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FROM THYROID THERAPY TO SYSTEMIC CRISIS: PTU-INDUCED C-ANCA VASCULITIS ACCOMPANIED BY COLD-AGGLUTININ DISEASE AND ORGAN FAILURE

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ABSTRACT

Introduction: Propylthiouracil (PTU) is typically used as first line therapy for hyperthyroidism but is associated with a spectrum of adverse effects including vasculitis, that may lead to acute renal failure and exceptionally to pancreatitis, represents the most severe.

Case description: Here we present the case of a 43-year-old woman with a history of Graves' disease until recently on PTU therapy, who presented with fever and myalgia complicated by cold agglutinin disease, acute renal failure and pancreatitis. Subsequent laboratory studies and thorough physical examination excluding other causes revealed the presence of antibodies against leukocyte proteinase 3. Prompt initiation of immunosuppressive therapy and plasmapheresis led to immediate improvement of the patient's clinical condition and laboratory tests.

Conclusion: Clinicians should maintain a high index of suspicion for autoimmune phenomena in patients receiving PTU even after cessation of the medication. Early recognition, immediate discontinuation of the drug, and timely initiation of immunosuppressive therapy are essential to prevent irreversible organ damage.

KEYWORDS

Propylthiouracil, vasculitis, acute renal failure, c-ANCA, cold agglutinin disease

LEARNING POINTS

- Propylthiouracil is a well described trigger for the development of drug-induced vasculitis, seldom even long after cessation of therapy.
- In patients presenting with multi-organ failure the differential diagnosis should broaden to include systemic autoimmune vasculitis with atypical features.
- The cornerstone of therapy in drug induced autoimmune vasculitis is the immediate withdrawal of the offending agent and initiation of immunosuppressive therapy.

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INTRODUCTION

Propylthiouracil (PTU) is a widely used antithyroid medication, primarily prescribed for the management of Graves' disease. While generally effective, PTU can cause adverse effects ranging from mild, non-specific symptoms such as urticaria, pruritus, fever, arthralgias and myalgias to serious complications including cytopenias, hepatotoxicity and nephrotic syndrome[1].

One of the most significant and potentially life-threatening complications associated with PTU therapy is the development of vasculitis. PTU has been linked to the formation of autoantibodies, particularly with myeloperoxidase (MPO) - anti-neutrophil cytoplasmic antibodies (ANCA), and less frequently with leukocyte proteinase 3 (PR3) – ANCA, which can lead to systemic ANCA associated vasculitis. Clinically, PTU-induced ANCA vasculitis is characterized by constitutional symptoms, arthralgia, leukocytic skin rash, pulmonary involvement, acute kidney injury and positive ANCA-serology[2].

Although PTU intake is not typically linked with the development of cold agglutinin disease (CAD), rare instances have been reported previously[3]. CAD is a form of autoimmune haemolytic anaemia mediated by IgM antibodies that cause red blood cell agglutination in response to cold temperatures, often secondary to infections or lymphoproliferative disorders. It typically presents with symptoms such as fatigue, pallor, jaundice, and haemoglobinuria[4]. Drug-induced CAD is exceedingly rare, and no direct causal relationship with PTU has been established.

We report a rare and complex case of c-ANCA positive vasculitis after PTU therapy complicated with CAD and multisystem organ dysfunction. Early recognition of atypical systemic manifestations in patients receiving antithyroid medications and timely drug withdrawal, along with prompt administration of appropriate therapy is crucial to prevent irreversible organ damage. By emphasizing these uncommon but severe clinical sequelae, this report aims to emphasize that vigilance for atypical systemic presentations in patients undergoing PTU treatment can be lifesaving.



Figure 1. Trends of renal function and inflammation marker (C-reactive protein) before and after therapy. Abbreviations: CREAT, creatinine; CRP, C-reactive protein.

CASE DESCRIPTION

A 43-year-old woman with a history of Graves' disease that had been treated with PTU for several years, which she discontinued 1 month prior to presentation, was admitted to hospital with myalgia, malaise, and acute-onset epigastric pain accompanied by nausea. On examination, she was febrile but hemodynamically stable, with livedo reticularis observed on the lower extremities.

