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**Michael J. Winters · R. Morrison Hurley**
**David S. Lirenman**

# ANCA-positive glomerulonephritis and IgA nephropathy in a patient on propylthiouracil

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**Abstract** A 14-year-old girl developed acute renal failure after 3 years therapy with propylthiouracil (PTU) for Grave's disease. Serologic evaluation showed antineutrophil cytoplasmic antibodies (ANCA) directed against proteinase 3 and myeloperoxidase. Renal biopsy showed a crescentic glomerulonephritis (GN) as well as evidence of IgA nephropathy (IgAN). PTU was discontinued and the patient was treated with prednisone and cyclophosphamide. ANCA became negative and renal function improved, but did not normalize. A second biopsy showed evidence of IgA nephropathy only. Propylthiouracil use has been associated with ANCA positive pauci-immune glomerulonephritis, but not with IgA nephropathy. An overlap syndrome between IgAN and ANCA-positive GN, however, has been described. This patient may have had a preexisting IgAN, with acute pauci-immune GN secondary to PTU, or this may be the first description of an overlap syndrome of IgAN and ANCA vasculitis all caused by PTU therapy.

**Keywords** IgA nephropathy · Antineutrophil cytoplasmic antibody · Crescentic glomerulonephritis · Propylthiouracil · Hyperthyroidism

## Introduction

Propylthiouracil (PTU) is a thioureylene derivative commonly used to treat hyperthyroidism. Fever, arthralgia, rash and granulocytopenia are the most common side effects; however, more serious complications such as hepatitis, vasculitis and a lupus-like syndrome may occur [1]. Antineutrophil cytoplasmic antibody (ANCA)-positive glomerulonephritis (GN) with, or without, systemic vasculitis has been well documented in association with PTU in both children and adults [2–7]. Other renal pathology including lupus nephritis [8], Wegener's granulomatosis [9], as well as acute and chronic interstitial nephritis [10, 11] have also been associated with PTU use.

We report a case of a 14-year-old girl on PTU for Graves' disease who developed ANCA-positive glomerulonephritis with evidence of IgA nephropathy.

M.J. Winters (✉)
Division of Nephrology, British Columbia's Children's Hospital,
Room 1A-14, 4480 Oak Street,
Vancouver, British Columbia, Canada, V6H 3V4
Fax: +1-604-8753649

R.M. Hurley
Division of Nephrology, British Columbia's Children's Hospital,
Vancouver, British Columbia, Canada

D.S. Lirenman
Division of Nephrology, British Columbia's Children's Hospital,
Vancouver, British Columbia, Canada

## Case report

Graves' disease was diagnosed in an 11-year-old girl in 1995 after a friend noticed a goiter. She was started on PTU and subsequently remained euthyroid on a stable dose of PTU.

In July 1998, at the age of 14 years, she developed a flu-like illness with periorbital edema, initially thought to be due to an allergic reaction. The flu-like illness resolved but she remained edematous. In October 1998, she was seen by a pediatric endocrinologist at our institution for consideration of radioactive iodine ablation therapy, due to the long duration of PTU therapy. At that time the edema had worsened and she was noted to have hematuria and proteinuria and she was referred to renal clinic.

At the time of presentation (November 1998), she was pale with a blood pressure of 132/71. She had mild facial fullness and 1+ pretibial edema bilaterally. ENT examination was normal and there was no exophthalmos. She had a palpable, firm, non-tender 4×4-cm goiter. There was no rash, arthritis, scleritis or other signs and symptoms of systemic vasculitis.

Laboratory investigations were as follows: Hg 73 g/l, WBC $3.18\times10^9$/l, platelets $284\times10^9$/l, $Na^+$ 138 mmol/l, $K^+$ 5.7 mmol/l, $Cl^-$ 115 mmol/l, $HCO_3^-$ 20 mmol/l, urea 13.9 mmol/l, creatinine 247 µmol/l, phosphate 2.42 mmol/l, $Ca^{2+}$ 1.97 mmol/l, and albumin 26 g/l. Urinalysis revealed: SpG 1.013, protein 5 g/l, 14 WBC/hpf, >100 RBC/hpf, and urinary protein excretion 7.94 g/24 h. Throat culture grew normal flora and ASOT was <25 IU/m. $C_3$ was 1.53 g/l, $C_4$ 0.6 g/l, IgG 8.97 g/l, IgA 3.94 g/l, IgM 2.57 g/l, TSH 7.77 mU/l, $T_4$ 77 nmol/l, and anti DS-DNA positive. Anti-myeloperoxidase ANCA and anti-proteinase-3 ANCA were both positive by enzyme immunoassay (the isotypes of these antibodies were not determined).

