

## CLINICAL VIGNETTE

# A Case of Propylthiouracil-associated Antineutrophil Cytoplasmic Antibody Development

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### **Abstract**

The development of positive antineutrophilic cytoplasmic antibody (ANCA) titers with associated symptoms is a rare complication of propylthiouracil (PTU) treatment in patients diagnosed with Grave's disease. We discuss the case of a 43-year-old woman who was treated with PTU and subsequently developed arthralgias. P-ANCA and c-ANCA titers were positive. At that time, PTU was discontinued and within 3 months, her symptoms completely resolved. We review the literature on PTU and ANCA development, its presentation, diagnosis and treatment. Our case together with the literature review indicates that in patients treated with PTU who develop new symptoms such as arthralgias, myalgias, ulcers or rashes, testing for ANCA and discontinuing the medication should be considered.

### **Case**

A 43-year-old woman with a twelve-year history of Graves' disease treated intermittently with propylthiouracil (PTU), presented for management of hyperthyroidism. She had been tapered off of PTU several times in the past, the longest period without medication being one year; however, relapses of the hyperthyroid state required re-initiation of PTU treatment. She had most recently restarted PTU at 300mg/day one week prior to presentation. Her review of systems was negative except for a mild upper respiratory tract infection, migraine headaches, fatigue, occasional tremor, and heat intolerance. She denied prior radiation exposure or family history of other endocrine or rheumatologic disorders.

On initial physical exam, the patient was in no apparent distress, with a mild resting tremor. Eye exam did not reveal evidence of exophthalmos. Her thyroid was slightly enlarged without palpable nodules. Lungs were clear to auscultation and cardiac exam revealed no murmurs. Skin was warm and there was no rash. Neurologic exam was unremarkable with normal reflexes and no peripheral edema.

Initial labs revealed a suppressed TSH, as well as elevated free T4 and free T3 (see table). Her thyroid stimulating immunoglobulin was positive at 160% of normal, thyrotropin binding inhibitor immunoglobulin was positive at 49.7%, and thyroperoxidase antibody was detectable at 58.4 IU/ml, all confirming the diagnosis of underlying Graves' disease. The patient was prescribed Propranolol and was continued on PTU 300mg/day.

Over the course of one year, her symptoms improved and thyroid function tests normalized, allowing her to taper the PTU to 50mg/day. However, two years after her initial presentation, her tremors and fatigue returned. Repeat thyroid function studies revealed a suppressed TSH and elevated free thyroxine and propranolol and PTU 150mg/day were resumed. Over the next few months, she began experiencing arthralgias most notably in her knees and shoulders. c-ANCA and p-ANCA were positive, while MPO and prot-3 Ab titers were negative. The ANA titer was borderline positive at 1:40. Subsequently, PTU was discontinued, due to concern that PTU may have contributed to the symptoms and positive serologies. By her next visit, 3 months after discontinuation of PTU, the arthralgias resolved, both ANCA titers decline, and thyroid function studies had normalized.

This case allows for an opportunity to review the literature regarding the development of ANCA in patients treated with PTU.

### **ANCA**

Antineutrophil cytoplasmic antibodies (ANCA) are characterized, via direct immunofluorescence, by either a perinuclear (p-ANCA) or cytoplasmic (c-ANCA) pattern of staining. ANCA target components of neutrophilic granules, namely myeloperoxidase (MPO), which is a target antigen for p-ANCA, and proteinase 3 (PR3), which is a target antigen for c-ANCA<sup>1-3</sup>. Via neutrophil and monocyte activation, ANCA leads to a dysregulated inflammatory process, resulting in tissue damage and

vasculitis<sup>4</sup>. ANCA positive vasculitis is associated with high morbidity and mortality, as well as toxicity from associated immunosuppressive treatments<sup>2</sup>. While c-ANCA is classically associated with conditions such as Wegener's granulomatosis, p-ANCA is seen more often with necrotizing glomerulonephritis and microscopic polyangiitis<sup>1,5,6</sup>. P-ANCA may become positive in a variety of nonvasculitic conditions such as inflammatory bowel disease, autoimmune liver disease, rheumatoid arthritis, cancer, and infection<sup>5</sup>.

