Long-term outcomes and clinicopathological characteristics of propylthiouracil-induced ANCA-associated glomerulonephritis: a case-control study

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Abstract

Objective

This retrospective study aims to determine the clinical and histological features and outcomes of propylthiouracil (PTU)-induced anti-neutrophil cytoplasmic antibody (ANCA) associated glomerulonephritis with primary ANCA-associated glomerulonephritis (AAGN).

Methods

Twenty-five patients diagnosed with PTU-induced AAGN and 379 patients with primary AAGN, who underwent diagnostic renal biopsies at Jinling Hospital between January 2005 and December 2020, were included in the study. The clinical and histological features and long-term renal outcomes were analysed.

Results

Patients with PTU-induced AAGN exhibited lower serum creatinine levels and higher MPO-ANCA titres compared with those with primary AAGN. Histopathological analysis identified crescentic and focal lesions as the predominant patterns in the PTU-induced group, which also exhibited a higher proportion of normal glomeruli and a lower percentage of global sclerosis. Although treatment regimens were comparable between groups, PTU-induced AAGN was associated with numerically lower, though statistically non-significant, rates of renal non-remission and relapse. During prolonged follow-up, serum MPO-ANCA positivity persisted existence in most PTU-induced AAGN patients. Kaplan-Meier survival analysis revealed a significantly higher renal survival rate in PTU-induced AAGN patients than those with primary AAGN ($p=0.018$).

Conclusion

Patients with PTU-induced AAGN demonstrated distinct clinical features and more favourable renal outcomes despite persistent positivity of MPO-ANCA, indicating a less aggressive disease course compared to primary AAGN.

Key words

propylthiouracil, ANCA-associated glomerulonephritis, vasculitis, prognosis

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Introduction

The primary treatments for hyperthyroidism include thyroidectomy, radioactive iodine (^{131}I) and anti-thyroid drugs (ATDs). ATDs are frequently as the initial treatment in China due to their effectiveness and ability to preserve thyroid structure. Propylthiouracil (PTU) and methimazole (MMI) are the most common prescribed ATDs in China. The typical treatment duration ranges from 18 to 24 months, with evidence suggesting that low-dose maintenance therapy can improve remission rates (1). However, PTU is associated with adverse effects, from mild skin rashes (2) to severe complications like agranulocytosis (3) and acute hepatic injury (2, 4). Additionally, observational studies have shown that ANCA-associated vasculitis (AAV) occurs in up to 3% of patients treated with ATDs. Notably, PTU has a three-fold higher risk of AAV than MMI, and this risk correlates with treatment duration (4, 5).

The pathogenesis of PTU-induced AAV remains incompletely understood. PTU induces molecular modifications in target antigens, like myeloperoxidase (MPO), which may trigger autoimmune responses (6). Several hypothetical mechanisms have been proposed. First, dysregulated formation of neutrophil extracellular traps (NETs) may promote ANCA production (7). Under physiological conditions, NETs are degraded by serum DNase-I (8). However, PTU metabolites may mask DNase-I recognition sites on NETs, forming DNase-I-resistant NETs (7, 9). Prolonged persistence of these NETs in circulation may facilitate sustained ANCA generation. Second, PTU may directly modify MPO structure, inducing a conformational shift in the heme iron-binding region from a rhombic to an axial geometry (10). This structural alteration may render MPO immunogenic, leading to immune tolerance breakdown and eliciting an antibody response. Third, MPO-ANCA IgG derived from patients with PTU-induced AAV may inhibit MPO's oxidative activity in a dose-dependent manner (11). This functional inhibition may represent an additional mechanism contributing to the pathogenesis of PTU-induced AAV. Among patients with PTU-induced ANCA, only a subset exhibit clinically apparent vasculitis (6, 12). The development of PTU-induced AAV is likely mediated by multifactorial risk factors, including genetic predisposition and environmental triggers.

The clinical manifestations and severity of PTU-induced AAV show significant inter-patient variability (6). Studies have shown that the kidneys, joints and muscles are commonly affected in vasculitis (13). Notably, the prognosis of drug-induced AAV is significantly better than that of primary AAV (14). Patients with primary AAGN typically present with rapidly progressive glomerulonephritis (RPGN), associated with high risks of end-stage kidney disease (ESKD) and increased mortality (15). However, research on renal outcomes in PTU-induced AAGN is limited, and the clinicopathological distinctions from primary AAGN remain unclear. Therefore, this study focuses on PTU-induced AAGN and performs a retrospective comparative analysis of the epidemiology, clinical and histological features, and outcomes compared to primary AAGN.

