Case Reports in Nephrology and Dialysis

Case Rep Nephrol Dial 2024;14:36–41
DOI: 10.1159/000536618
Received: November 1, 2023
Accepted: January 28, 2024
Published online: March 4, 2024

Single Case

Propylthiouracil-Induced Antineutrophil Cytoplasmic Antibody-Associated Vasculitis with Overlap IgA Nephropathy: A Case Report

Georgina Oakman Cindy Ong

Renal Unit, Bendigo Health, Bendigo, VIC, Australia

Keywords

Antineutrophil cytoplasmic antibody-associated vasculitis · Propylthiouracil · IgA nephropathy · Case report

Abstract

Background: The anti-thyroid medication propylthiouracil (PTU) is a recognised cause of drug-induced antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Pauci-immune crescentic glomerulonephritis is the characteristic feature of this condition on renal biopsy. We present a case of PTU-induced AAV with the unusual histological finding of overlap IgA nephropathy (IgAN) in a young female with treatment-resistant Graves' disease. ***Case Report:*** A 26-year-old female presented with an acute kidney injury, macroscopic haematuria, and proteinuria 14 months after starting PTU for Graves' disease. She had a history of established thyroid eye disease and a previous severe adverse reaction to carbimazole. Her autoantibodies were strongly positive for myeloperoxidase-ANCA (199 U/mL). Renal biopsy demonstrated both necrotising crescentic glomerulonephritis and prominent (3+) mesangial deposition of IgA. She was treated with glucocorticoids and rituximab with sustained improvement in her renal function but persisting mild proteinuria and microscopic haematuria. PTU was ceased following a dose of radioactive iodine (RAI). Twelve months post-RAI, her Graves' orbitopathy remained stable, and her thyroid function was gradually normalising. ***Conclusion:*** This was a case of drug-induced AAV with histological features of overlap IgAN. We suggest that this patient had pre-existing subclinical IgAN and then developed AAV secondary to PTU. The management of her thyroid disease was complex given the PTU-induced vasculitis, previous reaction to carbimazole, the risks of a thyroidectomy on immunosuppression, and the possible worsening of her eye disease with RAI. The glucocorticoids and Rituximab prescribed for vasculitis may have prevented the progression of her Graves' orbitopathy after RAI.

Correspondence to:
Georgina Oakman, gloakman@bendigohealth.org.au

Case Rep Nephrol Dial 2024;14:36–41
DOI: 10.1159/000536618

Introduction

The anti-thyroid medication propylthiouracil (PTU) is a recognised cause of drug-induced antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) [1]. The reported frequency of ANCA seropositivity in patients receiving PTU ranges from 15 to 64% [2]. Autoantibodies against myeloperoxidase (MPO) are more common than those against proteinase 3 (PR3) [2]. Only a minority of patients with detectable serum ANCAs will develop clinical manifestations of vasculitis which may include constitutional symptoms, rash, glomerulonephritis, or pulmonary haemorrhage [2].

The histological hallmark of renal AAV is pauci-immune, necrotising crescentic glomerulonephritis, characterised by little or no staining for immunoglobulins [3]. Despite this association with pauci-immunity, some glomerular immune complex deposition has been regularly reported in primary AAV [4, 5] and PTU-induced AAV [6, 7]. Strongly positive staining (>2+) for immune complexes on immunofluorescence is considered uncommon. The presence of immune complexes in AAV has been associated with a greater degree of proteinuria [4]; however, their specific role in disease pathogenesis remains poorly understood.

We herein present a case of PTU-induced, anti-MPO-positive AAV with unusual histological features of overlap IgA nephropathy (IgAN). We also discuss the challenges associated with the management of Graves' disease in the setting of adverse reactions to both PTU and carbimazole, immunosuppression, and established orbitopathy.

Case Presentation

A 26-year-old Caucasian female was referred to her local renal outpatient service with an acute kidney injury, proteinuria, and haematuria. She was a current smoker with a background of depression and Graves' disease.

