CEN Case Rep (2017) 6:22–28
DOI 10.1007/s13730-016-0237-y

CASE REPORT

Antithyroid drug-associated MPO-ANCA-positive tubulointerstitial nephritis in a type 2 diabetes patient: a case report

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Received: 10 March 2016 / Accepted: 25 September 2016 / Published online: 3 October 2016
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Abstract A 54-year-old man diagnosed with type 2 diabetes and hyperthyroidism was prescribed propylthiouracil (PTU) after the patient developed hepatic dysfunction on thiamazole. At 50 mg/day of PTU, he was stable with thyroid-stimulating hormone receptor and thyrotropic antibody titers remaining stable. After four years of taking PTU, he was referred to the Department of Nephrology due to a rapid increase in his serum creatinine (Cr) level. He showed impaired renal function (Cr 2.26 mg/dL; estimated glomerular filtration rate (eGFR), 25 mL/min). In addition, urinary β2-microglobulin (β2 MG) was increased to 71,980 μg/L and was positive for myeloperoxidase (MPO)-anti-neutrophil cytoplasmic antibody (ANCA) (33.9 U/mL). Gallium scintigraphy demonstrated a remarkable accumulation in both kidneys. The patient was diagnosed with tubulointerstitial nephritis based on a renal biopsy, the results of which suggested that it might have been induced by PTU. He was treated with prednisolone (PSL) at 30 mg/day. As a result, within two weeks, Cr, eGFR, and urinary β2 MG levels were progressively improved to 1.72 mg/dL, 34 mL/min, and 22,020 μg/L, respectively. Therefore, we tapered off the PSL with a dose of 5 mg/day after approximately one year. There have been no exacerbated renal function parameters. Although there are many reports on patients developing MPO-ANCA-positive crescentic glomerulonephritis after the administration of PTU, we report on a relatively rare case in which interstitial nephritis occurred after the administration of PTU.

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Keywords Tubulointerstitial nephritis · Propylthiouracil · Hyperthyroidism · MPO-ANCA · Type 2 diabetes

Introduction

In hyperthyroidism, the secretion capacity (activity) of the thyroid hormones, triiodothyronine (T3) and/or thyroxine (T4) becomes excessive when the tissues in the thyroid gland are abnormally activated [1, 2]. Hyperthyroidism includes various symptoms: increased heart rate, elevation of blood pressure, arrhythmia, excessive sweating, shaking of hands, nervousness, anxiousness, insomnia, weight loss, increased stool frequency, diarrhea (in some cases), and amenorrhea [1, 2].

Current treatment of hyperthyroidism includes pharmacotherapy, radioisotope therapy, and surgical treatment [3]. Pharmacotherapy is an important therapy, which includes thiamazole and propylthiouracil (PTU) [1]. Although these drugs are effective and widely used, side effects including urticaria, serious hepatic dysfunction, and agranulocytosis have been reported [1, 2]. Approximately 56 % of patients with anti-neutrophil cytoplasmic antibody (ANCA)-related nephritis are primarily myeloperoxidase (MPO)-ANCA-positive and frequently present with rapidly progressive glomerulonephritis (RPGN) [4]. The typical histopathologic picture for RPGN is considered to be necrotizing crescentic glomerulonephritis, which forms many cellular to fibrocellular crescents on the glomerulus [5]. In 1993, Dolman et al. first reported RPGN (i.e., ANCA-related nephritis) as a side effect of antithyroid drugs. Thereafter, many reports of such cases exist to date [6]. However, reports on MPO-ANCA-positive interstitial nephritis are rare. We treated a male patient with hyperthyroidism who developed MPO-ANCA-positive tubulointerstitial nephritis

apparently due to a 4-year oral administration of PTU as an antithyroid drug. This case is regarded as a very rare case and is considered to be worth examining.

Case report

Timeline of disease development

At 50 years of age, the patient was diagnosed with type 2 diabetes and treated by a local physician. However, he stopped treatment on his own accord after three months. At 51 years of age, he visited our hospital due to weakness of lower extremities and general malaise. In addition to type 2 diabetes, hyperthyroidism was revealed, and oral administration of thiamazole was initiated. However, he developed thiamazole-induced hepatic dysfunction and was switched to oral propylthiouracil (PTU). At 52 years of age, he developed double vision and was diagnosed with thyroid ophthalmopathy and steroid-pulse therapy was initiated. At 55 years of age, due to general malaise and a rapid increase in serum creatinine (Cr) level, he visited the Department of Nephrology at our hospital. An influence of PTU was suspected as the results from a blood test showed MPO-ANCA to be slightly positive, and therefore the administration of PTU was discontinued. In addition, a possibility of tubulointerstitial damage was considered, as the urinary β2-microglobulin (β2 MG) level was high. The patient was hospitalized for intensive examination and treatment of renal disease.

