the clinical manifestation, renal pathology and outcome of patients with ANCA positive vasculitis associated with propylthiouracil treatment in Siriraj Hospital.*
***Material and Method:*** *Retrospective study in 7 patients with Graves' disease who were treated with propylthiouracil and developed ANCA-positive glomerulonephritis between 2000-2008.*
***Results:*** *Seven cases with Graves' disease who received propylthiouracil whose ages were 43 $\pm$ 14 years. The duration of propylthiouracil treatment was 68.5 $\pm$ 39 months and the doses were 50-150 mg per day. Six cases had P-ANCA and one case had C-ANCA in the serum. Proteinuria ranged from 0.49-2.9 gram per day. Mean serum creatinine was 2.05 mg/dl with creatinine clearance of 44 $\pm$ 35 ml/min. The propylthiouracil was withdrawn in every patient and corticosteroid was administered. Renal remission was found until 1 year of follow-up.*
***Conclusion:*** *ANCA positive glomerulonephritis associated with propylthiouracil is not uncommon. The average onset of glomerulonephritis is 2 years or more. The propylthiouracil dosage was not necessary high. Urinalysis and other glomerulonephritis symptoms should be screened for early diagnosis and appropriate treatment in patients treated with PTU.*

***Keywords:*** *ANCA positive Glomerulonephritis, Propylthiouracil*

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Circulating antineutrophil cytoplasmic autoantibody (ANCA) was first reported in 1982 by Davies et al[1] in patients with pauci-immune necrotizing glomerulonephritis with crescents, and is now regarded as a serologic marker for active pauciimmune necrotizing crescentic glomerulonephritis and systemic vasculitis such as Wegener's granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome[2]. Furthermore, ANCA is detected in a number of other vasculitic diseases, including drug-induced systemic vasculitis including propylthiouracil (PTU), hydralazine, minocycline, penicillamine, allopurinol, procainamide, carbimazole, thiamazole, clozapine and phenytoin. All have been known to induce ANCA-positive vasculitis in adult patients. Propylthiouracil (PTU) has been reported to induce ANCA positive vasculitis in adult patients since the reports of Stankus et al[3] and Dolman et al[4,5]. The objectives of this study were 1) to determine the clinical manifestations of propylthiouracil-associated ANCA-

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positive glomerulonephritis patients at Siriraj Hospital 2) to examine the renal pathologies of these patients 3) to identify the risk factors for the occurence of the disease.

## Material and Method

A retrospective study in patients with ANCA positive glomerulonephritis and systemic vasculitis associated with antithyroid drug treatment was conducted in Nephrology Division Siriraj Hospital Mahidol University for the period between 2000 and 2008. A total of seven adult patients who were administered PTU for Graves' disease were identified. "Pauci-immune" was defined as a score of 2+ or lower in staining for any Ig (on a scale of 0 to 4+) observed by immunofuorescence microscopy. Other small-vessel vasculitic diseases, such as systemic lupus erythematosus, cryoglobulinemia, Henoch-Schonlein purpura, hepatitis related small-vessel vasculitis, and other identifiable conditions induced by medications other than antithyroid drugs were excluded from the study as well as patients with Goodpasture's syndrome. Renal involvement was inferred when hematuria, proteinuria, or both were present on urinalysis with or without renal impairment or hypertension. Renal biopsy specimens for light and immunofluorescence microscopy were processed by established methods. Glomerular involvement was expressed as a percentage of the glomeruli affected with cellular crescents with or without necrosis, fibrocellular crescents, fibrous crescents, and global sclerosis. Interstitial lesions such as interstitial inflammation, interstitial fibrosis, and tubular atrophy were graded semiquantitatively on a scale of 0 to 3 (grade 0 = neg, grade 1 < 25%, grade 2, 25-50%, grade 3 > 50%). The presence of extrarenal manifestations of vasculitis was diagnosed as previously reported. Systemic involvement included fever, general malaise, and weight loss. Pulmonary involvement was defined by the presence of hemoptysis, pulmonary hemorrhage, respiratory failure, or radiographic infiltrations without evidence of infection. Upper respiratory tract involvement was defined as longstanding sinusitis or otitis media despite antibiotic and anti-allergy therapies, or the presence of ulcers in the nasal passage with or without epistaxis. Musculoskeletal involvements included arthralgias, arthritis, myalgia, and muscle weakness. Cutaneous disease was defined by a characteristic palpable purpuric rash with or without ulcerations and/or pathologically confirmed leukocytoclastic angiitis. Gastrointestinal vasculitis was presumed when abdominal pain and/or gastrointestinal bleeding was present. Neurologic involvement included seizures or multifocal neural deficit (mononeuritis multiplex). Ocular disease was defined by episcleritis, keratitis, uveitis, and retinal vasculitis. Hematuria was graded as "gross" or "positive" (three or more red blood cells per high-power fields in spun urine). Proteinuria was performed and evaluated by 24-h quantitative measurement.