Her thyroid disease had been diagnosed 14 months previously and was initially treated with carbimazole 20 mg BD. She developed a severe urticarial rash after approximately 2 weeks and was changed to PTU. Due to persistent hyperthyroidism and mild Graves' orbitopathy, her PTU dose was uptitrated. Prior to the presentation described in this case report, she had been taking 250 mg BD for approximately 5 months. She was also waitlisted for a total thyroidectomy.

The patient was asked to present to the Emergency Department for further assessment. On review, she described a 2-month history of foamy, "Coca-Cola-coloured" urine with associated vague lower abdominal pain. She denied any recent illnesses, rash, epistaxis, haemoptysis, chest pain, or arthralgias. A history of thyroid and renal disease was reported by her maternal great grandmother. Her blood pressure was 130/80 mm Hg on admission. Physical examination was unremarkable apart from a diffuse goitre and some mild proptosis.

Her serum creatinine on presentation was 157 μmol/L. Blood taken 5 months prior had demonstrated normal renal function (serum creatinine 77 μmol/L and estimated glomerular filtration rate >90 mL/min/1.73 m^2). She had moderate proteinuria (spot protein creatinine ratio 234 mg/mmol) and albuminuria (albumin:creatinine ratio/ACR 158 mg/mmol). Urine microscopy confirmed haematuria. On review of her previous investigations, microscopic haematuria was detected on a urine sample taken 9 months prior to presentation in the absence of infection. An ultrasound of the renal tract was normal.

A renal biopsy was performed shortly following admission (Fig. 1). This demonstrated necrotising glomerulonephritis with crescents in 19% of the viable glomeruli. Immunoperoxidase staining was strongly positive for mesangial IgA (3+). Mild mesangial hypercellularity was seen throughout the sample. Her serology subsequently demonstrated

Case Rep Nephrol Dial 2024;14:36–41
DOI: 10.1159/000536618

positive titres for p-ANCA and MPO-ANCA (199 U/mL). c-ANCA, PR3-ANCA, ANA, and anti-GBM titres were negative.

In view of the high MPO-ANCA titre, she was managed as presumed AAV with high-dose intravenous methylprednisolone (500 mg daily) for 3 days. Her creatinine improved to 144 μmol/L, and she was discharged on oral glucocorticoids with a weaning plan as per the PEXIVAS protocol [8]. Four doses of weekly induction intravenous Rituximab (750 mg) were arranged as an outpatient. Counselling regarding smoking cessation was provided.

The management of her thyroid disease was complex given the PTU-induced vasculitis, previous reaction to carbimazole, the risks of a thyroidectomy on immunosuppression, and possible worsening of her eye disease with RAI. Her thyroid function tests at the time of this admission demonstrated normal free T3 (4.9 pmol/L) and T4 (12.0 pmol/L) but ongoing suppression of her TSH (0.30 mIU/L). Her thyroid stimulating immunoglobulin titre was 3.65 IU/L (normal <0.55). Thyroid peroxidase antibodies were also detectable. She was assessed by an ophthalmologist who advised that her Graves' orbitopathy was only mild, and hence she received radioactive iodine (320 MBq) shortly following discharge. Her PTU was subsequently ceased.

Approximately 12 months post this index admission, the patient remained well. She continued 6 monthly maintenance doses of rituximab (500 mg with a further 500 mg 2 weeks later). Marked B cell depletion post-rituximab was confirmed with flow cytometry. Her renal function improved (serum creatinine 89 μmol/L, estimated glomerular filtration rate 77 mL/min/1.73 m^2, Fig. 2). She did continue to have mild microscopic haematuria, proteinuria (protein creatinine ratio 66 mg/mmol), and a persistent elevation of her MPO-ANCA titre (168 U/mL). Perindopril 2.5 mg daily was commenced in the outpatient setting. Her thyroid function was approaching normal (TSH 0.33 mIU/L with normal T3 and T4). Her thyroid stimulating immunoglobulin titre had also improved to 0.32 IU/L when it was rechecked 4 months following her initial presentation. She did not require any further anti-thyroid treatment, and her eye disease remained stable. Six monthly maintenance Rituximab will be continued for 2 years. The CARE Checklist has been completed by the authors for this case report and is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536618).

