Propylthiouracil induced anti-neutrophil cytoplasmic antibody associated vasculitis: A case report and review of the literature

Luísa Pereira[1], Ana Cabrita[1], Anabela Guedes[1],Teresa Jerónimo[1], André Fragoso[1], Sandra Sampaio[1], Pedro Leão Neves[1,2]

[1]Nephrology Department. Centro Hospitalar Universitário do Algarve. Faro. Portugal
[2]Medicine and Biomedical Sciences Department. Algarve's University. Faro. Portugal

NefroPlus 2020;12(1):82-86

ABSTRACT

The development of antineutrophil cytoplasmatic antibody (ANCA) during therapy with propylthiouracil (PTU) is not uncommon but occasionally has clinical significance. Risk factors associated with the development of ANCA associated systemic vasculitis when taking PTU have been described. We report and discuss a case with PTU-induced ANCA vasculitis with severe systemic manifestations, which improved with discontinuation of the antithyroid drug, plasmapheresis and on starting systemic immunosuppressive therapy.

Keywords: ANCA. Kidney-lung syndrome. Propylthiouracil. Systemic vasculitis.

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis are a collection of relatively rare autoimmune diseases of unknown cause, characterized by inflammatory cell infiltration causing blood vessels necrosis. They present with a wide variety of signs and symptoms and, if left untreated, carry a significant burden of mortality and morbidity.

Several triggers have been associated with development of this entity, including chemicals, infection and drugs. Propylthiouracil (PTU) is a common anti-thyroid drug, which has been linked to ANCA associated vasculitis induction, although the exact mechanism remains unclear[1,2].

Despite the fact that progression into clinical overt vasculitis is rare, PTU-induced vasculitis may have different organ involvement patterns. Kidney involvement or ANCA-associated nephritis often presents as a rapidly progressive GN (RPGN) that can lead to end stage renal disease (ESRD) if not recognized and promptly treated.

Suspension of PTU alone or with associated immunosuppressive therapy may allow remission of vasculitis, even in severe cases[3].

CASE REPORT

A 74-year-old woman presented to the Emergency Department with a 6-month history of asthenia and anorexia, without fever or significant weight loss. She also reported hemoptoic productive cough and dyspnea for the last 5 days, reason why she was treated with amoxicillin/clavulanate.

On physical examination she was afebrile, pale, breathless, with lower limbs edema. Pulmonary auscultation revealed bilateral crackles and chest X-ray showed multiple alveolar infiltrates with perihilar confluence (fig. 1).

She remained hospitalized in the Medicine Department with the diagnosis of community-acquired pneumonia, hypochromic microcytic anemia (hemoglobin, 7.6 g/l) and acute kidney injury (creatinine, 4.35 mg/dl). Empirical antibiotic therapy was started with ceftriaxone and azithromycin, after blood and urine cultures were obtained.

Four days later, clinical deterioration occurred with dyspnea, moderate hemoptysis, hemoglobin decrease and progressive creatinine rise (maximum of 7.1 mg/dl), with hematuria and

Corresponding: Luisa Helena Pereira
Nephrology Department.
Centro Hospitalar Universitário do Algarve.
R. Leao Penedo, 8000-386 Faro, Portugal
luisahelenapereira91@gmail.com

Revisión por expertos bajo la responsabilidad de la Sociedad Española de Nefrología.

