

Propylthiouracil-Associated Antineutrophil Cytoplasmic Autoantibody-Positive Vasculitis: Retrospective Study of 19 Cases

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ABSTRACT. Objective. To investigate the features, followup data, and outcomes of patients with propylthiouracil (PTU)-associated antineutrophil cytoplasmic autoantibody (ANCA)-positive vasculitis.

Methods. Nineteen patients with PTU-associated ANCA-positive vasculitis diagnosed in our hospital from 2000 to 2006 were analyzed retrospectively.

Results. Our data showed a female predominance among the patients. Eleven patients had involvement of more than one organ. Renal involvement was the most common manifestation. Fourteen patients underwent renal biopsy. Four patients had focal proliferative glomerulonephritis with crescent formation. Two had necrotizing glomerulonephritis with crescent formation. Two patients had minor glomerular abnormalities, 2 had IgA nephropathy, one had membranous nephropathy, one had focal proliferative glomerulonephritis, one had granulomatous interstitial nephritis, and the remaining one had focal segmental glomerular sclerosis. Immune complex glomerulonephritis was found in 3 patients. On indirect immunofluorescence, 17 patients were perinuclear-pattern ANCA-positive, one was positive for atypical ANCA, and one was positive for cytoplasmic-pattern-ANCA. By ELISA, 4 patients were positive for both myeloperoxidase (MPO)-ANCA and proteinase-3 (PR3)-ANCA, one was positive for PR3-ANCA only, and the others were positive for MPO-ANCA only. For the treatment of vasculitis, 5 patients received prednisone alone, 10 received prednisone and cyclophosphamide, and the remaining 4 did not receive prednisone or cyclophosphamide. During followup, 15 patients achieved remission, 3 patients died, and one patient depended on dialysis. In general, MPO-ANCA concentration did not correlate with disease progression, and a delayed decrease of MPO-ANCA concentration was found in most patients who achieved remission.

Conclusion. Most patients with PTU-associated ANCA-positive vasculitis had good outcomes; however, severe cases existed. We suggest early recognition and adequate treatment are necessary to improve outcome. (First Release Nov 1 2007; J Rheumatol 2007;34:2451–6)

Key Indexing Terms:

PROPYLTHIOURACIL ANTINEUTROPHIL CYTOPLASMIC AUTOANTIBODY VASCULITIS

Circulating antineutrophil cytoplasmic autoantibody (ANCA) specified for myeloperoxidase (MPO) or proteinase-3 (PR3) is closely associated with small-vessel vasculitis such as Wegener's granulomatosis (WG), microscopic polyangiitis

(MPA), and Churg-Strauss syndrome (CSS)¹. Certain drugs have been associated with the induction of ANCA and the onset of ANCA-associated vasculitis². Propylthiouracil (PTU) is one of the drugs most widely used in treating hyperthyroidism. It is associated with "minor" side effects like cutaneous reactions (usually urticaria or macular rashes), arthralgia, gastrointestinal upset, etc. Further, it is associated with potentially life-threatening complications that include ANCA-positive vasculitis³. Since Dolman, *et al*⁴ published 6 cases of PTU-induced ANCA-positive vasculitis in 1993, PTU has received more attention for being among the most common drugs that induce such disease⁵. However, PTU-induced ANCA-positive vasculitis is mainly published as case reports; few retrospective studies have been published.

We retrospectively analyzed the data of 19 patients with ANCA-positive vasculitis associated with PTU treatment.

MATERIALS AND METHODS

Patients and selection criteria. Nineteen patients diagnosed in Shanghai

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Ruijin Hospital between 2000 and 2006 with complete followup were enrolled in our retrospective study. The diagnoses were based on the following criteria: ANCA was detected positive by indirect immunofluorescence technique (IIF) and antigen-specific ELISA; the signs and symptoms of vasculitis were present and related to taking PTU; and patients with other medical conditions that mimicked vasculitis were excluded, especially infections, malignancies, and other definable types of vasculitis⁶. The presence of manifestations of vasculitis was diagnosed according to the Birmingham Vasculitis Activity Score (BVAS) 2003⁷ after excluding other causes (infection, etc.).