Creatinine clearance (Ccr) was calculated as Cockcroft-Gault formulation (ml/min) = (140-age) x (Wt in kg) x (0.85 if female)/(72 x sCr). Hypertension was defined as a systolic and diastolic BP greater than140/90 mmHg. Clinical syndromes were modified from the World Health Organization clinical syndromes[14]. End-stage renal disease (ESRD) was defined when a patient required chronic dialysis or renal transplantation. A state of euthyroidism was defined when clinical symptoms associated with hyperthyroidism disappeared and levels of thyroxine, triiodothyronine, and thyroid-stimulating hormone were within normal ranges. Criteria for evaluating treatment responses in patients with ANCA-positive glomerulonephritis and systemic vasculitis were based on the report by Nachman et al[15]. Remission was defined as stabilization or improvement of renal function, resolution of hematuria, and resolution of extrarenal manifestations of systemic vasculitis. Persistence of proteinuria was not considered indicative of persistence of disease activity. Remission on therapy was defined as the achievement of remission while still receiving immunosuppressive medication or corticosteroid at a dose greater than 7.5 mg/d prednisolone or its equivalent. Treatment resistance was defined as (1) progressive decline in renal function with the presence of an active urine sediment or (2) persistence or emergence of any extrarenal manifestation of vasculitis despite immunosuppressive therapy. Relapse of nephritis was defined as occurrence of at least one of the following: (1) rapid rise in serum creatinine concentration accompanied by an active urine sediment; (2) a renal biopsy demonstrating active necrosis or crescent formation.

### *Statistical analysis*

Data are presented as mean $\pm$ SD, descriptive statistic method

## Results

All seven patients had biopsy-proven pauci-immune NCGN and were seropositive for ANCA. The study group consisted of 7 females. The mean age at

onset was 43 ± 14yr (ranged, from 29 to 66 yrs). One patient presented with NCGN alone (patients 4), and six patients had NCGN with extrarenal organ systemic vasculitis (Table 1). One of seven patients was asymptomatic. She was detected by the national urine screening program for hematuria and proteinuria (Patient 4). Presenting symptoms of the remaining five patients are shown in Table 1.

The distribution of organ system involvement was shown in Table 1. All patients had clinical evidence of renal disease and biopsy-proven pauci-immune glomerulonephritis. Three patients presented with nephritic syndrome and hypertension (patient 1,3,7). Two of seven patients had prodromal flu-like symptoms, including fever and malaise(patient 2,7). These systemic symptoms appeared within 2 months before the onset of overt vasculitic or nephritic disease. Among six patients with ANCA-positive NCGN and extrarenal organ system vasculitis, three had pulmonary hemorrhage, four had purpuric rash, and four had arthralgia and arthritis involving both large and small joints. Ocular involvement was not found in all patients. No seizure or peripheral neuropathy was observed in patients in the present study. The mean period of PTU administration was 5.7 ± 3.4 years (range, 2 to 12 years). PTU was discontinued in all patients after renal function deterioration. All patients received no antithyroid drug during the follow-up period. Six patients in this study had perinuclear pattern (P)-ANCA, and one patient had cytoplasmic pattern (C)-ANCA or PR3-ANCA. The laboratory data at the time of diagnosis was shown in Table 2. Hematuria was observed in all patients. The mean protein excretion was 1.19 ± 1.05 gram per day. Four patients (patient 1,3,4,7) had high serum creatinine. Mean Ccr was 44 ± 38 ml/min/1.73 $m^2$ (range, 12 to 102 ml/min/1.73 $m^2$).