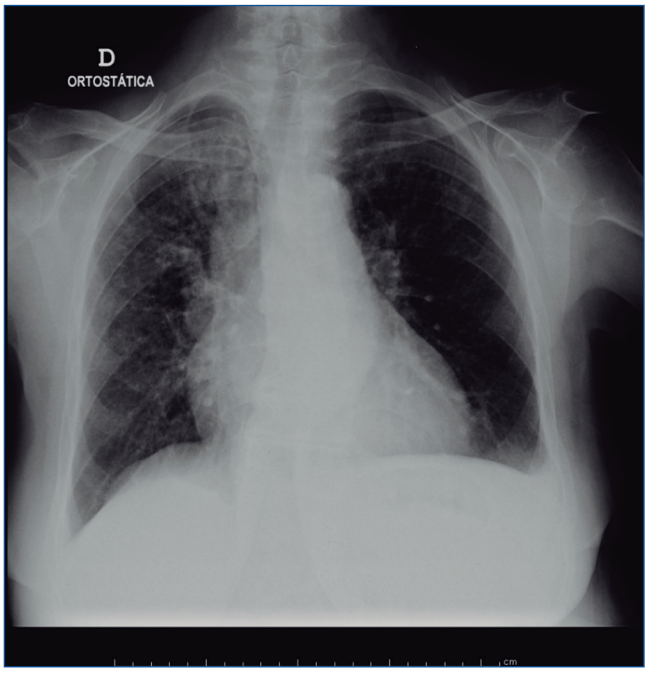

Figure 1. Initial chest radiography with bilateral multiple patchy opacities.

proteinuria (1 g/24 h). At this time, the patient was transferred to the Nephrology Department.

Thoracic computed tomography (CT) revealed multiple pulmonary infiltrates (fig. 2); upper digestive endoscopy/colonoscopy excluded gastrointestinal bleeding; hemolytic parameters were negative; blood and urine cultures were negative, and there were no signs of chronic kidney disease on renal ultrasound, favoring an acute onset.

Considering this rapidly progressive renal failure and diffuse alveolar hemorrhage, a kidney-lung syndrome was considered, and a complete immunological study was performed, while she started hemodialysis, plasmapheresis (7 sessions) and treatment with 3 pulses of methylprednisolone (500 mg/day).

Few days later, immunological study revealed positive (>300 IU/ml) ANCA myeloperoxidase (MPO), without any other relevant findings. Thyroid function tests were within the normal range.

As the patient was medicated with PTU for several years and this drug is associated with ANCA associated vasculitis, a causal relationship was suspected with PTU, which was immediately discontinued.

Additionally, she started monthly cyclophosphamide pulses (500 mg), which were continued for 2 months after discharge followed by maintenance azathioprine (75 mg/day) and steroid tapering.

There was a favorable clinical and biochemical evolution, with progressive improvement of dyspnea and no further hemoptysis episodes. She was also able to suspend hemodialysis, maintaining nephrology surveillance. At Endocrinology outpatient clinic, PTU was replaced by methimazole (MMI), 5 mg once daily.

At evaluation 18 months later, we assisted to a stable creatinine improvement (1.87 mg/dL) and progressive decline of proteinuria (0.368-0.416 g/24 h), after corticosteroid and azathioprine withdrawal. She had no pharmacological complications or adverse reactions. ANCAs title remained negative (table 1).

DISCUSSION AND CONCLUSION

The presented case refers to PTU-induced ANCA associated vasculitis with diffuse alveolar hemorrhage and kidney dysfunction as initial manifestation with concomitant anemia, diffuse pulmonary infiltrates and hemoptysis.

Kidney-lung syndromes are serious and even fatal conditions if not promptly diagnosed and treated. They are defined by a combination of diffuse alveolar hemorrhage and glomerulonephritis. Pulmonary-renal syndromes are not a single entity, being caused by a wide variety of diseases such as systemic vasculitis which includes granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Other causes comprise Goodpasture's syndrome, associated with autoantibodies to the alveolar and glomerular basement membrane and systemic lupus erythematosus[4,5].

In patients treated with antithyroid drugs, there is a reported prevalence of ANCA which varies from 4 to 46%. Although ANCA are present with relative frequency in these patients, the prevalence of vasculitis is much lower (0-1.4%)[3,6].

In the case described, the patient was treated with PTU for several years. Given that this drug is associated with ANCA vasculitis, a causal relationship with PTU was established.

PTU is an antithyroid drug of the thioamide group. Adverse side effects include elevated liver enzymes, leukopenia, rash and arthralgia. Rarely, it can be associated with vasculitis, accounting for about 93% of thionamide-induced cases[6,7].