Materials and methods

Patients

This single-centre, retrospective study included 379 patients with primary AAGN and 25 patients with PTU-induced AAGN which was confirmed by renal biopsy at the National Clinical Research Centre for Kidney Diseases, Jinling Hospital, between January 2005 and December 2020. The study was conducted in accordance with the Declaration of Helsinki and approved by the Independent Ethics Committee of Jinling Hospital (Approval no. 2025DZKY-064-01).

The inclusion criteria were as follows: 1) positivity for ANCA; 2) renal biopsy specimens containing ≥ 6 glomeruli available for light microscopy examination, with histopathological findings consistent with pauci-immune renal vasculitis; 3) a follow-up duration of at least 3 months; 4) absence of other secondary vasculitides or coexisting renal diseases, such as dual anti-glomerular basement membrane disease, diabetic nephropathy, and membranous nephropathy.

All patients were diagnosed with pauci-immune glomerulonephritis by renal biopsy. The diagnosis of primary AAGN patients was based on the Chapel Hill diagnostic criteria (16). PTU-induced AAV was defined as the presence of clinical features of vasculitis and positive ANCA antibodies following PTU treatment. Patients with other secondary causes of vasculitis, including malignancies and autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis, were excluded (13, 17). PTU-induced AAV patients exhibiting renal involvement (*e.g.* haematuria, proteinuria, decreased renal function, etc.) were further diagnosed as PTU-induced AAGN based on renal pathological findings.

Renal histopathology

Renal biopsy specimens were examined by light, immunofluorescence and electron microscopy according to the standard procedures by two kidney pathologists independently. Renal histopathology was classified into four categories according to Berden *et al.*: focal (with >50% normal glomeruli), crescentic (with >50% of glomeruli exhibiting cellular crescents), mixed (with ≤50% normal, ≤50% crescentic, and ≤50% globally sclerotic glomeruli), and sclerotic (with >50% globally sclerotic glomeruli) (18). The degree of kidney tubular lesions was scored semi-quantitatively and described as T0 ≤25%, 25% <T1 ≤50% and T3 >50%. Inconsistencies between the two pathologists were resolved by discussion and consensus.

Clinical and laboratory parameters

Baseline demographic, clinical and laboratory data of the patients were collected at the time of renal biopsy. The eGFR was calculated by the CKD-EPI formula. Vasculitis activity was evaluated using the Birmingham Vasculitis Activity Score (BVAS) method (19).

Patients were categorised into three clinical subtypes according to the 2022 ACR/EULAR classification criteria for AAV: microscopic polyangiitis (MPA) (20), granulomatosis with polyangiitis (GPA) (21), eosinophilic granulomatosis with polyangiitis (EGPA (22).

Treatment

Patients with severe kidney injury or pulmonary haemorrhage underwent intravenous methylprednisolone pulse therapy (500 mg/d for 3–6 days) and immuno-adsorption or plasma exchange therapy. Induction treatment included glucocorticoids alone or glucocorticoids combination with mycophenolate mofetil (MMF), intravenous cyclophosphamide (CTX) therapy or rituximab (RTX). The PTU drug was immediately discontinued once the diagnosis was confirmed, and the remaining treatment was the same as that for primary AAGN patients.

Follow-up and kidney response

Patients were followed until the development of end-stage kidney disease (ESKD) or the last follow-up date of January 31, 2025. ESKD was defined as the initiation of haemodialysis, peritoneal dialysis, renal transplantation, or an eGFR of less than 15 ml/min/1.73m^2 for 3 months.

Renal remission was defined as a stable or improved eGFR with allowance for persistent mild proteinuria and/or haematuria and the absence of extra-renal disease activity (extra-renal BVAS=0) (23). Renal relapse was defined as the occurrence of increased disease activity after a period of remission (23), with one or more of the following manifestations: worsening haematuria or proteinuria, an increase in serum creatinine level of >30%, and a decline in eGFR of >25% (24, 25). All such changes were required to be attribute solely to active vasculitis, excluding other potential confounding conditions such as hypertension and diabetic nephropathy. Worsening proteinuria or haematuria was defined as an increase of at least 1+ on urine dipstick analysis (25). Relapse can be divided into major or minor one with the major relapse defined as life- or organ-threatening (23). An increase in creatinine of less than 30% is classified as a minor relapse.