The histologic data of the renal biopsies at diagnosis was summarized in Table 3. The mean percentage of glomeruli with cellular, fibrocellular, and fibrous crescents was 61.14 ± 29.60%; crescents were

**Table 1.** Clinical manifestations of ANCA-positive patients with GN associated with PTU treatment[a]

| Patient | Age/Gender | Clincal at onset[b] | Organ System Involvement | Duration of PTU Therapy (year) | Therapy | Duration to remission (month)[c] |
|---|---|---|---|---|---|---|
| 1 | 29 Female | Gross hematuria | R , C | 8 | pulse methylprednisolone<br>oral prednisolone<br>oral cyclophosphamide | 10 |
| 2 | 35 Female | Arthalgia , Fever | R , C , M , S | 4 | oral prednisolone | 1 |
| 3 | 36 Female | Hemoptysis<br>Arthralgia<br>Purpura<br>Gross hematuria | R , C ,M , P | 12 | pulse methylprednisolone<br>oral prednisolone<br>oral cyclophosphamide | 6 |
| 4 | 63 Female | None | R | 2 | oral prednisolone<br>oral cyclophosphamide | 2 |
| 5 | 37 Female | Edema | R , C , M | 7 | pulse methylprednisolone<br>oral prednisolone<br>oral cyclophosphamide | 2<br>loss F/U |
| 6 | 36 Female | Hemoptysis<br>Arthralgia | R , M , P | 4 | oral prednisolone<br>oral cyclophosphamide | 1 |
| 7 | 66 Female | Hemoptysis<br>Fever | R , P , S | 3 | pulse methylprednisolone<br>oral prednisolone<br>oral cyclophosphamide | 12 |

[a] ANCA, antineutrophil cytoplasmic antibody; NCGN, necrotizing crescentic glomerulonephritis; PTU, propylthiouracil; R, renal involvement; S, systemic involvement; P, pulmonary involvement; C, cutaneous involvement; M, musculoskeletal involvement; O, ocular involvement; MMI, methimazole;

[b] None, one patient was asymptomatically detected by a national urine screening program.

[c] See criteria for treatment response in Materials and Methods section.

**Table 2.** Laboratory findings of ANCA-positive glomerulonephritis patients associated with PTU treatment□

| Patient | ANCA pattern | | Urinalysis | | Serum Creatinine (mg/dl) | Creatinine clearance (ml/min per 1.73 $m^2$) | Dose PTU per day |
|---|---|---|---|---|---|---|---|
| | Immuno fluorescence | ELISA | Hematuria (HPF) | Proteinuria (gram per day) | | | |
| 1 | P | MPO | 50-100 | 2.90 | 2.6 | 24 | 50 |
| 2 | P | MPO | 30-50 | 0.90 | 0.8 | 102 | 150 |
| 3 | P>1:1280 | MPO | 100-200 | 0.10 | 3.2 | 23 | 50 |
| 4 | P | MPO | 50-100 | 2.43 | 2.7 | 16 | 50 |
| 5 | C | PR3 | 50-100 | 0.49 | 1.3 | 37 | 100 |
| 6 | P | MPO | >100 | 0.60 | 0.5 | 96 | 50 |
| 7 | P | MPO | 50-100 | 0.93 | 3.3 | 12 | 50 |

□ MPO, myeloperoxidase; HPF, high-power field.