PTU can induce positive ANCA-vasculitis with polyclonal autoantibodies, although the mechanism is not fully understood. The altered state of self-tolerance present in these patients or an interaction between MPO and PTU resulting in an immunogenic compound may be responsible for development of the ANCA[8].

PTU decreases thyroid hormone production by inhibiting the enzyme thyroid peroxidase. The nucleotide and amino acid structures of the latter and MPO approach a similarity of 50%, which could explain an interaction between PTU and the target antigens of ANCA, in particular MPO. Following activation, the neutrophils may release a large quantity of MPO and transform drugs into free radicals, resulting in vessel-wall injury[6,8-10].

Plus, PTU can accumulate in neutrophils, binding to MPO and changing its structure, which may serve as a neoantigen and

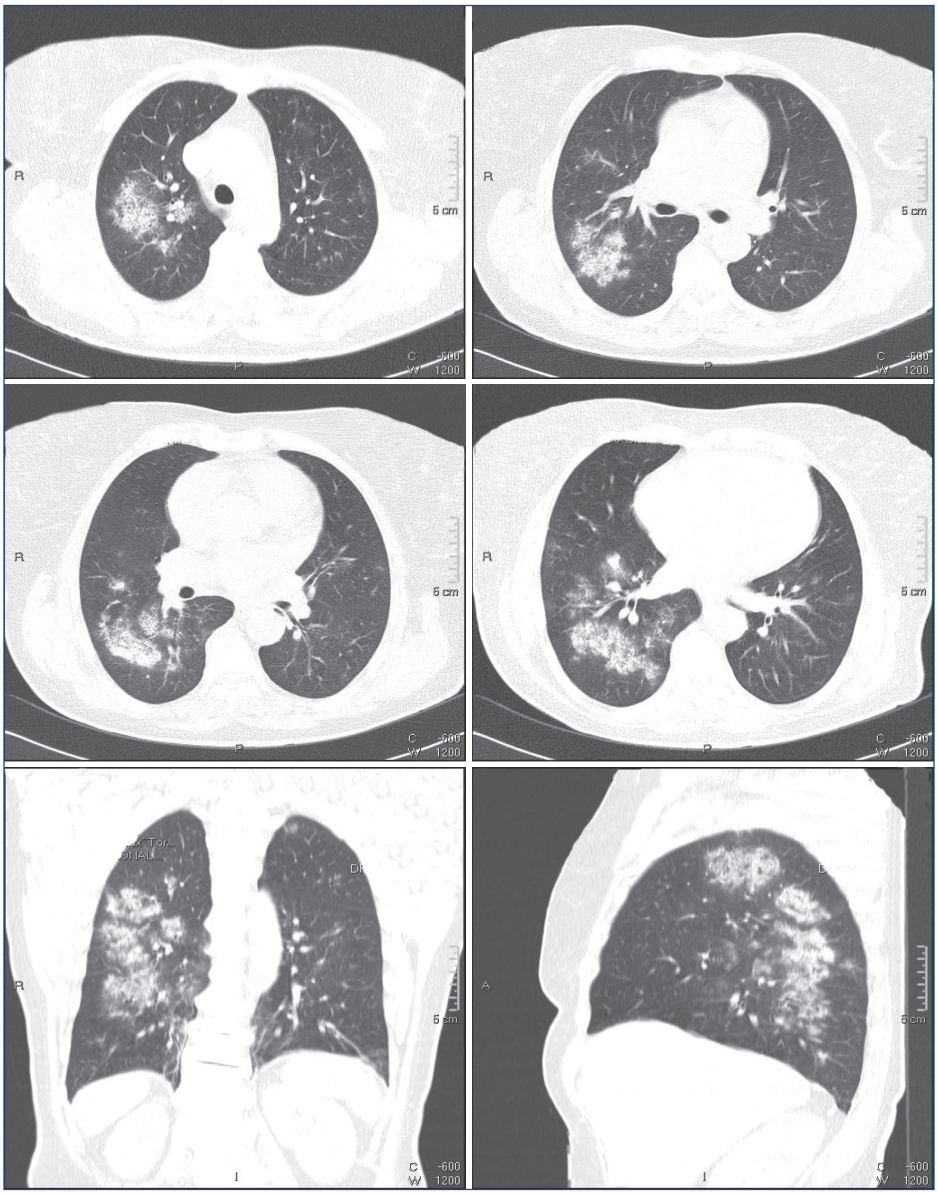

Figure 2. **Thoracic CT showing bilateral multifocal consolidation along the bronchovascular bundle with mild ground-glass opacity, particularly in the right lung; axial (first 4 images), coronal and sagittal planes, respectively.**

trigger formation of autoantibodies. On the other hand, MPO itself might affect the structure of PTU and transform it into immunogenic cytotoxic metabolites, triggering ANCA production[6,8].

Therefore, PTU withdrawal seems to be essential in the treatment of all patients with PTU-induced ANCA associated vasculitis, and it might be also enough for those with non-specific systemic symptoms[2].

Positivity for ANCA does not necessarily predict the onset of symptoms and signs of vasculitis. Similarly, the presence of ANCAs without associated vasculitis indicates that ANCAs alone are not sufficient to induce vasculitis[11-13]. The rising titer level of ANCAs correlates with further risk of disease but does not predict when it will occur[14].