Conditions at admission

Height, 168.3 cm; weight, 74.0 kg; temperature, 37.0 °C; pulse, 69 bpm, regular; blood pressure, 151/78 mmHg; bulbar conjunctiva, no anemia; palpebral conjunctiva, no jaundice; pharynx and tonsils, no redness or swelling; thyroid gland, no swelling; heart sound, no abnormality; lung field, no pulmonary sound; abdomen, soft and flat; liver and spleen, not palpable; superficial lymph node, not palpable. There were no neurologic findings of increased pathologic reflex, tendon reflex, or laterality.

Laboratory findings at admission

We performed a series of blood and urine tests as we checked for tubulointerstitial damage. As shown in Table 1, urinary findings indicated that daily protein was mildly high (1.13 g/day) and urine biochemical tests indicated that the β2 MG (spot urine) level was high (71,980 μg/L). Bence Jones protein was not observed. White blood cell (WBC) count was slightly elevated to 10,100/mm^3 and mild anemia was revealed [hemoglobin (Hb), 10.9 g/dL]. Elevated sedimentation rate (40 mm/h) was observed. The results of the blood biochemistry tests showed elevation in: serum urea nitrogen, 29.4 mg/dL; serum creatinine level, 2.26 mg/dL; β2 MG, 6.48 mg/L; BNP, 27.5 pg/mL; and iPTH, 107.40 pg/mL. The level of 24 hours Cr clearance was decreased to 21.4 mL/min. There were no abnormal findings in the results of the liver function tests. The results of the serum immunological tests showed elevated C-reactive protein (1.020 mg/dL) and serum immunoglobulin (IgG 1826 mg/dL). In the complement tests, component 3 (C3) was 136 mg/dL; complement hemolytic activity (CH50) was over 60.0 U/ml and antinuclear antibody was increased by 80 times; and rheumatoid factor (RF) was increased to 23.4 U/dL. The level of these complements was increased when compared with the normal range. In addition, the MPO-ANCA level was increased to 33.9 U/mL. The results regarding thyroid function and blood glucose levels were within the normal range (Table 1). In addition, the electrocardiogram showed no significant abnormal findings.

Image findings at admission

There were no abnormal findings on the chest plain radiograph. On the abdominal echography, the left kidney was 104.7 × 63.9 cm and the right kidney was 117.4 × 58.8 cm. The cortical level of both kidneys was increased slightly, but the central echo complex was preserved. Mild atrophy of both kidneys was found with abdominal plain computerized tomography (CT) scanning. Linton et al. previously suggested 67 Ga scintigraphy as an excellent screening test for the presence of acute interstitial nephritis to help identify which patients with unexplained acute renal failure require renal biopsy [7]. Thus, we performed 67 Ga scintigraphy, which showed significant uptake in both kidneys.

Results of the renal biopsy

After receiving informed consent from the patient, we performed renal biopsy on day 2 of hospitalization for a closer inspection of the potential causes of the renal impairment. The results are shown in Fig. 1. In the light microscopical findings of the renal biopsy, 10 glomeruli without swelling were found. Of these, two glomeruli showed slightly increased mesangial matrix but were approximately normal (Fig. 1a, c). The thickening of the glomerular capillary wall was also mild. There were no findings of hyalinization, adhesion or crescentic glomerulonephritis. No invasion of neutrophils was observed. The interstitium became wide and edematous, and we observed inflammatory cell infiltrates mainly composed of lymphocytes and a few plasma cells. However, there was no

Table 1 Physiological parameters from the urine, blood, biochemical and immunological tests