Statistical methods

Categorical variables are expressed as numbers (percentage), and results were compared using χ^2 test or Fisher's exact test. Quantitative variables are expressed as means±SD (for data that were normally distributed) or medians (Q1, Q3) (for data that were not normally distributed) and compared using t-test or the Mann-Whitney U-test. *p*-values were adjusted using the Benjamini-Hochberg procedure to control the False Discovery Rate (FDR). An FDR-corrected *p*-value of <0.05 was considered statistically significant. Kaplan-Meier survival analysis was used to estimate patient and renal survival with differences assessed using the log-rank test. Data analysis was conducted using R Studio version 2023.03.0, an integrated development environment for R version 4.2.3 (R Core Team, Vienna, Austria). Statistical significance was established at a two-sided *p*-value <0.05.

Results

Demographic and clinical characteristics between PTU-induced AAGN and primary AAGN patients

A cohort of 404 patients was included in this study, comprising 379 with primary AAGN and 25 with PTU-induced AAGN. The baseline clinical and demographic characteristics of the patients are summarised in Table I. MPO-ANCA positivity was observed in 375 (92.8%) patients, while 36 (8.9%) were positive for PR3-ANCA. Seven (1.7%) patients were double-positive for both MPO-ANCA and proteinase 3 (PR3)-ANCA. All of the 25 PTU-induced AAGN patients were MPO-ANCA positive, and one of them was also positive for PR3-ANCA. Additionally, MPO-ANCA titres in patients with PTU-induced AAGN were significantly higher than that in the patients with primary AAGN [214.9 (153.6, 287.3) *vs.* 179.6 (97.7, 241.2), *p*=0.045].

Of the 25 PTU-induced AAGN patients, 24 (96%) were female with a median age of 46 years (IQR: 27, 55). The median BVAS at diagnosis was 14 (IQR: 12, 18) and the median duration of PTU exposure was 36 months (IQR: 32, 60). Compared to primary AAGN patients, those with PTU-induced AAGN had a significantly higher proportion of females (96.0% *vs.* 53.6%, *p*=0.009) and a longer median duration of vasculitis symptoms [1 (0, 5) *vs.* 0 (0, 0), *p*=0.009]]. Although not statistically significant,

Table I. Demographic and clinical features of primary AAGN and PTU-induced ANCA patients.

Characteristic	Overall (n=404)	PTU-induced AAGN (n=25)	Primary AAGN (n=379)	*p*-value	*p*-adjust*
Female gender, n (%)	227 (56.2)	24 (96.0)	203 (53.6)	**<0.001**	**0.009**
Age, years	51.0 (38.0, 59.2)	46.0 (27.0, 55.0)	52.0 (39.0, 60.0)	0.066	0.102
Body Mass Index, kg/m^2	22.0 (19.6, 24.3)	19.7 (17.3, 22.9)	22.0 (19.7, 24.4)	**0.020**	**0.045**
Duration of vasculitis, months	0.6 (0.3, 1.0)	1.0 (0.7, 5.0)	0.5 (0.3, 0.9)	**<0.001**	**0.009**
BVAS scores	17.0 (13.0, 20.0)	14.0 (12.0, 18.0)	17.0 (14.0, 20.0)	0.056	0.095
PR3-ANCA titres, AU/ml	165.1 (82.4, 302.6)	82.4 (82.4, 82.4)	194.5 (83.1, 303.6)	0.401	0.440
MPO-ANCA titres, AU/ml	181.2 (103.7, 247.5)	214.9 (153.6, 287.3)	179.6 (97.7, 241.2)	**0.017**	**0.045**
Clinical classification, n (%)				0.343	0.389
EGPA	2 (0.5)	0 (0.0)	2 (0.5)		
GPA	28 (6.93)	0 (0.00)	28 (7.4)		
MPA	374 (92.6)	25 (100.0)	349 (92.1)		
Extra-renal vasculitis symptoms§, n (%)	286 (70.79)	14 (56.00)	272 (71.77)	0.146	0.199
Respiratory system involvement, n (%)	159 (39.4)	3 (12.0)	156 (41.2)	**0.007**	**0.024**
Laboratory parameters					
Serum creatinine, umol/L	226.7 (134.4, 415.3)	101.7 (76.0, 173.3)	235.0 (144.0, 432.7)	**<0.001**	**0.009**
eGFR, ml/min/1.73 m^2	24.0 (12.0, 44.5)	56.0 (28.0, 84.0)	22.0 (11.0, 41.5)	**<0.001**	**0.009**
Uric acid, umol/L	422.0 (346.0, 494.0)	344.0 (260.0, 456.0)	426.0 (353.2, 496.8)	**0.003**	**0.017**
Albumin, g/L	36.0 (32.3, 39.5)	38.1 (35.9, 40.3)	35.7 (32.0, 39.5)	**0.044**	0.088
Urine protein, g/24h	1.5 (1.0, 2.6)	1.3 (0.9, 2.6)	1.6 (1.0, 2.6)	0.226	0.274
Urine red blood cells, /μl	266.7 (76.0, 715.0)	375.0 (78.8, 645.9)	254.2 (76.0, 731.7)	0.859	0.885