Long-term exposure to PTU was found to be associated with an increased incidence of PTU-induced ANCA associated vasculitis, although there are no clear data on the cumulative threshold dose of PTU that would induce vasculitis[2,6].

About three-quarters of cases have been reported in women, which reflect the higher prevalence of thyroid disease in females. The average age of these patients is 44 years[15].

The most frequent clinical manifestation of vasculitis associated with PTU is renal dysfunction (in 67%) featuring from mild hematuria and proteinuria to rapidly progressive glomerulonephritis. Arthralgia was described in 48% of patients, fever in 37% and skin lesions in 30%. Pulmonary manifestations are less frequent occurring in about 26% of patients and include diffuse

Table 1. Laboratory data

	First presentation	Dx	Discharge	Month 3	Month 6	Month 18	Normal range
Hemoglobin (g/dL)	7.6	6.6	9.3	11.9	12	10.2	11.5-15.5
MCV (fL)	78.3	79	83.7	77	78	80	77-95
Ferritin (mg/dL)	278.5	433	N/A	118	220	225.7	20-300
CRP (mg/L)	35.2	139	<3	<3	<3	<3	<5
Screatinine (mg/dL)	4.35	7.1	3.1	2.7	2.31	1.87	0.6-1.1
ProtU (g/24hours)	1.13	1.5	1	0.9	0.41	0.36	0.03-0.140
Hematuria (RBC/ HPF)	147	25	N/A	0	0	2	0-4
MPO-ANCA (IU/mL)	N/A	>300	N/A	5	5.2	2.4	<15
PR3-ANCA (IU/mL)	N/A	10.6	N/A	Negative	Negative	Negative	<15
TSH (µUI/L)	0.47	N/A	1.22	0.93	1.54	1.09	0.35-4.94
FT4 (ng/dL)	1.29	N/A	1.8	2.6	2.8	2.4	0.52-3.88

ANCA: antineutrophil cytoplasmatic antibodies; CRP: C-reactive protein; Dx: diagnostic; FT4: free thyroxine; HPF: high power field; MCV: mean corpuscular volume; MPO: myeloperoxidase; N/A: not available; PR3: proteinase 3; ProtU: proteinuria; RBC: red blood cells; Screatinine: serum creatinine; TSH: thyroid stimulating hormone.

alveolar hemorrhage, diffuse interstitial pneumonia, bronchiolitis obliterans with organizing pneumonia and adult respiratory distress syndrome[1,2,4,12,14,16].