Urine qualitative analysis/spot urine	
Protein	1+
Glucose	3+
Occult blood	±
Urobilinogen	±
White blood cell	–
Bacteria	–
Bence Jones protein	–
Urinary sediment/spot urine	
Red blood cell	Less than 1/HPF
White blood cell	1–4/HPF
Squamous epithelium	Less than 1/HPF
Bacteria	–
Urine biochemical test/spot urine	
β2-microglobulin (β2 MG)	71,980 μg/L
N-acetyl-β-D-glucosidase (NAG)	9.8 IU/L
Urine protein	310 mg/dL
Urine creatinine	34 mg/dL
Urine protein (spot urine)	1.1 g/gCr
Examination for urine collection	
Urine protein (urine collection)	1.13 g/day
24 h creatinine clearance	21.4 mL/min
Selectivity index	0.26
Blood count	
White blood cell	10,100/μL
Red blood cell	400×10^4/μL
Hemoglobin	10.9 g/dL
Hematocrit	35.8 %
Platelet	8.9×10^4/μL
Reticulocyte	28.7 %
Biochemical	
Total protein	8.0 g/dL
Albumin	4.2 g/dL
Total bilirubin	0.5 mg/dL
Aspartate aminotransferase (AST)	9 IU/L
Alanine aminotransferase (ALT)	10 IU/L
Alkaline phosphatase (ALP)	321 IU/L
Lactate dehydrogenase (LDH)	160 IU/L
Gamma glutamyl transpeptitase (γ-GTP)	24 U/L
Choline esterase (ChE)	320 IU/L
Glucose	108 mg/dL
Hemoglobin A1c (HbA1c)	6.0 %
Natrium	144 mEq/L
Kalium	3.8 mEq/L
Chlorine	109 mEq/L
Inorganic phosphorus	2.7 mg/dL
Calcium	9.1 mg/dL
Magnesium	1.6 mg/dL
Ferritin	155.1 ng/mL
Transferrin saturation (TSAT)	21 %
Blood urea nitrogen	29.4 mg/dL
Creatinine	2.26 mg/dL
Uric acid	3.9 mg/dL
N-acetyl-β-D-glucosidase (NAG)	9.8 IU/L
β2-microglobulin (β2 MG)	6.48 mg/L
Brain natriuretic peptide (BNP)	27.5 pg/mL
Intact parathyroid hormone (iPTH)	107.40 pg/mL
Immunological	
C-reactive protein (CRP)	1.020 mg/dL
Immunoglobulin G (IgG)	1826 mg/dL
Immunoglobulin G4 (IgG4)	24.0 mg/dL
Immunoglobulin A (IgA)	276 mg/dL
Immunoglobulin M (IgM)	77 mg/dL
Complement 3/4 (C3/C4)	136/34 mg/dL
Complement hemolytic activity (CH50)	60.0 ↑U/mL
Antinuclear antibody	80 times
Rheumatoid factor (RF)	23.4 U/mL
P-ANCA/qualitative analysis	–
C-ANCA/qualitative analysis	–
MPO-ANCA	33.9 U/mL
PR3-ANCA	1.3 U/mL
Anti-ssDNA antibody	Less than 10 AU/mL
Anti-dsDNA antibody	Less than 10 IU/mL
Anti-SS-A antibody	–
Anti-SS-B antibody	–
Anti-Scl-70 antibody	–
Anti-Jo-1 antibody	–
Anti-RNP antibody	–
Anti-Sm antibody	–
Anti-GBM antibody	–
Soluble interleukin-2 receptor (sIL-2R)	1220 U/mL
Thyroid gland	
Free Triiodothyronine (Free T3)	2.89 pg/mL
Free thyroxine (Free T4)	0.95 ng/dL
Thyroid stimulating hormone (TSH)	1.673 μIU/mL
TSH receptor antibody	0.7 IU/L
Blood sedimentation	
Erythrocyte Sedimentation Rate (ESR) (60 min)	40 mm
Allergy	
Drug-induced lymphocyte stimulation test(PTU)	–

P-ANCA perinuclear antineutrophilic cytoplasmic antibody, *C-ANCA* cytoplasmic antineutrophilic cytoplasmic antibody, *MPO-ANCA* myeloperoxidase antineutrophilic cytoplasmic antibody, *PR3-ANCA* proteinase 3 antineutrophilic cytoplasmic antibody