**Table 3**. Histologic findings of renal biopsies

| Patient | Number of Glomeruli Evaluated | Normal Glomeruli[a] (%) | Glomerular Lesions[a] | | | | Tubulointerstitial Lesions[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Cellular Crescent (%) | Fibrocellular Crescent (%) | Fibrous Crescent (%) | Global Sclerosis (%) | Interstitial Inflammation (0-3) | Interstitial Fibrosis (0-3) | Tubular Atrophy (0-3) |
| 1 | 16 | 43 | 38 | 19 | 0 | 0 | 3 | 3 | 3 |
| 2 | 18 | 78 | 17 | 0 | 5 | 0 | 0 | 1 | 1 |
| 3 | 10 | 20 | 30 | 40 | 0 | 10 | 3 | 2 | 1 |
| 4 | 28 | 10 | 14 | 32 | 36 | 2 | 3 | 3 | 3 |
| 5 | 35 | 0 | 5 | 8 | 51 | 36 | 2 | 3 | 3 |
| 6 | 15 | 67 | 0 | 7 | 7 | 19 | 1 | 1 | 1 |
| 7 | 22 | 54 | 0 | 4 | 4 | 38 | 1 | 1 | 1 |

[a]Percentage of total number of glomeruli evaluated
[b]Semiquantitatively graded on a scale of 0 to 3. (grade 0= neg, grade1<25%, grade2 25-50%, grade 3 >50%)

found in 50% of the glomeruli in four of seven patients.

The patients were basically treated with the following initial protocols (Table 1). Seven patients received oral corticosteroids; four(patients 1,3,5,7) had pulse methylprednisolone before the initiation of oral prednisolone and cyclophosphamide. The other two patients (patients 4 and 6) received oral corticosteroids plus oral cyclophosphamide. The mean period of prednisolone administration was $5 \pm 4$ months (range, 1 to 12 months). Patients were followed for a mean of $5 \pm 4$ months (range, 1 to 12 months). No relapse of nephritis or vasculitis was observed during the follow-up period. All patients had normal renal function and a state of euthyroid at the last visit. None of the patients progressed to renal dysfunction or ESRD.

## Discussion

The purpose of this retrospective study was to analyze the clinical features and outcome in patients with ANCA-positive disease associated with PTU treatment. For this purpose, we reviewed the literature and compared the clinical spectrum of our cases with other reports of ANCA-positive disease associated and unassociated with PTU and also adult with non-drug-induced ANCA-positive disease. Clinical findings and laboratory data are summarized in Table 4.

The present study showed a clear female predominance of PTU-associated ANCA-positive disease in adult. A female predominance was also noted in hyperthyroid cases associated with PTU treatment. Although the reason for this marked gender difference

**Table 4.** Clinical manifestations and laboratory data of ANCA-positive vasculitis in adults [a]

| | This Study n = 7 | Previous study[6-12] n = 15 | Previous study of non-Drug-Induced GN[15,18] n = 107 |
|---|---|---|---|
| Follow-up period (mo) [b] | 5 ± 4 (1-12 ) | 9 ± 8 (1 to 29) | 30 (0.2 to 146) |
| Gender (M:F) | 0:7 | 1:2.8 | 1:0.8 |
| Onset age (yr) | 43 ± 14 | 49.5 ± 17.8 | 57.8 ± 17.0 |
| Duration of PTU administration (months;range) | 68.5 ± 39.0 (24-144) | 40 ± 18 (11 to 84) | NA |
| ANCA positivity | | | |
| P-ANCA | 6 (85.7%) | 15/15 (100%) | 68 (63.6%) |
| C-ANCA | 1 (14.3%) | 2/10 (20%) | 39 (36.5%) |
| Proteinuria (g/day) | 1.19 ± 1.05 (0.49-2.9) | 2.0 ± 1.6 g/d (n = 6) 2.0 (0.5 to 4.0) | 2.7 ± 2.8 g/d 4.5 (0.8 to 21.6) |
| Mean serum creatinine (mg/dl;range) | 2.05 (0.5-3.3) | NA | NA |
| Mean creatinine clearance (ml/min ) | 44 ± 38 | | |
| CRI and/or ESRD | 0 | 3 (20.0%) | 23 (23.7%) |
| Mortality | 0 | 0 (0%) | 12 (12.4%) |
| Relapse | 0 | 0 (0%) | 22 (22.6%) |