ANCA analysis. All patients had been tested for the presence of ANCA by indirect immunofluorescence (Euroimmun, Lubeck, Germany). Tests for anti-MPO, anti-PR3 antibodies were performed in all sera by ELISA (Euroimmun). The normal MPO-ANCA and PR3-ANCA concentrations were below 20 RU/ml.

Clinical data. The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault formula⁸. Nephrotic syndrome was defined as proteinuria > 3.5 g/24 h and serum albumin < 30 g/l. Hypertension, according to the JNC 7 (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) was defined as systolic blood pressure > 140 mm Hg and/or diastolic pressure > 90 mm Hg or if antihypertensive medication was needed. Renal insufficiency was defined as an elevated creatinine level attributable to the disease (serum creatinine > 1.3 mg/dl). Disease activity at initial clinical presentation was evaluated by the BVAS 2003⁷.

Renal biopsies. Renal biopsy specimens were processed for light microscopy, electron microscopy (EM), and immunofluorescence (IF) study. A classic direct IF technique using antibodies against IgA, IgG, IgM, C3, C4, C1q, and fibrin was performed for the IF study. Pauci-immunity was defined as 2+ or less staining for immunoglobulins (on a scale of 0 to 4+) by direct IF assay and no electron-dense deposits observed by EM. Immune complex deposition was defined as immune deposits of an intensity of more than 2+ and/or electron-dense deposits observed by EM^{9,10}.

Treatment. Treatment protocols varied among patients and depended on the presentation at diagnosis. Briefly, PTU was discontinued in all the patients. Antithyroid drugs were administered only if necessary and according to patients' clinical manifestation, laboratory data, and allergy history. Patients were treated with prednisone or prednisone together with cyclophosphamide depending on the clinical presentation after PTU cessation only if necessary. However, if patients presented with rapidly progressive glomerulonephritis or active systemic manifestation at diagnosis, prednisone together with cyclophosphamide was administered. Prednisone was given at a dose of 0.5–0.8 mg/kg for the first 1 to 2 months, followed by a tapering schedule during the following months. Intravenous cyclophosphamide was given at a dose of 0.5 g/1.73 m² and adjusted according to patients' leukocyte count.

Outcome. Criteria for evaluating treatment response in patients were based on the report by Nachman, *et al*¹¹. 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.

Statistics. All statistical analyses were computed using SPSS 11.0 for Windows (SPSS Inc., Chicago, IL, USA). Data were presented as mean ± SD, unless otherwise indicated. Differences of quantitative parameters between groups were performed with t-test (for normally distributed data) or nonparametric test (for non-normally distributed data). A p value less than 0.05 was considered to be statistically significant.

RESULTS

Demographic features, clinical and pathological features, laboratory presentation (Table 1). Nineteen patients were identified (18 women, 1 man), with a median age of 40.16 ± 17.14 years at presentation (range 18–75 yrs).

Hypertension was found in 5 patients (26.32%). Mean sys-

tolic pressure at presentation was 121.58 ± 19.44 mm Hg (range 100–160 mm Hg) and mean diastolic pressure was 76.32 ± 10.52 mm Hg (range 60–95 mm Hg).

Of the 19 patients with PTU-associated ANCA-positive vasculitis, systemic symptoms like fever were found in 11 patients (57.89%), arthralgia in 7 (36.84%), weight loss in 6 (31.58%), muscle pain in 8 (42.11%), and fatigue in 7 (36.84%).

Renal involvement was the most common manifestation, occurring in 18 patients (94.74%). Six patients presented with elevated serum creatinine attributable to the vasculitis. Gross hematuria was present in 3 patients and microscopic hematuria was found in 15 patients. One patient presented with rapidly progressive glomerulonephritis and depended on hemodialysis (Patient 3). No patient presented with nephrotic syndrome at diagnosis. Renal biopsy was performed in 14 patients (Table 1). Of the 14 patients, immune complex glomerulonephritis was found in 3, one (Patient 3) had 3+ IgA and C3 deposition in the mesangium, one (Patient 7) had 3+ IgA and IgM deposition in the mesangium, and one (Patient 8) had subepithelial deposits as well as 3+ glomerular capillary loop staining for IgG. Pauci-immunity was found in the remaining 11 patients.