Values are given as the mean ± SD or median (Q1, Q3). Categorical data are expressed as number (%).
MPO: myeloperoxidase; PR3: protease 3; EGPA: eosinophilic granulomatosis with polyangiitis; MPA: microscopic polyangiitis; GPA: granulomatosis with polyangiitis; ENT: ears, nose, and throat; BVAS: Birmingham vasculitis activity score.
*p-values were adjusted using the Benjamini-Hochberg procedure. An FDR-corrected p-value of <0.05 was considered statistically significant.
§Extra-renal vasculitis symptoms refer to symptoms caused by ANCA-associated vasculitis in organs other than the kidneys.

the median BVAS was lower in the PTU-induced AAGN group [14 (12, 18) *vs*. 17 (14, 20), p=0.095]. Additionally, PTU-induced AAGN patients exhibited significantly lower serum creatinine levels [101.7 (76.0, 173.3) *vs*. 235.0 (144.0, 432.7), p=0.009] and reduced uric acid levels [344.0 (260.0, 456.0) *vs*. 426.0 (353.2, 496.8), p=0.017].

Among the 404 patients, 374 (92.6%) were classified as MPA, 28 (6.93%) as GPA, and 2 (0.5%) as EGPA. Although no statistically significant difference was observed in the distribution of clinical subtypes between the groups, it is noteworthy that all the 25 patients with PTU-induced AAGN were exclusively of MPA. Among these 25 patients, clinical manifestations included fever in 6 (24.0%), arthralgia in 5 (20.0%), respiratory symptoms in 3 (12.5%), ear-nose-throat (ENT) involvement in 2 (8.0%), and neurological symptoms in 1 (4.0%). 11 (45.0%) patients exhibited no extrarenal manifestations. Respiratory involvement was significantly less frequent in the PTU-induced AAGN group (12% *vs*. 41.2%, p=0.024).

Renal histopathological features

The histopathological characteristics of the two groups are summarised in Table II. A notable discrepancy in pathological classification was observed between the PTU-induced AAGN and primary AAGN groups (p=0.047). The proportions of the mixed class (12.0% *vs*. 33.0%) and the sclerotic class (12.0% *vs*. 22.4%) were lower in the PTU-induced AAGN group than that in the primary AAGN group. In contrast, the proportions of the focal class (44.0% *vs*. 23.8%) and the crescentic class (32.0% *vs*. 20.8%) were higher in the PTU-induced AAGN group. A significantly higher percentage of normal glomeruli was observed in the PTU-induced AAGN group [47.7 (27.8, 66.7) *vs*. 26.7 (11.5, 47.2), p=0.017]. Similarly, the PTU-induced AAGN group exhibited a significantly lower percentage of globally sclerotic glomeruli [10.0 (0.0, 32.1) *vs*. 26.0 (9.8, 43.8), p=0.045]. No significant differences were observed in the severity of acute tubulointerstitial lesions. The severity of interstitial fibrosis and tubular atrophy (IF/TA) lesions differed significantly between groups (p=0.024). The prevalence of severe IF/TA lesions (>50%) was higher in the primary AAGN group [81 patients (21.4%)] than in the PTU-induced AAGN group [2 patients (8.0%)].