Initial laboratory investigations revealed low-grade anaemia with increased mean corpuscular volume and a decreased red blood cell count suggestive of CAD. The direct Coombs test was positive for C3d, C3b, and IgG. Lactate dehydrogenase was elevated, whereas serum haptoglobin, and reticulocyte count were within normal limits. C-reactive protein was elevated, and urinalysis demonstrated microscopic haematuria with proteinuria. During hospitalization, the patient developed progressive acute kidney injury, worsening inflammatory markers *(Fig. 1)*, declining haemoglobin levels, generalized oedema and progressive development of pleural effusions noted on serial radiographs *(Fig. 2)*.

Further investigations showed elevated serum and urine amylase levels, and contrast-enhanced abdominal computed tomography (CT) scan demonstrated pancreatic oedema with a small peripancreatic fluid collection, without evidence of cholelithiasis, along with bilateral perinephric effusion *(Fig. 3)*. Extensive infectious and autoimmune

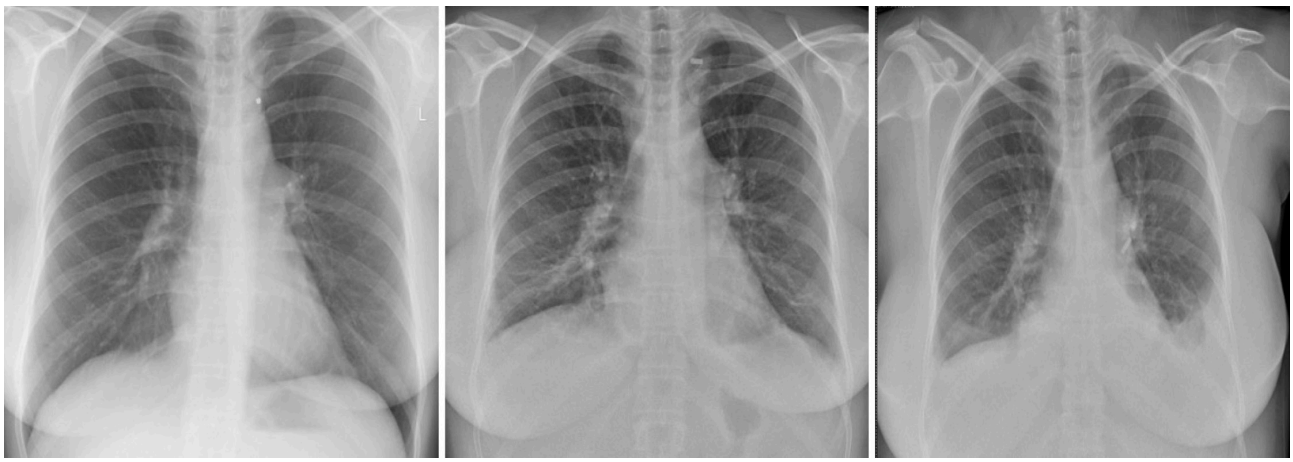


Figure 2. Serial chest X-rays demonstrating the progressive development of pleural effusions.

serologic testing, including antibodies against *Mycoplasma pneumoniae*, hepatitis B virus, Epstein-Barr virus, hepatitis C virus, human immunodeficiency virus, cytomegalovirus, glomerular basement membrane, cryoglobulins, antinuclear antibodies and IgG4 antibodies, was negative. Immunologic workup revealed positive anti-proteinase 3 (PR3) antibodies. The overall constellation of findings was highly suggestive of PTU-induced autoimmune disease, despite the interval since drug discontinuation.

The patient was treated with intravenous methylprednisolone and cyclophosphamide, in addition with three sessions of haemodialysis and seven sessions of plasmapheresis, which resulted in significant clinical and laboratory improvement, with serum creatinine declining to near-baseline values within 2 weeks *(Fig.1)*[2]. Also, the patient was started on sulfamethoxazole-trimethoprim for routine prophylaxis. The long-term exposure to PTU, absence of alternative triggers, and rapid response to immunosuppressive therapy supported the diagnosis of PTU-induced autoimmune disease.