[a]PTU-GN, propylthiouracil-associated glomerulonephritis; PR3, proteinase-3; CRI, chronic renal insufficiency; ESRD, end-stage renal disease; NA, not available.
[b]Mean follow-up period.

is unclear, this may be because the incidence of Graves' disease is approximately five times higher in female than in male. ANCA-positive NCGN or MPA is considered to be a disease of elderly or middle-aged individuals. The age at onset in this study (43 ± 14 yr) is slightly higher than that in previous study (49.5 ± 17.8 yr)[15]. The peak incidence of Graves' disease in adult mostly occurs primarily during middle-age.

The period of administration of PTU was 5.7 ± 3.4 years. The development of vasculitis may appear at any time after treatment has begun as previously reported[12]. PTU was discontinued in all of seven patients in this study. No relapse of Graves' disease was observed despite no antithyroid treatment during administration of prednisolone.

Six from seven patients in this study had MPO-ANCA. A predominance of MPO-ANCA was also noted in adult patients with PTU-associated ANCA-positive disease[6-13] (Table 4). The pathogenesis of this disease is not clearly understood. PTU has been shown to accumulate in neutrophils and bind to MPO, resulting in a change of MPO structure. This alteration in configuration may induce ANCA in susceptible individuals. However, the prevalence of MPO-ANCA is not due to a cross-reaction between MPO and thyroid peroxidase, because no correlation between MPO-ANCA titers and antithyroid peroxidase titers was recognized in either this study or previous report[16]. In the present study, three patient presented with rapidly progressive glomerulonephritis. Most parients have crescents in the pathology and global sclerosis is also predominant in this histology. However after PTU withdrawl and steroid administration, the renal functions showed improvement to full recovery only in those with normal renal function. Therefore, early recognition with prompt management might rescue the renal function of these patients. Clinical improvement was seen in all seven patients in the present study

after 5 ± 4 months of follow-up. No patient progressed to end stage renal disease or death during the follow-up period. Renal function improved and remained well, with an overall good prognosis. One possible reason for good prognosis is that patients with PTU-associated ANCA-positive disease had only mild clinical findings at the time of initiation of therapy. Secondly, discontinuation of PTU may contribute to good prognosis, because vasculitis or nephritis improved after discontinuation of PTU without immunosuppressive therapy in some adult patients with PTU-associated ANCA-positive disease, accompanied with a decreased ANCA titers[6]. Six from seven patients in this study had perinuclear pattern (P)-ANCA, and one patient had cytoplasmic pattern (C)-ANCA. Treatment for NCGN should be given appropriately depending on the severity of the illness. Corticosteroids and/or cyclophosphamide should be administered if renal manifestations are severe or rapidly progressive or if biopsy findings show crescentic glomerulonephritis. In the present study, one patient was treated with corticosteroids alone and six were treated with corticosteroids plus cyclophosphamide. The beneficial effects of the corticosteroid-cyclophosphamide combination over corticosteroids alone have been reported in patients with non-drug-induced ANCA positive disease[15].

In conclusion, seven adult patients with ANCA-positive NCGN associated with PTU treatment were analyzed. It was found in a middle-aged female with Graves' disease after two years of PTU with variable dosage. Clinical manifestations include respiratory, renal, musculoskeletal system or may be asymptomatic. Easy and inexpensive laboratory screening is urinalysis. Early detection can reverse the disease progression.