Pulmonary manifestations were found in 6 patients (31.58%): one (Patient 19) presented with respiratory failure and depended on artificial ventilation, one (Patient 16) had radiological infiltration revealed by computerized tomography scan without evidence of infection, 2 (Patients 17 and 18) had hemoptysis; other symptoms like cough with sputum production or wheeze were found in all 6 patients. Clinical signs of vasculitic skin and mucous involvement that included purpura, mouth ulcer, and skin rash and ulcers were observed in 4 cases and biopsy-proven skin vasculitis was found in one patient (Patient 10). Ear, nose, and throat involvement was observed in 2 patients (Patients 16 and 19), with manifestations such as tinnitus, decline of hearing, bloody nasal discharge, or sinusitis. No neurological, gastrointestinal, or other organ involvements were observed at diagnosis. Eleven of 19 patients had more than one organ involvement at presentation.

Regarding immunological findings, antinuclear antibody was found in 8 patients (42.11%). Two patients (10.53%) were positive for antithyroid peroxidase antibody and 5 (26.32%) were positive for antithyroglobulin antibody. Three patients (15.79%) had hypergammaglobulinemia.

Antithyroid drugs. The mean duration of PTU therapy of 19 patients was 4.74 ± 3.46 years (range 1–14 yrs). PTU was discontinued in all patients. One patient had thyroidectomy; 2 patients had ¹³¹I treatment; 4 patients were switched from PTU to methimazole, and the remaining 12 patients received no antithyroid drug during the followup periods (Table 2). The total dosage of PTU ranged from 73 to 474 g.

Treatment and outcome (Table 2). Corticosteroids were administered in 15 patients (Patients 1–7, 9–12, 15, 16, 18, and 19). Cyclophosphamide was added in 10 patients

Table 1. Patients' characteristics, clinical and pathological features, and laboratory presentation at diagnosis.

Patient	Age, yrs/ Sex	Disease Extent	Fever	BVAS	Serum Creatinine, mg/dl	Proteinuria, mg/24 h	Hematuria	Renal Histology Pathological Diagnosis	Duration of Crescent, %	Duration of PTU Therapy, yrs
1	19 F	K, S, A	Y	13	0.58	380	M	Focal proliferation glomerulonephritis with crescent formation	3	2
2	37 F	K, L, A	Y	17	1.75	763	M	Focal segmental glomerular sclerosis	0	3
3	20 F	K	N	13	6.41	2030	M	Crescentic IgA nephropathy	68	5
4	50 F	K, A	Y	13	0.85	433	M	Minor glomerular abnormalities	0	2
5	44 F	K	N	9	0.80	99	M	Focal proliferative glomerulonephritis with crescent formation	30	6
6	46 M	K, L	Y	13	0.60	416	M	Focal proliferative glomerulonephritis	0	7
7	25 F	K	N	10	0.70	340	G	Focal proliferative IgA nephropathy with crescent formation	7	4
8	43 F	K	N	13	0.59	1060	M	Membranous nephropathy	0	4
9	51 F	K, A	Y	13	0.66	1010	G	Focal proliferative glomerulonephritis with crescent formation	20	12
10	69 F	K, A, S	Y	23	0.57	483	M	NA		3
11	31 F	K, A	Y	15	1.97	1400	M	Necrotizing glomerulonephritis with crescent formation	40	1
12	47 F	K	N	15	1.71	480	M	Necrotizing glomerulonephritis with crescent formation	25	14
13	18 F	K	N	9	0.60	53	M	NA		3
14	26 F	K	N	15	0.57	794	M	NA		5
15	18 F	K	N	15	1.44	1028	G	Focal proliferative glomerulonephritis with crescent formation	20	3
16	75 F	K, L, S, E	Y	30	0.71	64	M	Granulomatous interstitial nephritis	0	3
17	45 F	L, K	Y	21	1.39	600	M	NA		2
18	63 F	L, A	Y	9	0.95	67	None	NA		2
19	36 F	L, K, S, E	Y	34	0.57	718	M	Minor glomerular abnormalities	0	7

K: kidney; S: Skin/mucous; A: arthralgia; L: lung and lower airway; E: ear, nose, and throat. M: microscopic hematuria; G: gross hematuria. PTU: propylthiouracil. NA: not available.