Disease severity is generally milder and the overall prognosis is better, probably because of cessation of the potential immunogenic stimulus. In patients with organ involvement, the duration of immunosuppressive therapy and whether long-term maintenance therapy is needed is still inconclusive, but might be shorter than that in primary ANCA associated vasculitis[1,2,6].

Treatment recommendations for PTU-induced vasculitis depend on the severity of the disease and should be based on individual assessment. The first measure is the drug withdrawal. In situations of severe vasculitis with diffuse alveolar hemorrhage and kidney failure, as in the case presented, immunosuppressive treatment with systemic corticosteroids at high doses is recommended. There are controversies over whether immunosuppressive agents such as cyclophosphamide should be added to corticosteroids. Considering renal dysfunction and diffuse alveolar hemorrhage, we added plasmapheresis and immunosuppression therapy, as for ANCA associated vasculitis from other causes[1,2,8,11].

Induction therapy should be tapered over several months, although there are no specific guidelines about time and dosage. The precise duration of maintenance therapy thereafter is unclear. In the absence of specific guidelines, the therapy can be extrapolated from other causes of vasculitis with alveolar hemorrhage and renal dysfunction, guided by clinical issues with close monitoring of the patient. Despite of intensive therapy, renal function may not return to normal range[2,3,8,11].

After discontinuation of the offending drug, the use of immunosuppressive therapy and evidence of clinical/biochemical quiescence, ANCA might remain positive for up to several years, so caution is needed when monitoring the disease activity of PTU-induced ANCA associated vasculitis[2,6].

For the treatment of hyperthyroidism, even though PTU and MMI may have possible cross-sensitivity due to structural similarities, there are less reported ANCA associated vasculitis cases related to MMI, with no relapse of vasculitis after switching from one to another[2,6].

Based on reported cases and literature, patients with PTU treatment should be screened for ANCAs positivity before starting

this drug and periodically during follow-up, for early disease detection and consequent prognosis improvement[6].

Referring to our case, diagnostic confirmation of alveolar hemorrhage could have been done by bronchoscopy, although transbronchial biopsies rarely provide a positive diagnosis of pulmonary vasculitis as diagnostic tissue is seldom obtained. Integrating clinical and radiological data of our patient (hemoptysis, hemoglobin decrease and the CT images), pulmonary involvement was assumed, and treatment was initiated with a good response. Additional imaging studies are dictated by the clinical scenario. If the patient did not get better and maintained hemoptysis, bronchoscopy would have been performed.

Regarding kidney biopsy, although it remains the default option for confirming a diagnosis of renal vasculitis and there might be some risk of an incomplete and incorrect diagnosis, it has also several risks. Not performing a kidney biopsy may be considered if there is typical presentation of a renal vasculitis with positive MPO-ANCA. Positive PR3 or MPO-ANCA in a patient with suspected nephritis has a >95% association with histology revealing necrotizing, crescentic glomerulonephritis, usually with few or no immune deposits[17]. In our case, since the patient had a typical presentation of a vasculitis and ulterior MPO positive antibody, we started treatment empirically, including plasmapheresis, which is known to increase the risk of bleeding. Knowing that renal biopsy could have an important role concerning prognosis, after recovery we tried to convince the patient to do the biopsy, but she refused. However, even the most severe subgroups can respond to therapy and maintain dialysis independence and, considering that no biopsy features guide the choice or duration of therapy, we did not insist[17]. Her clinical course until now has been unremarkable, but we did advise her that if she had a relapse, it could be necessary to perform the kidney biopsy.

Even though, this case report highlights the importance of diagnosis suspicion and the establishment of a potential cause of ANCA associated vasculitis, namely PTU, so that it can promptly be stopped. Also, this clinical presentation of a life-threatening kidney-lung syndrome is unusual in PTU associated ANCA vasculitis, justifying the need for treatment with plasmapheresis and immunosuppressive agents, as for ANCA associated vasculitis from other causes.

Disclosure statement

Luísa Pereira, Ana Cabrita, Anabela Guedes, Teresa Jerónimo, André Fragoso, Sandra Sampaio and Pedro Leão Neves have no conflicts of interest to declare.