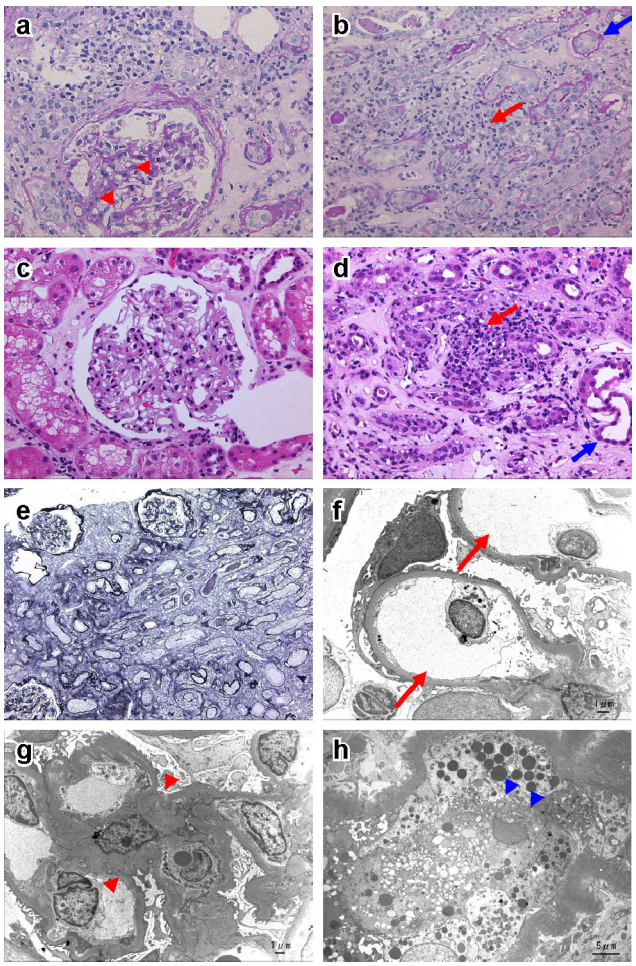

Fig. 1 Histopathological images of the kidney tissue are shown. Periodic acid-Schiff (PAS) staining (**a**, **b**), hematoxylin-eosin (HE) staining (**c**, **d**) and periodic acid methenamine silver (PAM) staining (**e**) was performed on kidney sections. The mesangium lesion was almost stable (**a** *red arrowhead*). An inflammatory infiltrate was not apparent in the glomerular lesion (**a**, **c**), but an interstitial lesion was edematous and infiltrated by chronic inflammatory cells, especially lymph cells and a few plasma cells (**b**, **d** *red arrow*). A tubular lesion, especially proximally, was atrophic and degenerative (**b**, **d** *blue arrow*). In electron microscope, no swelling of glomerulus endothelial cells was found and the capillary lumen was almost preserved (**f** *red arrow*). In the mesangium region, there was no increase of cells and in part the substrate was slightly increased, but remained almost normal (**g** *red arrowhead*). Denaturation was added to the tubular epithelium, and some were found to have a large number of lysosome (**h** *blue arrowhead*)

invasion of eosinophils or neutrophils (Fig. 1b, d). In addition, fibrosis was not found. Although the renal tubules in the interstitium showed narrowing of the lumen and the protein cast, no neutrophils were found in it (Fig. 1b, d, blue arrow). However, the epithelium of the proximal tubules showed a high degree of denaturing and atrophy due to interstitial changes. The interstitial arteries were slightly thickened. Invasion of inflammatory cells to the peritubular capillary was not found. Fibrinogen was diffusely present as shown with a fluorescent antibody method, in accordance with the interstitial tissue. However, deposition of immunoglobulin and complements were not observed in the glomerulus or interstitial tissue (data not shown). In the electron microscope findings, no swelling of the glomerulus endothelial cells was found and the capillary lumen was almost preserved (Fig. 1f). In the mesangium region, there was no increase in cells and part of the substrate was slightly increased (Fig. 1g). The tubulointerstitium showed edematous and an increase in fiber cells. Denaturation was added to the tubular epithelium demonstrating that some of them had a large number of lysosomes (Fig. 1h). Based on the above-mentioned histopathological findings, the final diagnosis was tubulointerstitial nephritis.