### **Propylthiouracil-associated ANCA vasculitis and other factors**

The development of ANCA can be seen in drug-induced vasculitis<sup>7</sup>. A number of drugs have been implicated in the development of ANCA, including hydralazine, sulfasalazine, propylthiouracil (PTU), carbimazole and methimazole. The prevalence of ANCA is significantly higher in patients treated with PTU, compared to those treated with methimazole or carbimazole<sup>8-11</sup>. While the majority of drug-induced ANCA is associated with anti-MPO and p-ANCA, it has also occurred in association with anti-PR3/c-ANCA<sup>2,12,13</sup>.

The literature reports 20 to 40 percent of patients treated with PTU for hyperthyroidism become ANCA positive. Of these patients, nearly one-fifth develop features consistent with vasculitis<sup>5,9,13-16</sup>.

While PTU-induced ANCA-positive vasculitis has occurred in patients with toxic multinodular goiter, it is seen most often in association with underlying Graves' disease<sup>8,11,17</sup>. Having an underlying autoimmune disorder itself, does not appear to render patients more susceptible to the development of ANCA vasculitides, as there is no association between ANCA and Hashimoto's thyroiditis<sup>8</sup>.

Duration of PTU therapy is positively correlated with ANCA development. Most cases have treatment greater than 18 months<sup>11,12,15</sup>, and Ozduman Cin reported ANCA positivity further increased with prolonged PTU therapy<sup>18</sup>. One series revealed an average PTU treatment duration of 37 months prior to development of ANCA and/or clinical symptoms of vasculitis<sup>17</sup>, but it has been reported to occur from a few months to several years of treatment<sup>8,13</sup>. An association between PTU dosage and ANCA development has not been established, although most cases reported treatment with at least 150-300mg/day of PTU, which may or may not have been tapered during the course of treatment<sup>5,19</sup>.

No significant association between age and PTU-induced ANCA has been reported; however, it has been shown to occur more frequently in women, but this finding may be due to a higher prevalence of Graves' disease in women<sup>20,21</sup>.

### **Mechanism of PTU-induced ANCA**

The exact mechanism of PTU-induced ANCA development is unknown. Recently, Nakazawa reported that abnormal conformation and impaired degradation of neutrophil extracellular traps (NETs) induced by PTU are involved in the pathogenesis of PTU-induced MPO ANCA production and MPO ANCA-associated vasculitis. This suggests that disordered NETs can be critically implicated in the pathogenesis of MPO ANCA-associated vasculitis<sup>22</sup>. Negative ANCA titers in patients with hyperthyroidism prior to PTU initiation makes underlying thyroid disease a less likely culprit<sup>11</sup>.

It is postulated that PTU acts as a hapten, binding MPO. PTU has been shown to accumulate in neutrophils and become oxidized by MPO and hydrogen peroxide to the reactive intermediate PTU-sulphonate<sup>23</sup>. This is thought to induce T cell sensitization and polyclonal B cell activation, leading to autoantibody (ANCA) development, ultimately resulting in vascular injury<sup>2,5,8,23,24</sup>. However, unlike PTU, Carbimazole and methimazole have not been shown to accumulate in neutrophils and behave as haptens, which may partly account for the significantly reduced incidence of ANCA in patients treated with carbimazole, compared to PTU<sup>8,9</sup>.