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## การศึกษาลักษณะทางคลินิค ผลทางพยาธิวิทยาของชิ้นเนื้อไต และผลการรักษาของผู้ป่วยโรค Propylthiouracil-Associated Antineutrophil Cytoplasmic Antibody-Positive Vasculitis ในโรงพยาบาลศิริราช

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***วัตถุประสงค์:*** *ANCA ในกระแสเลือด ได้ถูกค้นพบและรายงานครั้งแรกเมื่อปี ค.ศ. 1982 ซึ่ง ANCA เป็น marker ที่สำคัญที่พบในโรค active pauci immune necrotizing crescentic glomerulonephritis (NCGN) และโรคในกลุ่ม vasculitis เช่น Wegener's granulomatosis, microscopic polyangiitis (MPA) และ Churg – Strauss syndrome และอาจพบในโรคอื่น ๆ เช่น drug induced systemic vasculitis ได้แก่ propylthiouracil, hydralazine, minocycline, penicillamine, allopurinol, procainamide, carbimazole, thiamazole, clozapine, และ phenytoin Propylthiouracil(PTU) สามารถก่อให้เกิด ANCA – positive vasculitis ได้ในผู้ป่วยวัยกลางคน การศึกษานี้เป็นการศึกษาเพื่อติดตามดูอาการและผลการรักษาผู้ป่วยโรค Antineutrophil cytoplasmic antibody (ANCA) – positive vasculitis ที่สัมพันธ์กับการใช้ยา propylthiouracil (PTU) และ มีผลการตรวจ myeloperoxidase – specific ANCA – positive ผลการตรวจชิ้นเนื้อไตเป็น pauci – immune necrotizing crescentic glomerulonephritis associated with propylthiouracil*

***วัสดุและวิธีการ:*** *retrospective study ในผู้ป่วยไทยที่เป็น Graves' disease และได้รับการรักษาด้วยยา PTU และได้รับการวินิจฉัยเป็น ANCA–positive glomerulonephritis and systemic vasculitis associated with antithyroid drug treatment จากผล renal biopsy ใน specimen ที่แสดงถึง pauci–immune NCGN ร่วมกับมี ANCA positive โดยรวบรวมข้อมูลจากผู้ป่วยในโรงพยาบาลศิริราช ตั้งแต่ 2543 – 2551*

***ผลการศึกษา:*** *ผู้ป่วยที่ได้รับการวินิจฉัยเป็น Graves' disease และได้รับยา propylthiouracil มีอายุเฉลี่ย 43±14 ปี ระยะเวลาของการได้รับการรักษาด้วยยา propylthiouracil อยู่ที่ประมาณ 68.5±39 เดือนโดยปริมาณที่ได้รับคือ 50-150 มิลลิกรัมต่อวัน ผู้ป่วยซึ่งผลการตรวจเลือดเป็น P-ANCA มีจำนวนหกราย และอีกหนึ่งรายผลการตรวจเป็น C-ANCA ระดับโปรตีนรั่วในปัสสาวะมีค่าเฉลี่ยอยู่ที่ 0.49-2.9 กรัมต่อวัน ค่าเฉลี่ยระดับ serum creatinine 2.05 mg/dl และ creatinine clearance 44±35 ml/min. ผู้ป่วยทุกรายได้หยุดใช้ยา propylthiouracil และได้รับการรักษาด้วย corticosteroid การทำงานของไตกลับสู่สภาวะปกติในช่วงระยะเวลาหนึ่งปี*

***สรุป:*** *: : โรค ANCA positive glomerulonephritis associated with propylthiouracil เป็นโรคที่พบในผู้ป่วย Graves' disease ที่ได้รับยา propylthiouracil โดยระยะเวลาที่พบโรคหลังได้รับยามากกว่าหรือเท่ากับสองปีขึ้นไปโดยปริมาณของยาที่ได้รับนั้นไม่จำเป็นต้องเป็นปริมาณที่สูง ดังนั้นผู้ป่วยที่ได้รับการรักษาด้วยยาpropylthiouracil ควรได้รับการตรวจปัสสาวะ เมื่อมีลักษณะที่สงสัย glomerulonephritis เพื่อให้ได้การวินิจฉัยที่รวดเร็วและการรักษาที่เหมาะสมต่อไป*