Figure 3. *Abdominal computed tomography scan showing pancreatic edema with a small peripancreatic fluid collection along with bilateral perinephric collections.*

DISCUSSION

Therapy with PTU is a well described trigger for the development of drug-induced vasculitis[5]. PTU-related ANCA-associated vasculitis typically manifests as a systemic inflammatory syndrome with constitutional symptoms and small vessel involvement affecting the skin, kidneys, lungs and occasionally the eyes or nervous system. Renal impairment and pulmonary haemorrhage represent the most serious complications, and obstructive or pruritic skin lesions are commonly described[2,5]. In our patient, although fever and myalgia were present, several typical features, including arthralgia, ocular inflammation, pulmonary haemorrhage, necrotizing cutaneous lesions, and neurological involvement were absent, while cutaneous findings were limited to livedo reticularis.

The underlying pathophysiology involves mechanisms such as neutrophil priming, formation of neutrophil extracellular traps (NETs) and the subsequent development of autoantibodies commonly directed against MPO. In contrast, the development of c-ANCA-associated vasculitis is rarely mediated by drugs and is most often reported in primary vasculitis such as in granulomatosis with polyangiitis[2]. Nevertheless, rare cases of PTU have been already described in the literature, and the present case further supports this underrecognized association[6].

Studies have shown that the duration of PTU use before the development of vasculitis is highly variable, with most cases occurring after prolonged use. However, a clear causal link remains unproven. Long-term PTU exposure may increase the formation of the immunogenic metabolite PTU-sulfonate, which promotes T-cell sensitization and antibody mediated vasculitis[7]. Moreover, PTU can trigger abnormal conformation and impaired degradation of NETs structures resulting in MPO-ANCA generation[8].

While ANCA positivity is relatively common in patients treated with PTU, it does not predict the progression to systematic disease. Balavoine et al.[9] showed that although ANCA seropositivity may occur in up to 20-40% of patients receiving PTU, only a minority develop clinically significant vasculitis. Therefore, routine ANCA screening in asymptomatic patients is not currently recommended and should be reserved for patients who develop suggestive clinical features[9]. Our case supports this approach, as ANCA testing was prompt by evolving systemic manifestations rather than performed for surveillance.

The risk of ANCA formation and occurrence of vasculitis appears significantly higher with PTU compared with other antithyroid drugs. According to a recent prospective study, although ANCA may occasionally develop in patients treated with methimazole, progression to systemic vasculitis is uncommon[10]. Additionally, Balavoine et al. concluded that PTU carries the highest risk among antithyroid agents for clinically significant ANCA-associated vasculitis[9].

Research indicates that antibody titres in ANCA-positive patients can persist for years after discontinuation of the medication, particularly in those with initially higher levels. This fact highlights the importance of ongoing clinical vigilance for the potential development of vasculitis even after PTU-withdrawal as seen in our case[11].

In our case the coexistence of CAD represents a unique immunological phenomenon. Commonly, CAD is caused secondary to *Mycoplasma pneumoniae*, Epstein-Barr virus infection, or lymphoid malignancies[4]. Although drug-related CAD is extremely rare, PTU has previously been implicated, likely through polyclonal B cell activation leading to cold-reactive antibody production via molecular mimicry or immune dysregulation[12]. Immune crosstalk between cold agglutinin disease and ANCA-associated vasculitis may exist rendering early identification and targeted therapy essential.

The diagnosis in this case was challenging, requiring careful integration of clinical, laboratory, and immunologic data. Nowadays, the diagnosis of ANCA-associated vasculitis

relies primarily on ANCA serology, which is a sensitive and widely available tool. Thus, kidney biopsy has shifted to a secondary diagnostic role, primarily preserved for cases with diagnostic uncertainty, negative serology despite high clinical suspicion or to further characterize renal involvement[13].