Discussion

This was a case of PTU-induced AAV with overlap IgAN in a young female with Graves' disease. She was successfully treated with glucocorticoids, rituximab, and the withdrawal of PTU.

The typical epidemiology of PTU-induced AAV is reflected in this case. It is generally seen in young females [2], although this is likely due to the prevalence of autoimmune thyroid disease in this demographic. Moreover, PTU-induced AAV is typically a milder disease with a better prognosis than primary AAV, provided that PTU is promptly withdrawn [2]. This is also consistent with our patient's clinical course; severe renal impairment and proteinuria were absent, and she responded well to PTU cessation and immunosuppression. A similar case of PTU-induced, MPO-positive AAV in a 44-year-old female with Graves' disease was described recently by Wong et al. [9]. Although this patient presented with more severe disease manifestations including pulmonary haemorrhage, she also had a good response to PTU withdrawal and immunosuppression (oral cyclophosphamide). Plasma exchange was also utilised in this case; recent evidence suggests that this reduces the risk of end-stage kidney disease but increases the risk of serious infections in primary AAV [10]. Data specific to PTU-induced AAV is lacking.

Case Reports in Nephrology and Dialysis

Case Rep Nephrol Dial 2024;14:36–41
DOI: 10.1159/000536618

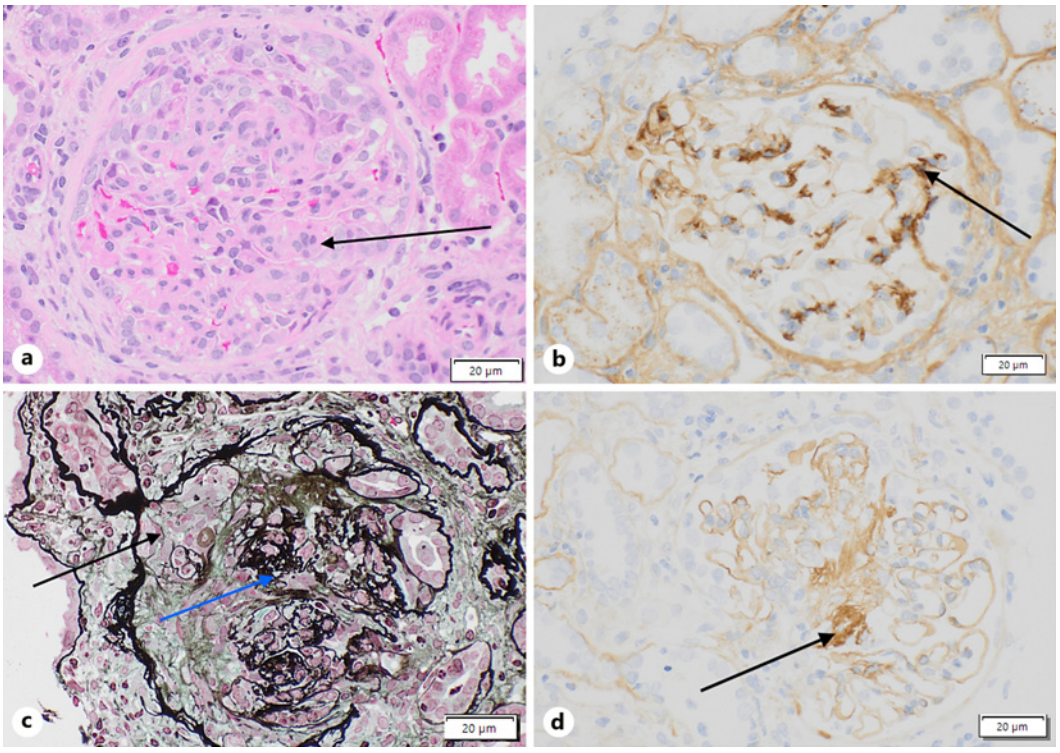

Fig. 1. Renal biopsy histology. All images are displayed at ×20 magnification. **a** Haematoxylin and eosin stain: glomerulus showing diffuse mesangial hypercellularity (black arrow). **b** IgA immunoperoxidase stain: strongly positive mesangial IgA deposition (black arrow). **c** Silver Masson stain: glomerulus with a fibrocellular crescent (black arrow) and segmental sclerotic lesion (blue arrow). **d** Fibrinogen stain: area of fibrinoid necrosis (black arrow).

