Case Report

Case of propylthiouracil-induced ANCA associated small vessel vasculitis

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Introduction

The aetiology of antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis is unknown, although environmental triggers have been proposed. There are a few published reports of an association between treatment with the antithyroid drug propylthiouracil and the occurrence of ANCA positivity and ANCA-associated vasculitis. We discuss a patient treated with propylthiouracil who developed an ANCA-positive vasculitis with glomerulonephritis and pulmonary haemorrhage.

Case report

In 1993 a previously healthy 30-year-old woman was diagnosed as having autoimmune thyrotoxicosis. She was treated with carbimazole for 5 months, then converted to propylthiouracil as she wished to conceive. In November 1996 she was admitted with a 4-week history of deafness, tinnitus, and general malaise. In the week prior to admission she had developed progressive dyspnoea and frank haemoptysis. On clinical examination she was tachypnoeic, pale and apyrexial. Heart rate was 92/min and blood pressure 110/80 mmHg. On chest auscultation there were bilateral coarse basal crackles to both mid-zones. There were no other abnormal clinical findings.

Investigation results included haemoglobin 4.8 g/dl, white cell count 4.5 x 10⁹/l with a normal differential and platelets 349 x 10¹²/l. Serum urea was 10.7 mmol/l and creatinine 68 μmol/l. Creatinine clearance was reduced at 51 ml/min. Urine analysis showed blood (+ + +) and protein (+ + +) and albuminuria was quantified as 0.008 g/l. Erythrocyte sedimentation rate (ESR) was 51 mm/h and C-reactive protein (CRP) 156 mg/l (normal range < 10). ANCA was positive with a perinuclear pattern at a titre of 1:400 with an anti-myeloperoxidase (anti-MPO) specificity (anti-proteinase 3 [anti-PR3] was not detectable), anti-nuclear antibodies (ANA) were positive at a titre of 1:100. Anti double-stranded DNA (anti-dsDNA) and anti-glomerular basement membrane antibodies were negative. Complement levels were normal. Chest X-ray showed bilateral alveolar shadowing consistent with pulmonary haemorrhage (Figure 1). Corrected gas transfer (KCO) was elevated at 3.67 (173% greater than predicted). An ultrasound scan of the kidneys was normal. Renal biopsy showed focal segmental necrotizing lesions associated with extracapillary proliferation typical of a vasculitic glomerulonephritis (Figure 2). Staining for immunoglobulin and complement components was negative.

She was treated with 6 x 2.5 l plasma exchanges, pulse methyl prednisolone (500 mg/day for 3 days) followed by oral prednisolone (60 mg/day), and oral cyclophosphamide (2 mg/kg/day). Propylthiouracil was discontinued. She made an uncomplicated recovery. Chest X-ray, urinalysis, CRP, and ESR returned to normal. Her KCO is now 55% of the predicted normal. She remains strongly pANCA positive with a titre of 1:400. ANA has become negative.

Fig. 1. Chest X-ray on admission showing bilateral alveolar shadowing consistent with pulmonary haemorrhage.
Hypersensitivity vasculitis associated with propylthiouracil may affect any organ with skin lesions being the most common [11]. Our patient is extremely unusual in that she presented with pulmonary haemorrhage and renal vasculitis. To our knowledge there have only been three other reports of pulmonary haemorrhage associated with propylthiouracil-induced ANCA positive vasculitis [10,12,13], of which only one had renal involvement [10]. Treatment included withdrawal of propylthiouracil in all the patients, one patient also received treatment with corticosteroids [13], both our patients and one reported by D’Cruz [10] received steroids and cyclophosphamide. The patient reported by Romas [12] received no immunosuppressive treatment. All patients (including our own) improved following treatment.

Vasculitis has also been reported with the use of carbimazole and methimazole. D’Cruz [10] reported a patient who, a month after discontinuation of carbimazole, developed a Wegener’s type illness. Treatment included plasma exchange, cyclophosphamide, and prednisolone. Of the three patients reported by Tanemoto, one was receiving both propylthiouracil and methimazole, the causative drug could not be identified and both were discontinued, with resolution of symptoms [6].