A percutaneous renal biopsy showed mesangial matrix expansion with segmental scarring. Fibrocellular crescents were present

in 5 of 15 glomeruli and there was extensive focal tubular atrophy. Segmental fibrinoid change was found in several glomeruli. Electron microscopy showed scattered mesangial and relatively small subendothelial deposits. Immunofluorescence showed strong granular mesangial staining for IgA, as well as weaker staining for IgG, IgM and $C_3$. This was felt to be consistent with IgA nephropathy; however, given the history of PTU therapy, and ANCA positivity, the segmental scarring and crescents were also considered consistent with PTU-induced pauci-immune glomerulonephritis.

The patient was started on prednisone 20 mg 3 times daily, and PTU was discontinued. Her creatinine peaked at 320 µmol/l and subsequently fell to 191 µmol/l and her prednisone was decreased to 60 mg every other day. In mid-December – her creatinine had climbed again to 231 µmol/l and she was started on cyclophosphamide 100 mg daily. She was also treated with calcium carbonate for hyperphosphatemia, propranolol and furosemide for hypertension and erythropoietin (EPO) for persistent anemia. At that time – her ANCA remained positive despite discontinuation of PTU. Her creatinine stabilized between 150 and 200 µmol/l and cyclophosphamide was tapered and finally discontinued in March 1999. By this time – her ANCA had become negative.

A second renal biopsy was performed in April 1999 to help decide on further management. It showed mesangial matrix expansion and increased mesangial cellularity. No crescents were present; however, 13 of 15 glomeruli showed segmental sclerosis. Electron microscopy showed scattered small granular mesangial deposits and occasional subendothelial electron-dense deposits. Immunofluorescence again showed predominately IgA staining. The biopsy was felt to be consistent with IgA nephropathy alone, with no evidence of active necrotizing GN. The prednisone was tapered and she was started on fish oil (Maxepa) and enalapril as she remained proteinuric. Her Hg was 129 g/l and EPO was discontinued. Her Hg slowly decreased to 85 g/l by August 1999 when enalpril was discontinued.

When last seen in May 2001 – she was clinically well with a blood pressure of 113/70. Investigation revealed: creatinine 161 µmol/l, urea 12.7 mmol/l, Hg 91 g/l and 24-h urine protein 3.64 g. There were no sediment abnormalities on urinalysis. She remains on a tapering dose of prednisone (currently 3 mg every other day), as well as fish oil (Proceba), calcium supplements, and folic acid. More recently – she was started on L-thyroxine because of a rise in her TSH and a drop in free T4. EPO was restarted as her Hg plateaued at 90 g/l and extensive hematological investigations did not reveal any cause for her anemia apart from her renal insufficiency.

## Discussion

ANCA are autoantibodies directed against constituents of neutrophil primary granules. They are serologic markers of a variety of systemic vasculitides including Wegener's granulomatosis (WG), microscopic polyarteritis and pauci-immune necrotizing and crescentic glomerulonephritis. ANCA are classified as cytoplasmic (C-ANCA) or perinuclear (P-ANCA) based on their appearance on indirect immunofluorescence microscopy [12]. C-ANCA is commonly associated with WG, whereas P-ANCA is more frequently found in pauci-immune necrotizing, crescentic glomerulonephritis and microscopic polyarteritis. The most common antigen for C-ANCA has been identified as proteinase 3. P-ANCA have been reported to be directed against a number of antigens including myeloperoxidase (MPO), human-leukocyte elastase, and lactoferrin. Eighty to 90% of P-ANCA in patients with systemic vasculitis, pauci-immune necrotizing and crescentic glomerulonephritis are directed against MPO [2,12,13]. Most ANCA are of the IgG subtype, although IgM and IgA ANCA have also been described [13].

ANCA-positive vasculitis is a rare but well recognized complication of PTU therapy. Both C-ANCA and P-ANCA-related disease has been described. Most patients present with systemic symptoms including fever, fatigue, arthritis, scleritis and rash. Nephritis, with or without systemic involvement, is present in about two-thirds of patients [7]. Respiratory involvement, including alveolar hemorrhage and classic WG, has also been reported [9, 14]. Duration of therapy prior to onset of symptoms ranges from weeks to years [2–7]. Crescentic or necrotizing GN is similar to that seen in non-drug-induced ANCA disease. Mesangial proliferation is also occasionally seen and immunofluorescence is uniformly negative or pauci-immune. Mild cases are treated with cessation of PTU. When more significant disease, such as crescentic GN, is present – steroids and/or cyclophosphamide have been used. Renal function usually improves and ANCA levels decrease or disappear; however, patients with crescents at presentation are at high risk of developing chronic renal failure [7].

The mechanisms of ANCA production and vasculitis in PTU therapy remain unclear. Metabolites of the drug may compete with thymidine triphosphate as a substrate, therefore inhibiting synthesis of DNA in peripheral blood lymphocytes and producing abnormal immune regulation. Alternatively, drug metabolites may bind to cellular macromolecules on neutrophils, serving as a hapten for antibody production [1]. Kitahara proposed that during PTU therapy – if neutrophils are activated by infection, a large quantity of MPO is released from neutrophils, transforming the drug into free radicals, resulting in endothelial injury [4].