Treatment and renal response

The treatment and follow-up data are presented in Table III. PTU was discontinued in all patients upon diagnosis. No significant differences were observed between the two groups regarding the use of extracorporeal circulation or immunosuppressive therapy regimens. Among the 25 PTU-induced AAGN patients, 2 patients (8.0%) required dialysis at the time of biopsy. Methylprednisolone pulse therapy was administered to 16 patients and immunoadsorption (IA) or double-filtration plasmapheresis (DFPP) was performed for 4 patients (16.0%). Induction therapy by glucocorticoid monotherapy was conducted for 8 patients (32.0%). Combination therapies were as follows: glucocorticoids plus intravenous CTX in 8 (32.0%) patients, glucocorticoids plus mycophenolate mofetil in 9 (36.0%) patients. None of the 25 patients in the PTU-induced AAGN group received RTX treatment. In the primary AAGN group, while 6 patients (1.6%) in the primary AAGN group received RTX treatment.

Table II. Description of histopathological features in primary AAGN and PTU-induced ANCA patients.

Characteristic	Overall (n=404)	TU-induced PAAGN (n=25)	Primary AAGN (n=379)	*p*-value	*p*-adjust*
Normal glomeruli rate, %	28.6 (12.0, 48.1)	47.7 (27.8, 66.7)	26.7 (11.5, 47.2)	**0.004**	**0.017**
Global sclerotic glomeruli rate, %	25.0 (8.9, 43.6)	10.0 (0.0, 32.1)	26.0 (9.8, 43.8)	**0.019**	**0.045**
Focal segmental sclerosing globules rate, %	0.0 (0.0, 10.5)	0.0 (0.0, 7.7)	0.0 (0.0, 10.9)	0.502	0.533
Crescents, %	25.4 (10.5, 42.7)	14.7 (4.6, 50.0)	25.8 (11.4, 42.3)	0.179	0.234
Renal histologic class, n (%)				**0.022**	**0.047**
Mixed class	128 (31.7)	3 (12.0)	125 (33.0)		
Focal class	101 (25.0)	11 (44.0)	90 (23.8)		
Crescentic class	87 (21.5)	8 (32.0)	79 (20.8)		
Sclerotic class	88 (21.8)	3 (12.0)	85 (22.4)		
Acute tubulointerstitial lesions, n (%)				0.069	0.102
≤25%	217 (53.7)	19 (76.0)	198 (52.2)		
26-50%	133 (32.9)	4 (16.0)	129 (34.0)		
>50%	54 (13.4)	2 (8.0)	52 (13.7)		
Interstitial fibrosis/tubular atrophy, n (%)				**0.007**	**0.024**
≤25%	152 (37.6)	5 (20.0)	147 (38.8)		
26-50%	169 (41.8)	18 (72.0)	151 (39.8)		
>50%	83 (20.5)	2 (8.0)	81 (21.4)		

Values are given as the mean ± SD or median (Q1, Q3). Categorical data are expressed as number (%).
*p-values were adjusted using the Benjamini-Hochberg procedure. An FDR-corrected p-value of <0.05 was considered statistically significant.

Table III. Treatment and follow-up data in PTU-induced ANCA patients and primary AAGN.

Characteristic	Overall (n=404)	PTU-induced AAGN (n=25)	Primary AAGN (n=379)	*p*-value	*p*-adjust*
Initial RRT, n (%)	79 (19.6)	2 (8.0)	77 (20.3)	0.214	0.270
MP pulse therapy, n (%)	326 (80.7)	16 (64.0)	310 (81.8)	0.055	0.095
IA/DFPP, n (%)	75 (18.6)	4 (16.0)	71 (18.7)	0.940	0.940
Induction therapy, n (%)				0.309	0.362
Glucocorticoids plus CTX	194 (48.0)	8 (32.0)	186 (49.1)		
Glucocorticoids plus MMF	116 (28.7)	9 (36.0)	107 (28.2)		
Glucocorticoids plus RTX	6 (1.5)	0 (0.0)	6 (1.6)		
Glucocorticoids alone	88 (21.8)	8 (32.0)	80 (21.1)		
Follow-up time, months	56.0 (21.8, 107.2)	89.0 49.0, 140.0)	56.0 (20.0, 104.5)	**0.018**	**0.045**
Kidney response, n (%)				0.060	0.097
No remission	143 (35.4)	4 (16.0)	139 (36.7)		
Kidney remission	261 (64.6)	21 (84.0)	240 (63.3)		
Renal relapse, n (%)	100 (38.3)	4 (19.1)	96 (40.0)	0.097	0.137
Scr at the last visit, mg/dL	2.1 (1.2, 5.7)	1.1 (0.8, 2.1)	2.4 (1.2, 5.7)	**0.002**	**0.014**
eGFR at the last visit, ml/min/1.73 m^2	27.0 (9.0, 56.8)	50.0 (30.0, 76.0)	26.0 (9.0, 53.0)	**0.010**	**0.031**
ANCA positive at the last visit§, n (%)	235 (58.2)	22 (88.0)	213 (56.2)	**0.004**	**0.017**
ESKD patients, n (%)	182 (45.1)	6 (24.0)	176 (46.4)	**0.048**	0.091