REFERENCES

1. Bilge NŞY, Kaşifoğlu T, Korkmaz C. PTU-induced ANCA-positive vasculitis: An innocent or a life-threatening adverse effect? Rheumatol Int. 2013;33:117-20.
2. Gao Y, Chen M, Ye H, Yu F, Guo XH, Zhao MH. Long-term outcomes of patients with propylthiouracil-induced anti-neutrophil cytoplasmic auto-antibody-associated vasculitis. Rheumatology. 2008;47:1515-20.
3. Ferreira C, Costa T, Marques AV. Diffuse alveolar haemorrhage secondary to propylthiouracil-induced vasculitis. BMJ Case Rep. 2015;2015:10-3.
4. Nachman PH, Murphy SL. ANCA-associated vasculitis, adult. Glomerulonephritis. 2019;17:333-48.
5. Von Vietinghoff S, Suhling H. Pulmonary renal syndrome. Nephrologe. 2019;14:143-54.
6. Schamp V, Verfaillie C, Bonroy C, Vande Walle J, Raes A, Dehoorne J. Propylthiouracil induced ANCA-associated vasculitis in a 14-year-old girl. Acta Clin Belgica Int J Clin Lab Med. 2015;70:127-9.
7. Nakamori Y, Tominaga T, Inoue Y, Shinohara K. Propylthiouracil (PTU)-induced vasculitis associated with antineutrophil antibody against myeloperoxidase (MPO-ANCA). Intern Med. 2003;42:529-33.
8. Jacobs EMG, Hartkamp A, Kaasjager HAH. PTU-associated cutaneous vasculitis with ANCA anti-MPO and anti-PR3 antibodies. Neth J Med. 2003;61:296-9.
9. Dolman KM, von dem Borne AEGK, Goldschmeding R, Zevenbergen G, Maingay D, Nikkels RE, et al. Vasculitis and antineutrophil cytoplasmic autoantibodies associated with propylthiouracil therapy. Lancet. 1993;342:651-2.
10. Lamt DCC, Lindsay RH. Accumulation of 2-[14c]propylthiouracil in human polymorphonuclear leukocytes. Biochem Pharmacol. 1979;28:2289-96.
11. Pietszkowski NC, De Carvalho GA, De Souza HN, Werka Jr CR, Borazo LA, Graf H, et al. Auto-imunidade ANCA (anticorpo anti-citoplasma de neutrófilos) positiva induzida por propiltiouracil: Relato de caso e revisão da literatura. Arq Bras Endocrinol Metabol. 2007;51:136-41.
12. Vanek C, Samuels MH. Central nervous system vasculitis caused by propylthiouracil therapy: A case report and literature review. Thyroid. 2005;15:80-4.
13. Noh JY, Asari T, Hamada N, Makino F, Ishikawa N, Abe Y, et al. Frequency of appearance of myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) in Graves' disease patients treated with propylthiouracil and the relationship between MPO-ANCA and clinical manifestations. Clin Endocrinol (Oxf). 2001;54:651-4.
14. Choi HK, Merkel PA, Walker AM, Niles JL. Drug-associated antineutrophil cytoplasmic antibody-positive vasculitis: Prevalence among patients with high titers of antimyeloperoxidase antibodies. Arthritis Rheum. 2000;43:405-13.
15. Fujieda M, Hattori M, Kurayama H, Koitabashi Y. Clinical features and outcomes in children with antineutrophil cytoplasmic autoantibody-positive glomerulonephritis associated with propylthiouracil treatment. J Am Soc Nephrol. 2002;13:437-45.
16. Silva SV, Ferreira JP, Carvalho S, Seabra F, Marinho A. Antineutrophil cytoplasmatic antibody positive systemic vasculitis in a patient treated with propylthiouracil. Acta Reumatol Port. 2013;38:302-5.
17. Jayne D. Vasculitis - When can biopsy be avoided? Nephrol Dial Transplant. 2017;32:1454-6.