Other renal pathologies including lupus nephritis, acute interstitial nephritis and chronic interstitial nephritis have also been reported in association with PTU therapy [8, 10, 11]. IgA nephropathy (IgAN), however, has never been described.

IgAN is the most common cause of glomerulonephritis in the world [15]. It most commonly presents with intermittent microscopic or gross hematuria. Between 15% and 35% of patients develop chronic renal failure, usually after many years. Acute renal failure occurs in less than 10% of patients, a small percentage of whom are found to have crescentic GN and a rapidly downhill course. These patients present in a similar manner to our case, with proteinuria, gross hematuria and/or hypertension [15–17].

Although ANCA is not commonly associated with IgAN, several researchers have reported IgA ANCA in HSP, a systemic vasculitis with identical renal pathology, and less commonly in IgAN [18–20]. The significance of IgA ANCA in HSP and IgAN, however, is controversial. Robson et al. [13] assessed the sera of 19 patients with active HSP or a history of HSP and all were negative for IgA ANCA by immunofluorescence. They suggested that positive results reported using an enzyme immunoassay

technique may be false positives due to the presence of contaminants in neutrophil extracts. Both Sinico and Saulsbury and colleagues have suggested that IgA rheumatoid factor, which may be present in the serum of patients with IgAN and HSP, may produce false positive results for IgA ANCA. They showed that extraction of IgA RF reduces IgA ANCA titers [21, 22]. Advocates of IgA ANCA in IgAN and HSP have found the ANCA to be directed against a novel 51-kDa protein [19]. In our patient ANCA specificity was directed against MPO and PR3.

More recently, IgG ANCA against MPO or PR3 have been reported in association with IgAN. Ramirez et al. [23] described a child with proven IgAN who later presented with an acute deterioration in renal function. Biopsy at that time showed crescentic GN and the patient's serum contained anti-MPO ANCA. Similarly, Allmaras et al. [24] described three adults with rapidly progressive IgAN who were found to have anti-MPO antibodies. Richer et al. [25] described adults with microscopic polyangitis and Churg-Strauss syndrome, respectively, who had MPO-ANCA and IgA deposits on renal biopsy. IgAN in association with C-ANCA and clinical evidence of WG have also been described [26, 27]. These cases may represent the coincidental presence of two diseases, or an overlap syndrome between rapidly progressive IgAN and ANCA-related vasculitis [24]. These patients may benefit more from immunosuppression than those with IgAN without ANCA [23].

The patient described in this report had ANCA-positive crescentic GN consistent with PTU-related disease on initial presentation. IgA deposits were found on biopsy, a finding not previously described in association with PTU use. Discontinuation of PTU and treatment with prednisone and cyclophosphamide was associated with an improvement in her renal function. Her ANCA has become negative. She continues, however, to have renal insufficiency, and a subsequent biopsy, although improved, remains consistent with IgA nephropathy.

There are several possibilities, which may explain the presentation and natural history of this patient's kidney disease:

1. She may have had previously unrecognized IgAN unrelated to PTU with her acute presentation being ANCA-positive GN secondary to PTU therapy. We were unable to find evidence of a urinalysis having been performed prior to her presentation with acute nephritis. Her urea and creatinine were tested in 1996 and were normal.
2. She may have presented with the overlap syndrome of IgAN with positive ANCA, with PTU having no role in inducing ANCA positivity. However, the presence of ANCA of different specificity is unusual in primary ANCA disease, but common in drug – induced ANCA [2, 12, 14]. The presence of both PR3-ANCA and MPO-ANCA makes it more likely that PTU had a role in inducing ANCA positivity in this patient.
3. She may have had rapidly progressive IgAN only and PTU – induced ANCA as an incidental finding not related to her renal pathology. The presence of ANCA without vasculitis in patients on PTU has not been well described. Dolman et al. [2] tested seven patients on PTU with no evidence of vasculitis, none of whom were ANCA positive. In contrast, Sato et al. report a high incidence of MPO-ANCA in children on PTU with no evidence of vasculitis [28]. In our case, clinical improvement was associated with disappearance of ANCA, suggesting that ANCA was related to the pathogenesis of her renal disease.
4. This may be the first description of an overlap syndrome of IgAN and ANCA vasculitis all caused by propythiouracil therapy.

Given the high prevalence of IgAN, and its often indolent course, we believe a preexisting IgAN, with acute pauci-immune GN secondary to PTU, is the most likely in this case. If the overlap syndrome between ANCA related vasculitis and IgAN now described by several investigators [23–25] does exist, it is possible that, like other ANCA-related diseases, this overlap syndrome may be caused by propylthiouracil therapy.

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