Course of the disease after hospitalization

Figure 2 shows the course of the disease in terms of treatment dosage and test results after hospitalization for almost a year. Treatment was originally intended to be initiated once the renal biopsy results confirmed the diagnosis. However, as serum Cr was slightly increased, the internal use of prednisolone (PSL) of 30 mg/day was initiated on day 5. Since the renal biopsy results demonstrated tubulointerstitial nephritis on day 9, the administration of PSL was continued. His response to treatment was good. We reduced the dose of PSL to 25 mg/day on day 19. The patient was discharged on day 26. We gradually reduced the dose of PSL during follow-up in the outpatient department. We followed him for approximately 350 days after he was hospitalized and observed no elevation in Cr or urine protein. His renal function maintained stable levels. However, urinary β2 MG repeatedly increased and decreased. Although the MPO-ANCA level at admission was 33.9 U/mL, it was decreased to 2.8 U/mL 350 days later.

Discussion

At admission, the patient's daily urinary protein and β2 MG levels suggested tubulointerstitial damage. The results of the blood biochemistry tests, including serum urea nitrogen, serum Cr level, β2 MG, Hb, and 24 h creatinine clearance were also compatible with renal damage. In addition, the WBC count was slightly elevated and the immunological tests showed elevated C-reactive protein, serum immunoglobulin, C3, and CH50. Elevated sedimentation rate was also observed. These results suggest that patient had chronic inflammation. Furthermore, 67 Ga scintigraphy showed significant uptake in both kidneys, suggesting the possibility of interstitial nephritis. Given that the RF and MPO-ANCA levels were increased, we

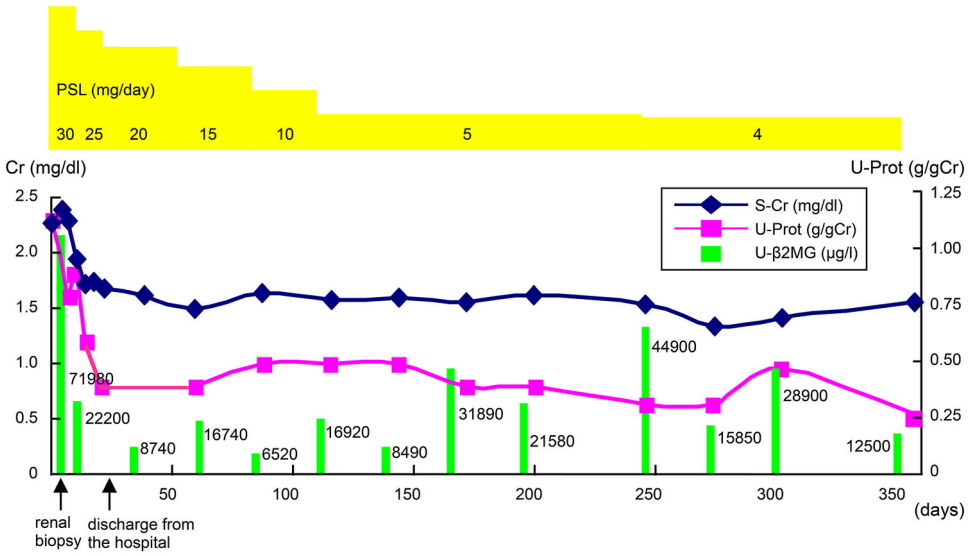

Fig. 2 The clinical course of the patient is shown. The administration of predonine was initiated at 30 mg/day, and then was decreased gradually. The response to the treatment was favorable

suspected tubulointerstitial nephritis due to the influence of PTU. Thus, we performed renal biopsy. The pathological findings allowed the final diagnosis of tubulointerstitial nephritis and we conclude that the MPO-ANCA-positive tubulointerstitial nephritis was caused by the antithyroid drug (PTU). In this case, thyroid function was preserved and the diabetes mellitus did not get worse.

Since the first report in 1993, there are many reports on patients developing RPGM (ANCA-related nephritis) due to the administration of antithyroid drugs [6]. However, case reports on patients who developed antithyroid drug-associated tubulointerstitial nephritis are very rare. The rate of becoming MPO-ANCA-positive after the administration of PTU in patients with hyperthyroidism is estimated to be 20.4 %, with no sex differences [8]. Although there are many patients with MPO-ANCA-related nephritis in old and middle age, the age range of patients that become ANCA-positive after the administration of PTU is 20–70 years; furthermore, it has been reported that there is no difference in the frequency of onset among age groups [9]. Additional reports suggest that long-term exposure to PTU may be a risk factor for the onset of ANCA-related vasculitis [10, 11].