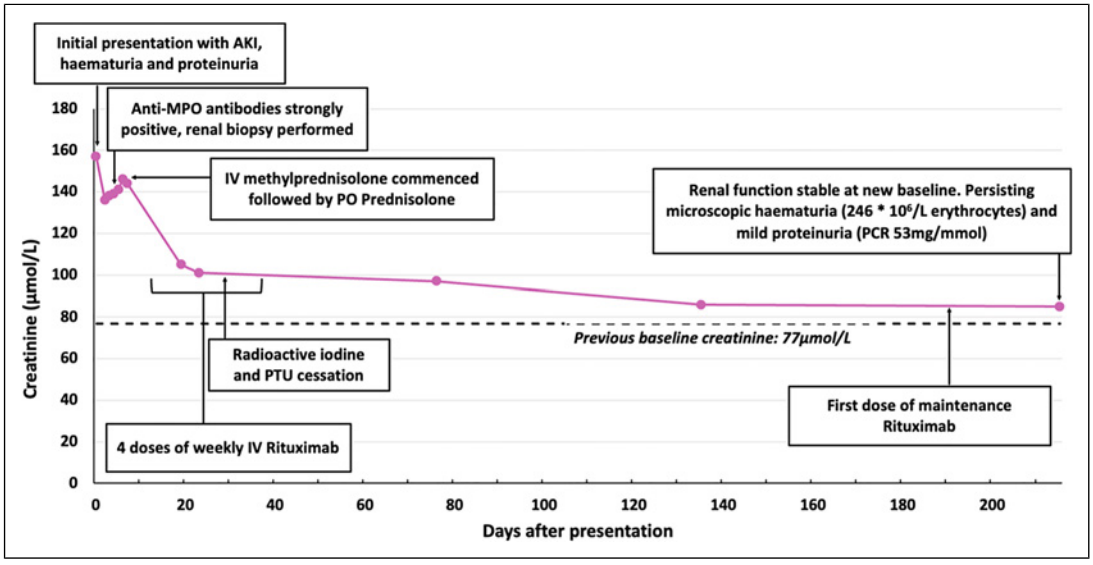

Fig. 2. Timeline of admission and treatment overlaid on a serum creatinine plot. AKI, acute kidney injury; MPO, myeloperoxidase; IV, intravenous; PO, oral; PTU, propylthiouracil; PCR, protein creatinine ratio.

Case Rep Nephrol Dial 2024;14:36–41
DOI: 10.1159/000536618

Interestingly, our patient's renal biopsy demonstrated strong mesangial positivity for IgA in addition to crescentic glomerulonephritis. Several possible explanations exist for this. We hypothesise that she had pre-existing subclinical IgAN given that microscopic haematuria was present in a previous urine sample. Overlap IgAN may also explain why she continues to have microscopic haematuria following treatment of her vasculitis, despite her renal function normalising. Alternatively, the mesangial immune complex deposition may also be secondary to AAV. Indeed, Eustace et al. [5] identified immune complexes in 54% of renal biopsies from patients with AAV using electron microscopy. However, strongly positive immunofluorescence staining (>2+) was very uncommon. 3+ staining was present in our patient's biopsy, which favours the hypothesis of pre-existing IgAN.