Values are given as the mean ± SD or median (Q1, Q3). Categorical data are expressed as number (%).
RRT: renal replacement therapy; IA: immunoadsorption; DFPP: double filtration plasmapheresis; CTX: cyclophosphamide; MMF: mycophenolate mofetil; RTX: rituximab.
*p-values were adjusted using the Benjamini-Hochberg procedure. An FDR-corrected p-value of <0.05 was considered statistically significant.
§ANCA positive refers to serum MPO-ANCA or PR3-ANCA >20 AU/ml.

Following induction immunosuppressive therapy, 143 of the 404 patients (35.4%) exhibited persistent renal non-response. Among the 261 patients who achieved remission, 100 (38.3%) experienced a disease relapse (including 4 PTU-induced and 96 primary AAGN patients). A major relapse occurred in 72 (72.0%) of these patients, and 49 (49.0%) progressed rapidly to ESKD. Extra-renal manifestations of vasculitis were observed exclusively in 24 patients with primary AAGN, and they all had pulmonary involvement with haemoptysis as the most common presentation. Compared with patients who had primary AAGN, those with PTU-induced AAGN had lower rates of renal non-response (16.0% *vs*. 36.7%, p=0.097) and relapse (19.1% *vs*. 40.0%, p=0.137), although these differences did not reach statistical significance.

Follow-up and renal outcomes

During a median follow-up period of 56 months (*IQR:* 21.8, 107.2), 182 patients (45.1%) developed ESKD (Table III). Among the 25 patients with PTU-induced AAGN, 6 (24.0%) progressed to ESKD. At the final follow-up, patients with PTU-induced AAGN exhibited a significantly higher eGFR than those with primary AAGN [50 (30, 76) *vs*. 26 (9, 53), p=0.031]. Despite the

lack of statistical significance, the incidence of ESKD was lower in patients with PTU-induced AAGN than in those with primary AAGN (24.0% *vs.* 46.4%, p=0.091). Kaplan-Meier survival analysis was performed to compare renal survival between the two groups, and the results are presented in Figure 1. The analysis demonstrated significantly superior renal survival in the PTU-induced AAGN group (Log-Rank, p=0.018). The 5-year renal survival rate was 83.6% in the PTU-induced AAGN group, compared to 63.7 % in the primary AAGN group.

The dynamics of MPO-ANCA levels in the 25 patients with PTU-induced AAGN are illustrated in Figure 2. Following discontinuation of PTU and initiation of immunosuppressive therapy, ANCA titres decreased in most patients, however, they remained persistently positive (defined as serum ANCA titres >20 AU/mL). At the final follow-up or endpoint, the ANCA positivity rate was significantly higher in the PTU-induced AAGN group compared to the primary AAGN group (88.0% *vs.* 56.2%, p=0.017).