(Patients 1–3, 9–12, 16, 18, and 19) because they presented with either active systemic manifestation or severe renal involvement or rapidly progressive glomerulonephritis at diagnosis. For the remaining 4 patients who did not receive any corticosteroids or immunosuppressant, one was pregnant (Patient 14); one (Patient 13) was not treated with prednisone or cyclophosphamide because her symptoms resolved shortly after PTU cessation; and the remaining 2 (Patients 8, 17) refused to take prednisone or cyclophosphamide.

Nineteen patients were followed for a mean of 26.11 ± 20.24 months (range 2–69 mo). Among 10 patients who had prednisone and pulse cyclophosphamide therapy, one (Patient 3) did not respond to treatment. She remained on dialysis for 2 years and later had renal transplantation. Two patients died during followup: one (Patient 12) progressed to endstage renal dysfunction (ESRD), she died of sepsis and heart failure; one (Patient 11) died of central vascular disease. The remaining 7 patients (Patients 1, 2, 9, 10, 16, 18, 19) all achieved remission during followup. Five patients who had oral prednisone alone (Patients 4–7, 15) achieved remission during followup. For the other 4 patients who did not receive any corticosteroids or immunosuppressant, 3 (Patients 8, 13, and 14) achieved remission after cessation of PTU for 3–12 months; the other

(Patient 17) progressed to ESRD and died of complications of ESRD. No relapse of nephritis or vasculitis was found among 15 patients who achieved remission during the followup period, and the mean interval between diagnosis and remission was 6.93 ± 4.23 months (range 2–13 mo).

ANCA serology at diagnosis and ANCA detection during followup (Table 3). All 19 patients in our study received ANCA serology test. On IIF, one patient (Patient 9) had atypical ANCA. One patient was positive for cytoplasmic pattern (C)-ANCA (Patient 19), and perinuclear pattern (P)-ANCA was present in the other 17 patients at diagnosis. By ELISA, 4 patients (Patient 2, 9, 11, 12) were positive for both MPO-ANCA and PR3-ANCA, 14 were positive for MPO-ANCA only, and the remaining patient was positive for PR3-ANCA only. During followup, one patient (Patient 17) refused to retest for ANCA, and ANCA serologies were available for the remaining 18 patients. ANCA was found negative in 2 patients (Patients 9 and 16) on IIF. Two patients (Patients 2 and 12), who were previously positive for both MPO-ANCA and PR3-ANCA at diagnosis, were now positive for MPO only. And MPO was present in the remaining 13 patients during followup. MPO-ANCA concentration at remission was not significantly different from that at diagnosis (91.52 vs 127.30; $p > 0.05$).

Table 2. Treatment and outcome in 19 patients who received PTU.

Patient	Treatment of Hyperthyroidism After PTU Cessation	Duration of Followup, mo	Initial Therapy	Outcome	Duration Between Diagnosis and Remission, mo
1	¹³¹ I	18	P+C	Remission	10
2	MMI	31	P+C	Remission	2
3	Thyroidectomy	42	P+C+PE	Renal transplant	NA
4	None	29	P	Remission	8
5	MMI	24	P	Remission	13
6	None	16	P	Remission	9
7	None	8	P	Remission	5
8	¹³¹ I	58	None	Remission	5
9	MMI	69	P+C	Remission	13
10	None	19	P+C	Remission	4
11	None	2	P+C	Death	NA
12	MMI	64	P+C	ESRD, death	NA
13	None	32	None	Remission	12
14	None	7	None	Remission	3
15	None	7	P	Remission	3
16	None	15	P+C	Remission	2
17	None	38	None	ESRD, death	NA
18	None	11	P+C	Remission	5
19	None	6	P+C	Remission	3

PTU: propylthiouracil. MMI: methimazole; P: prednisolone/methylprednisolone; C: cyclophosphamide; PE: plasma exchange; ESRD: endstage renal dysfunction; NA: not available.

Table 3. ANCA specificity, ANCA titer at presentation, remission and followup.