MPO is involved in tissue destruction in the early phase of the pathogenesis of tubulointerstitial nephritis, namely by causing the lysis of the endothelial cell membrane as well as the vascular basement membranes in the peritubular capillary [12, 13]. This mechanism eventually proceeds to the destruction of the peritubular capillary wall (vasculitis), and plays an important role in the pathogenesis of tubulointerstitial nephritis, which is associated with MPO-ANCA positive vasculitis.

Joyce et al. reported that, etiologically, TIN can be caused by drug-related, infectious, autoimmune-mediated, genetic, and idiopathic factors [14]. However, the most common cause of TIN is related to medication or drug exposure. Drug-induced TIN has been noted in 7–27 % of adult patients with unexplained nonoliguric or oliguric acute kidney injury (AKI) [15]. However, in our patient, antimicrobials, nonsteroidal anti-inflammatories (NSAIDs), diuretics, or neuropsychiatric drugs were not used when MPO was found to be positive. Although the patient had taken medicines, such as levocetirizine hydrochloride, alogliptin bendoate, telmisartan, and self-injections of insulin aspart before he suffered renal insufficiency, none of these have been reported as causing positive MPO-ANCA or interstitial nephritis [14]. Furthermore, we checked for infectious diseases associated with interstitial nephritis, such as viral (cytomegalovirus, hepatitis), bacterial, fungal, and parasitic infections. No infectious disease was seen in this patient, the patient did not show symptoms of infectious disease, and the patient did not suffer from pyelonephritis. Moreover, pathological findings were hardly seen in the glomerular lesion; thus, the pathological change was not be caused by autoimmune diseases or diabetes mellitus. In addition, the glomerular lesion was not very wide, and hyalinosis of the afferent arteriole and focal/segmental glomerular sclerosis were hardly seen; thus, these pathological findings were not caused by nephrosclerosis.

In our case, inflammatory cell infiltrates (mainly lymphocytes and plasma cells, and rarely eosinophils), were mainly seen in the tubulointerstitial lesion. Edema was also found in the renal interstitium. Although peritubular capillary lesions were hardly seen, the remaining peritubular capillary lesion was also infiltrated by inflammatory cells; thus, the peritubular capillary lesion might have been already destroyed by MPO-ANCA when we performed the renal biopsy. PTU appears to be only the drug taken by this patient for which the possibility of a MPO-ANCA positive

Table 2 The reports of antithyroid drug (PTU)-induced MPO-ANCA-positive tubulointerstitial nephritis in hyperthyroidism patients

	Year and reference	Author	Number of cases	Sex	Age	History	PTU dosing period when MPO-ANCA was positive
Case patient	2015	–	1	Male	54	Type 2 diabetes mellitus hyperthyroidism thyroid ophthalmopathy	4 years
1	2009 (9)	Dysseleer et al.	1	Female	90	Side effect of amiodarone	5 weeks
2	2007 (10)	Chen et al.	1/19	Male	–	–	<6 years

situation has been reported [4]. Furthermore, interstitial nephritis has been previously reported to be associated with positive MPO [12]. Therefore, we considered that the pathological findings showed diffuse and extensive tubulointerstitial changes, compatible with peritubular capillary vasculitis due to MPO-ANCA-positive vasculitis and interstitial nephritis, might be due to PTU.

To date, there have been only two case reports on patients developing interstitial nephritis due to the oral administration of antithyroid drugs (Table 2) [16, 17]. The characteristics of these cases suggest that relatively elderly women tend to develop MPO-ANCA-positive tubulointerstitial nephritis; however, there are few reported cases regarding such patients. Tubulointerstitial nephritis is hard to diagnose based on only common symptoms and is thought to require renal biopsy for the diagnosis. In the present patient, MPO-ANCA positive status was confirmed at approximately four years after the administration of PTU and the patient developed tubulointerstitial nephritis. Such cases have not been reported adequately and further accumulation of such cases is awaited.

Conclusion

We treated a patient who developed antithyroid drug-associated, MPO-ANCA-positive tubulointerstitial nephritis. The time between the administration of antithyroid drugs and onset of MPO-ANCA-positive allied nephropathy was long (4 years); therefore, long-term observation is necessary. Currently, there are few such reported cases and it appears to be very rare. For future examination of MPO-ANCA-positive tubulointerstitial nephritis, the accumulation of a larger number of cases is necessary.

Acknowledgments We would like to deeply thank the medical personnel in charge of treatment for the present patient.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest associated with this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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