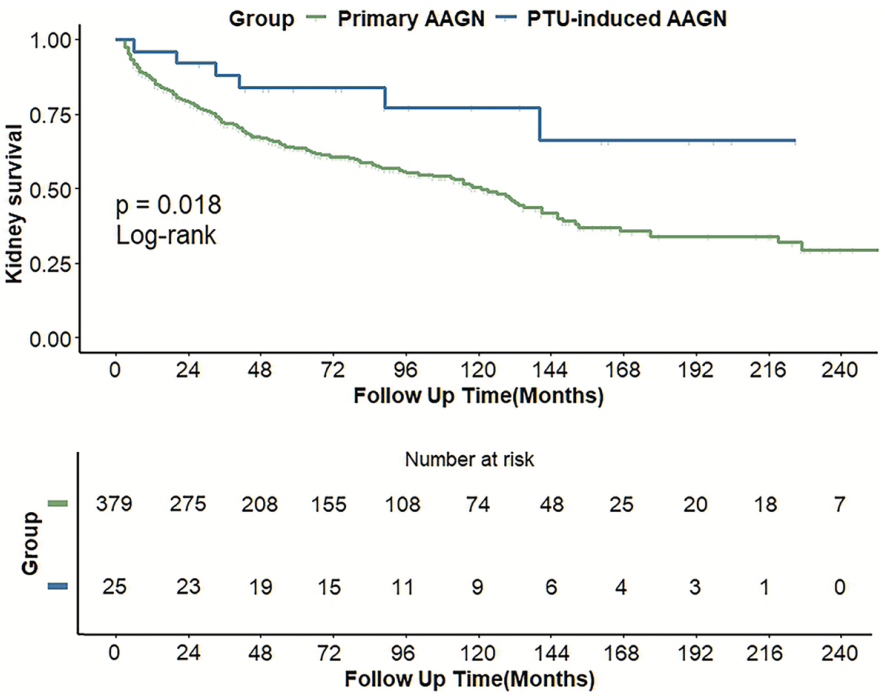

Fig. 1. Kaplan-Meier curve analysis for the probability of kidney survival between PTU-induced AAGN patients and primary AAGN.
The 5-year kidney survival rate was significantly lower in PTU-induced AAGN patients compared to the primary AAGN patients (p=0.018).

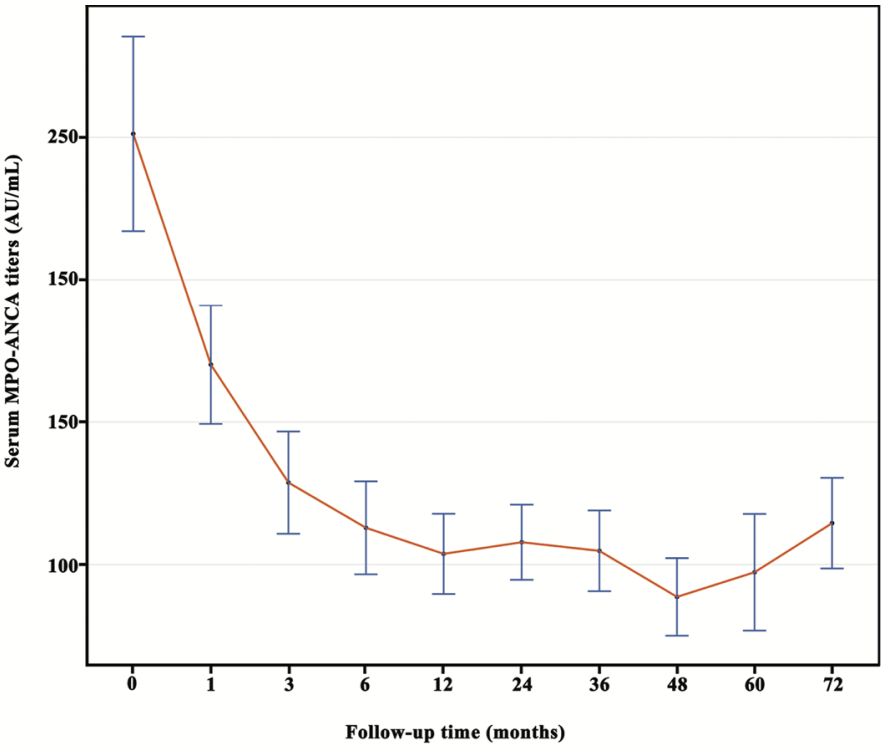

Fig. 2. The changes of MPO-ANCA level among 25 PTU-induced AAGN patients.

Discussion

Previous studies on PTU-induced AAV were primarily case reports. The present retrospective study has a cohort of PTU-induced AAGN patients, which is the largest to date. This study aimed to compare the clinical and pathological features and renal outcomes between PTU-induced AAGN and primary AAGN. We found that patients with PTU-induced AAGN had higher ANCA titres at diagnosis, and demonstrated persistent ANCA positivity during long-term follow-up. No significant differences in treatment strategies were observed between the two groups. Compared with patients with primary AAGN, those with PTU-induced AAGN exhibited better renal survival and less severe pathological changes.