Patient	ANCA Specificity At Diagnosis		ANCA Titer								
	IIF	ELISA	At Diagnosis			At Remission			Last/Current		
			IIF	PR3	MPO	IIF	PR3	MPO	IIF	PR3	MPO
1	P	MPO	1:1280	0	188.84	1:1280	0	145.18	1:1280	0	140.31
2	P	MPO, PR3	1:640	36.82	125.54	1:320	9.02	99.21	1:40	17.05	60.15
3	P	MPO	1:1280	0	107.32		NA		1:1280*	0	93.08
4	P	MPO	1:1280	11.5	303.59	1:640	0.20	164.97	1:1280	0	139.43
5	P	MPO	1:320	0	161.34	1:320	0	72.7	1:640	0	140.85
6	P	MPO	1:1280	0	129.03	1:320	0	149.92	1:160	0	141.38
7	p	MPO	1:1280	0	126.51	1:1280	0	95.77	1:640	0	96.69
8	P	MPO	1:320	0	68.35	1:160	0	58.27	1:640	0	77.21
9	Atypical	MPO, PR3	1:1280	31.91	40.63	1:320	10.27	29.5	Neg	0	2.27
10	P	MPO	1:1280	0	129.73	1:640	0	128.14	1:320	0	101.51
11	P	MPO, PR3	1:320	41.42	144.47		NA		1:320	34.27	142.27
12	P	MPO, PR3	1:640	25	239.85		NA		1:320	0	24.73
13	P	MPO	1:80	0	28.86	1:40	0.53	27.23	1:40	0	23.67
14	P	MPO	1:640	0	88.28	1:640	0	85.78	1:640	0	81.23
15	P	MPO	1:1280	0	212.11	1:1280	0	170.01	1:1280	0	183.88
16	P	MPO	1:80	0	90.67	1:160	0	47.07	Neg	0	15.61
17	P	MPO	1:1280	0	160.74			NA			
18	P	MPO	1:640	0	98.22	Neg	0	7.52	Neg	0	0.63
19	C	PR3	1:1280	226.48	0	1:640	182.99	0	1:640	114.52	0

* ANCA analysis of Patient 3 was performed before her renal transplant. IIF: indirect immunofluorescence technique; PR3: proteinase-3; MPO: myeloperoxidase; NA: not available.

DISCUSSION

Drug-induced ANCA-associated vasculitis is one of the major toxic reactions related to antithyroid-drug treatment, which was commonly found in PTU therapy. ANCA can be detected

at some time in about 20% of all patients treated with PTU; however, only a small number of patients developed evidence of vasculitis, which might appear at any time after treatment had begun^{3,5}.

The high frequency of ANCA in patients administered PTU might result from the interaction between PTU and MPO. Jiang, *et al*¹² discovered that PTU was highly cytotoxic in the presence of activated neutrophils. PTU can be accumulated in neutrophils and is oxidized to reactive intermediates that bind to MPO and provoke T cell sensitization, potentially leading to P-ANCA production^{2,13,14}. A study by Xiao, *et al*¹⁵ provided evidence that ANCA could cause systemic vasculitis *in vivo* and offers direct evidence that P-ANCA is pathogenic. In our study, most of our patients had P-ANCA/MPO-ANCA and such finding might be related to the pathogenesis of the disease.

MPO-ANCA plays an important role in the pathogenesis of the disease; however, the value of ANCA titers for monitoring disease remains disputable¹⁶. Nowack, *et al*¹⁷ discovered that ANCA titers failed to indicate disease activity in idiopathic ANCA-associated disease. As few studies observed the value of monitoring ANCA titer in PTU-associated ANCA-positive diseases, we investigated the MPO-ANCA titers in our patients (Table 3). Our results showed that most patients had a lower MPO-ANCA concentration at remission than at diagnosis; however, such difference was not significant and exceptions occurred. In all, a delayed decrease of ANCA titer was observed among most patients during followup with exceptions. From our study it remains uncertain whether MPO-ANCA concentration is an indicative factor for monitoring PTU-associated ANCA-positive disease.