Not all patients who are serum ANCA positive develop immediate clinical manifestations of vasculitis. Many are in remission for a period of time, while others may never develop symptoms despite being ANCA-positive<sup>9,14</sup>. One theory is based on several cases of PTU-induced ANCA vasculitis following recent flu-like illness. Vasculitis may develop only after neutrophils are appropriately primed by a viral or bacterial infection<sup>13</sup>. Another theory for the disparity of ANCA-positivity and clinical symptoms of vasculitis involves the role endothelial cell damage plays in the development of clinical vasculitis. Presence of anti-endothelial cytoplasmic antibody has been significantly associated with development of clinical vasculitis in patients with PTU-induced ANCA.<sup>14</sup>

### **Clinical Presentation**

Many patients with PTU-induced ANCA are asymptomatic. Those that become symptomatic tend to develop only one to a few isolated manifestations of vasculitis. Though much less common, clinical development of entire ANCA-associated syndrome such as Wegener's granulomatosis has been reported<sup>25</sup>.

Besides arthralgias, the most common manifestation are cutaneous, including ulcers, purpura, subcutaneous nodules, and bullae. Sule et al reported cutaneous involvement in PTU-associated vasculitis with different patterns of skin changes<sup>26</sup>. Hematuria and proteinuria secondary to renal dysfunction from biopsy-proven crescentic, membranous, and focal segmental necrotizing glomerulonephritis, have also been reported. The frequency of kidney involvement in PTU-associated ANCA-positive vasculitis is 58-66.7%<sup>27</sup>. More serious complications, such as neurological, diffuse alveolar hemorrhage, pericarditis, serositis, pyoderma gangrenosum, and erythema multiforme have also been reported<sup>2,5,17,19,28-31</sup>.

### **Diagnosis**

The clinical diagnosis of drug-induced disease may be difficult due to the non-specific nature and variability of patients' underlying thyroid diseases. Although PTU-induced ANCA has been shown to occur with either anti-MPO (p-ANCA) or anti-PR3 (ANCA) antibodies, it is more commonly associated with the former<sup>2,5,10,13,17,22,28,32</sup>. The presence of anti-elastase and anti-lactoferrin antibodies, which are tests for ANCA that target other neutrophil antigens, may also be diagnostic, and possibly correlate with disease activity<sup>2,8,9</sup>. As indicated previously, disease activity may be associated with the presence of anti-endothelial cytoplasmic antibodies<sup>14</sup>, however, no significant association between PTU-induced ANCA and ANA titers have been made<sup>2,19</sup>.

Diagnosis of PTU-induced ANCA is also supported by a history of treatment with PTU prior to development of ANCA, possible development of vasculitic symptoms, and decline in ANCA titers or resolution of symptoms on discontinuation of PTU<sup>13,17</sup>.

### **Treatment**

First-line treatment for PTU-induced vasculitis is discontinuation of PTU. In most patients, this is sufficient to allow resolution of symptoms.

Pathologic changes observed with ANCA development, particularly in renal biopsy specimens, have been shown to normalize after discontinuation of PTU.<sup>2,6,8,19,20</sup> Some patients, however, have persistent ANCA titers and symptoms despite discontinuation of PTU<sup>5,17</sup>. Corticosteroids are often used in these cases with resolution of symptoms<sup>19,28</sup>. Severe cases warrant more aggressive therapy, including cyclophosphamide or plasmapheresis<sup>2,28</sup>.

It is reasonable to periodically measure ANCA in patients treated with PTU, particularly those on greater than 18 months treatment. Given a markedly reduced association of ANCA-induced vasculitis with methimazole or carbimazole compared to PTU, greater use of the former drugs for medical treatment of hyperthyroidism may be advocated. Radioablation or surgery should also be considered in patients, as there is limited efficacy in long-term medical treatment with PTU, methimazole, or carbimazole for hyperthyroidism.<sup>11,17,33</sup>

One study found elevated serum levels of MPO-ANCA for more than 5 years after discontinuation of PTU<sup>32</sup>.

### **Conclusion**

This case illustrates the importance of being mindful of the morbidities that can be associated with the initiation of any new medication. Although this patient's symptoms resolved after discontinuation of PTU, some cases required the addition of potent corticosteroids to resolve symptoms<sup>5,17,19</sup>. While PTU associated ANCA positive vasculitis is rare, this complication should be considered when prescribing this medication to patients with Graves' disease.

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