In our case, serologic evaluation demonstrated c-ANCA positivity consistent with PR3 antibodies, along with evidence of haemolytic anaemia confirmed by a positive direct Coombs test. The progressive renal impairment, supported by rising serum creatine levels, and the presence of abnormal urinary sediment were suggestive of glomerulonephritis. The renal involvement was consistent with pauci-immune vasculitis, the classic pattern seen in ANCA-associated disease. The kidneys are the principal organs mainly affected in both drug-induced and primary vasculitis, and untreated cases may progress to rapidly progressive glomerulonephritis[2].

Although pancreatitis is an uncommon manifestation, abnormal distribution of the pancreatic blood flow due to ANCA-related vasculitis leading to a non-uniform pancreatitis has been reported[14]. In our patient, no alternative etiology for pancreatic oedema was identified, further suggesting vasculitis-related or autoimmune injury.

The cornerstone of therapy in drug induced autoimmune vasculitis is the immediate withdrawal of the offending agent, initiation of high dose corticosteroids, and supportive measures. In severe cases, such as ours, additional immunosuppressive therapy such as rituximab or cyclophosphamide may be necessary to control systemic inflammation. While plasmapheresis is not routinely indicated, limited studies suggest potential benefit in patients with serum creatine levels above 500 µmol/l by reducing circulating autoantibodies and delaying progression to end-stage kidney disease[15]. Over the past two decades, rituximab has emerged as the preferred induction agent, particularly in patients where fertility preservation is critical[2]. Recent studies have demonstrated non-inferiority of rituximab compared to cyclophosphamide as induction agent, with superior outcomes in PR3-ANCA positive patients and those with relapsing disease[16,17].

Survival outcomes in ANCA-associated vasculitis have improved significantly over the past 40-50 years, with 5-year survival rated now approaching 70-80%. Early diagnosis through screening for ANCA and advances in immunosuppressive therapy have played a pivotal role. Monitoring of the serum creatinine level and the presence of haematuria and/or proteinuria in urinalysis, of drug toxicity and early identification of comorbidities are essential for active surveillance of disease activity[2].

The patients need prolonged maintenance therapy with immunosuppressive medications to maintain remission. Thus, the doctors should be aware of the challenges the patients face as they experience not only the burden of the long-term treatment but also the side effects from it. Provisional prophylaxis against *Pneumocystis jirovecii* pneumonia with sulfamethoxazole-trimethoprim, routine vaccinations against influenza and pneumococcal infection, gastrointestinal bleeding prophylaxis and management of cardiovascular events -especially in PR3-ANCA positive patients- is strongly recommended for all patients. Especially in patients receiving cyclophosphamide, such in our case, lifelong surveillance for urothelial malignancies and non-melanoma skin cancers is imperative due to the elevated risk[2].

In the light of these considerations, future management of the underlying hyperthyroidism warrants careful planning. Given the severe systemic autoimmune reaction in this patient, re-exposure to PTU is contraindicated. Although methimazole carries a substantially lower risk of vasculitis, cross reactivity cannot be entirely excluded[10]. In patients who developed severe PTU-induced vasculitis, definitive therapy for Graves' disease – such as radioactive iodine ablation or total thyroidectomy-should be strongly considered to avoid recurrence[9].

In conclusion, PTU is an established treatment for hyperthyroidism but is associated with rare, potentially serious autoimmune complications, including vasculitis that may lead to acute renal failure, and, more exceptionally to CAD and systemic involvement such as pancreatitis. The uniqueness of this case lies in the presence of PR3-ANCA positivity rather than the more common MPO-ANCA subtype, the rare coexistence of cold agglutinin haemolytic anaemia and acute pancreatitis, and the delayed onset of severe disease despite PTU discontinuation 1 month earlier as well as the presence of atypical symptoms.

The coexistence of these autoimmune phenomena underscores the complexity of drug induced immune dysregulation and the diagnostic challenges it poses. Early recognition is crucial, as timely withdrawal of PTU combined with immunosuppressive therapy and/or plasmapheresis can prevent irreversible organ damage. This case contributes to the understanding of the spectrum of PTU-related autoimmune toxicity, reinforcing the need for close monitoring of patients on antithyroid medications, especially when presenting with non-specific systemic symptoms - even after discontinuation of long-term therapy.

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