The management of coexistent renal and thyroid disease in this case was challenging. Withdrawal of the offending medication is the mainstay of treatment for drug-induced AAV. However, there were concerns that abrupt PTU cessation in our patient would precipitate thyroid storm as high doses had been required to control her hyperthyroidism. A switch to carbimazole could normally be considered, except our patient had a previous significant cutaneous drug reaction to this agent. Carbimazole can also cause drug-induced AAV, but it is less frequently implicated than PTU [1]. Given these issues, alternatives to medical therapy were considered. A thyroidectomy on high-dose immunosuppression was felt to have an unacceptably high risk of post-operative complications. RAI was the remaining option; however, de novo or progression of Graves' orbitopathy with its use is well described [11]. This can be minimised by administration of oral prednisolone [11]. After a multi-disciplinary discussion, the patient proceeded to have RAI with steroid cover. Following treatment, her eye disease remained stable, and her thyroid function gradually normalised. It should also be noted that Rituximab is now recommended as a second-line treatment for Graves' orbitopathy in the 2021 European guidelines [11], and recent data suggests that it can help achieve remission in young patients with Graves' hyperthyroidism [12]. Consequently, Rituximab may have had a dual therapeutic effect on vasculitis and thyroid disease in our patient.

Conclusion

We have described a case of PTU-induced AAV with histological evidence of overlap IgAN. It is unclear whether the mesangial IgA deposition preceded or resulted from the AAV, but we propose that this patient had pre-existing subclinical IgAN and then developed AAV secondary to PTU. Withdrawal of PTU, corticosteroids, and rituximab resulted in a good recovery of renal function. Her thyroid disease was successfully managed with RAI.

Acknowledgement

The authors thank Professor Anthony Landgren for providing and annotating the renal biopsy images.

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of her medical case and any accompanying images. Ethical approval is not required for this study in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding was received for this work.

Author Contributions

Dr. Ong was the senior clinician involved in the care of this patient, conceived the original idea for the case report, and revised the manuscript prior to publication. Dr. Oakman collated the patient information and completed the initial draft of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

References

1 Gao Y, Zhao M-H. Review article: drug-induced anti-neutrophil cytoplasmic antibody-associated vasculitis. Nephrology. 2009;14(1):33–41.
2 Chen M, Gao Y, Guo X-H, Zhao M-H. Propylthiouracil-induced antineutrophil cytoplasmic antibody-associated vasculitis. Nat Rev Nephrol. 2012;8:476–83.
3 Kronbichler A, Shin J, Lee KH, Nakagomi D, Quintana LF, Busch M, et al. Clinical associations of renal involvement in ANCA-associated vasculitis. Autoimmun Rev. 2020;19(4):102495.
4 Neumann I, Regele H, Kain R, Birck R, Meisl FT. Glomerular immune deposits are associated with increased proteinuria in patients with ANCA-associated crescentic nephritis. Nephrol Dial Transplant. 2003;18(3):524–31.
5 Haas M, Eustace JA. Immune complex deposits in ANCA-associated crescentic glomerulonephritis: a study of 126 cases. Kidney Int. 2004;65(6):2145–52.
6 Chen Y-X, Yu H-J, Ni L-Y, Zhang W, Xu Y-W, Ren H, et al. Propylthiouracil-associated antineutrophil cytoplasmic autoantibody-positive vasculitis: retrospective study of 19 cases. J Rheumatol. 2007;34(12):2451–6.
7 Yu F, Chen M, Gao Y, Wang S-X, Zou W-Z, Zhao M-H, et al. Clinical and pathological features of renal involvement in propylthiouracil-associated ANCA-positive vasculitis. Am J Kidney Dis. 2007;49(5):607–14.
8 Walsh M, Merkel PA, Peh C-A, Szpirt WM, Puéchal X, Fujimoto S, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med. 2020;382(7):622–31.
9 Wong AH, Wong W-K, Looi L-M, Ratnasingam J, Lim S-K. Propylthiouracil-induced antineutrophil cytoplasmic antibodies-associated vasculitis with renal and lung involvement. Case Rep Nephrol Dial. 2022;12(2):105–11.
10 Walsh M, Collister D, Zeng L, Merkel PA, Pusey CD, Guyatt G, et al. The effects of plasma exchange in patients with ANCA-associated vasculitis: an updated systematic review and meta-analysis. BMJ. 2022;376:e064604.
11 Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol. 2021;185(4):G43–67.
12 Cheetham TD, Cole M, Abinun M, Allahabadia A, Barratt T, Davies JH, et al. Adjuvant rituximab-exploratory trial in young people with Graves disease. J Clin Endocrinol Metab. 2022;107(3):743–54.