Given the absence of standardised guidelines for PTU-induced AAGN, treatment strategies mirrored those employed for primary AAGN (6). In all cases, PTU was immediately discontinued upon diagnosis, followed by individualised immunosuppressive therapy based on disease activity and clinical presentation. No significant differences were observed in the utilisation of therapeutic plasma exchange or immunosuppressive agents between the two groups. Consistent with previous long-term studies that have reported more favourable outcomes in drug-induced AAV (26, 27), our study found that patients with PTU-induced

AAGN had significantly better renal survival compared to those with primary AAGN. Furthermore, patients with PTU-induced AAGN showed a higher prevalence of focal and crescentic classifications than those with primary AAGN. These patients also demonstrated a higher proportion of normal glomeruli and lower proportion of glomeruli with sclerosis. Repeat renal biopsies further revealed more advanced chronic lesions in patients with primary AAGN. These distinct histological features may contribute to the better renal prognosis observed in this group. Berden *et al*. established a classification system of four pathological phenotypes for AAGN, which shows corresponding 5-year renal survival rates of 93% for the focal, 76% for the crescentic, 61% for the mixed, and 50% for the sclerotic class (18). Subsequent studies have consistently validated this histopathological categorisation, confirming the most favourable renal prognosis in the focal class and the poorest outcomes in the sclerotic class (28-30). Both the proportion of normal glomeruli and the degree of glomerulosclerosis have been established as prognostic indicators in ANCA-associated vasculitis (31, 32). However, further investigation is necessary to validate these findings and to elucidate the mechanisms underlying the observed differences in histological presentation and renal survival between PTU-induced and primary AAGN.

Consistent with previous investigations (33, 34), all the patients with PTU-induced AAGN in our study demonstrated positivity of MPO-ANCA. Furthermore, our results showed significantly higher MPO-ANCA levels in PTU-induced AAGN than that in the patients with primary AAGN. Accordingly, the ANCA conversion rate was significantly lower in the PTU-induced AAGN cohort, consistent with our previous report (17). This sustained ANCA positivity is consistent with observations by Yazisiz *et al*., who reported persistent ANCA positivity in 10.3% of patients even in the absence of vasculitic manifestations after two years of PTU discontinuation (35). These findings suggest that patients with PTU-induced AAGN may coexist with long-term persistent ANCA. Similar to primary AAV, while ANCA are implicated in the pathogenesis of AAV, their usefulness as biomarkers for disease activity and prognosis is still under investigation (36). Several hypotheses may explain these observations. Immune stimulation by PTU can elevate MPO-ANCA titres. However, the affinity and pathogenicity of these antibodies are generally lower than those in primary AAV (37). PTU-induced MPO-ANCA exhibit a more restricted epitope recognition profile compared to those in primary AAV (14, 38). Immune activation by ANCA requires coligation of IgG's Fc and Fab fragments (39). However, the MPO-ANCA IgG3 subtype, known for its high-affinity binding to Fc receptors (40), is undetectable in PTU-induced AAV (41). Furthermore, ANCAs in PTU-induced AAV may react with a broader range of antigens, including cathepsin G, lactoferrin, human leukocyte elastase, and azurocidin (42), which are generally considered less pathogenic than MPO and PR3. These characteristics, lower affinity, restricted specificity, absence of IgG3, and broader antigen targeting, may necessitate higher titres to initiate vasculitis (6). Clinical improvement after PTU discontinuation may suggest immune response attenuation despite ANCA persistence.

There are several limitations to this study. First, the retrospective design and single-centre data collection may introduce potential biases. Second, the sample size of PTU-induced AAGN patients may limit further study to identify other differences between PTU-induced AAGN and primary AAGN. Third, the absence of longitudinal ANCA titre data in primary AAGN patients and the lack of ANCA titres prior to PTU initiation represent significant limitations of this study. Additionally, the hypothesis on the pathogenic mechanism of PTU and PTU-induced ANCAs characteristics, supported by existing research, requires further experimental validation to confirm their roles and clinical significance.

In conclusion, this retrospective study compared the clinicopathological features and renal outcomes of PTU-induced AAGN patients with those with primary AAGN. The results showed that PTU-induced AAGN patients had a better-preserved renal function, less severe pathological manifestations, and better long-term kidney outcomes. Furthermore, most patients with PTU-induced AAGN may have long-term persistent MPO-ANCA positivity. These findings suggest that PTU-induced AAGN has a distinct pathogenesis and disease course from the primary AAGN.

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