Some of our patients were multiple ANCA-positive, and similar results were also found by Slot and colleagues¹⁸ in their patients with antithyroid drug treatment. However, in the studies by Bonaci-Nikolic, *et al* and Fujieda, *et al*, no multiple ANCA positivity was found^{19,20}. Thus whether multiple ANCA positivity is a characteristic feature of patients with PTU-associated vasculitis requires further study.

In our study, there was a female predominance in our patients with PTU-associated ANCA-positive vasculitis. As PTU was mainly used in antithyroid therapy, such predominance might contribute to the female-predominant morbidity of hyperthyroidism.

Renal involvement was the most common manifestation in our patients, while in idiopathic vasculitis, renal involvement occurs in more than 50% of patients at presentation²¹. It seems that renal involvement is the most common symptom in both primary and PTU-induced vasculitis. Currently, there are few studies describing renal histological findings in patients with

PTU-associated ANCA-positive vasculitis, and most are case reports. Our data show that the most frequent lesion of our patients is a pauci-immune glomerulonephritis. However, in contrast to idiopathic ANCA-associated vasculitis, which usually involves pauci-immune glomerulonephritis⁵, some of our patients were found to have immune complex deposition in the kidney. Similar results were also found by Yu and colleagues in their patients²². As only a few studies have reported that PTU-associated vasculitis could coexist with primary glomerulonephritis, it remains unclear whether PTU is a causal factor in glomerulonephritis with immune complex deposition²³. In drug-induced vasculitis, withdrawal of agents usually results in resolution of the disease²⁴. In our study, renal involvement continued to progress in some of our patients while systemic or extrarenal symptoms resolved. As ANCA was detected in all those patients, we hypothesized that ANCA might play an important role in the progression of renal injury. Meanwhile, the duration of PTU therapy did not correlate with renal injury at diagnosis (Table 4). The result suggests that the duration of PTU therapy may not play an important role in disease severity.

Treatment for PTU-associated ANCA-positive vasculitis includes cessation of PTU therapy and giving corticosteroids and/or immunosuppressant, depending on the severity of the disease. To date, there are no guidelines on treatment in PTU-associated vasculitis. In our study, neither corticosteroids nor immunosuppressant were administered in 4 patients. Three patients achieved remission and one progressed to ESRD. However, the patient who progressed to ESRD presented with moderate renal insufficiency at diagnosis (serum creatinine 1.39 mg/dl, eGFR 40.17 ml/min) while the other 3 did not. Considering the beneficial effects of corticosteroids or corticosteroids together with cyclophosphamide in treating primary ANCA-positive diseases^{11,25,26}, we suggest such treatment might improve outcome in some patients with PTU-associated vasculitis, especially those with renal insufficiency. We did not evaluate the relative efficacy of the association of corticosteroids plus immunosuppressant versus corticosteroids alone because the 2 groups were not similar. The effects of treatment on outcome in those patients should be analyzed in a large-scale prospective study.

Regarding the outcome of PTU-associated ANCA-positive vasculitis, Fujieda, *et al*²⁰ investigated 7 pediatric patients: all patients achieved remission and no patient progressed to ESRD or death during followup. In our study, 3 patients died

Table 4. Duration of PTU therapy in patients with renal involvement (n = 18).

Renal Status at Diagnosis	Duration of PTU Therapy, yrs	p
Renal involvement with eGFR < 90 ml/min (n = 10)	3.80 ± 3.74	> 0.05
Renal involvement with eGFR ≥ 90 ml/min (n = 8)	5.63 ± 3.16	

eGFR: estimated glomerular filtration rate.

during followup. For renal survival, one patient received renal replacement therapy and 2 progressed to ESRD. Considering all our patients were adults and Fujieda's patients were children, the outcome might be better in pediatric patients. Usually, patients with PTU-associated vasculitis have better prognosis than those with idiopathic vasculitis because of less severe renal and extrarenal involvement². However, in our study, not all the patients with PTU-associated vasculitis had good outcome; severe cases were still present.

Most patients with PTU-associated ANCA-positive vasculitis had good outcome; however, severe cases occurred. Corticosteroids, corticosteroids plus immunosuppressant, and even hemodialysis should be administered in treating certain patients. Our experience suggests that early recognition and adequate treatment might be necessary to improve the outcome.

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