At the molecular level, the three different anti-thyroid drugs are all based on a heterocyclic compound containing a thiomide group, yet despite these structural similarities, there does not appear to be any cross sensitivity. In two of the patients reported by Tanemoto, methimazole was substituted for propylthiouracil and vice versa to control the hyperthyroidism without recurrence of the symptoms induced by the other drug [6]. Dolman also substituted methimazole by Dolman et al. in six female patients [1]. These patients developed ANCA against human neutrophil elastase and either proteinase 3 or myeloperoxidase (three patients had all three autoantibodies). All had normal renal function though three had microscopic haematuria but no proteinuria. Two patients had skin biopsies suggesting vasculitis and one had a nasal biopsy suggesting Wegener’s granulomatosis but there was no granuloma. Only one patient was treated with immunosuppressive therapy (cyclophosphamide and prednisolone), the others responded to withdrawal of the propylthiouracil.

There are 14 reports of ANCA associated pauci-immune glomerulonephritis associated with propylthiouracil, of which two occurred in children [2–9] (see Table 1). Three of these patients were treated with prednisolone and cyclophosphamide, not all improved with one of the treated children progressing to end-stage renal failure [4,10]. One was treated with cyclophosphamide alone [2]. Seven patients were treated with prednisolone alone, one deteriorated with a further decline in renal function [6–8]. Two patients showed improvement following discontinuation of their propylthiouracil, neither received immuno-suppressive treatment [6].

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Withdrawal of the propylthiouracil does not always result in a fall in titre or disappearance of circulating ANCA. Our patient has remained ANCA positive seven months after withdrawal of the propylthiouracil at high titre (pANCA 1:400). It is interesting to note that patients with the idiopathic disease who remain ANCA positive are at increased risk of relapse [16,17]. Despite propylthiouracil withdrawal these patients may still be at risk of disease recrudescence and should remain under long term follow-up.

Idiosyncratic reactions associated with propylthiouracil such as agranulocytosis or vasculitis usually occurs within weeks of the start of treatment although reports occurring several years after commencement of treatment are reported. In the patients reported duration of propylthiouracil treatment ranged from 1 week to 84 months.
Table 1. Reported cases of ANCA associated small vessel vasculitis and anti-thyrotoxicosis treatment

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex</th>
<th>Age</th>
<th>Symptoms</th>
<th>Drug</th>
<th>Duration on drug</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kitahari</td>
<td>F</td>
<td>39</td>
<td>Myalgia, fever, scleritis, proteinuria, nasal inflammation</td>
<td>PTU</td>
<td>5 years</td>
<td>C</td>
<td>Resolution on stopping PTU</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td>Arthralgia, malaise, ARF, rash</td>
<td>PTU</td>
<td>2 months</td>
<td>C, P</td>
<td>ESRF</td>
</tr>
<tr>
<td>Vogt</td>
<td>M</td>
<td>11</td>
<td>Arthralgia, fever, Splenomegaly, Impaired renal function</td>
<td>PTU</td>
<td>1 month</td>
<td>C, P</td>
<td>Stopped PTU</td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td>Impaired renal function</td>
<td>PTU</td>
<td>3 years</td>
<td>Reduced dose</td>
<td>Resolution</td>
</tr>
<tr>
<td>Yuasa</td>
<td>M</td>
<td>36</td>
<td>Impaired renal function</td>
<td>PTU</td>
<td>2 years</td>
<td>P</td>
<td>Resolution</td>
</tr>
<tr>
<td>Tanemoto</td>
<td>F</td>
<td>60</td>
<td>Impaired renal function</td>
<td>PTU</td>
<td>3 years</td>
<td>P</td>
<td>Resolution</td>
</tr>
<tr>
<td>M</td>
<td></td>
<td></td>
<td>Impaired renal function</td>
<td>PTU, M</td>
<td>3 years</td>
<td>P</td>
<td>Resolution</td>
</tr>
<tr>
<td>D'Cruz</td>
<td>F</td>
<td>82</td>
<td>Arthralgia, malaise, Proteinuria</td>
<td>PTU</td>
<td>4 years</td>
<td>C, P</td>
<td>Resolution</td>
</tr>
<tr>
<td>M</td>
<td></td>
<td></td>
<td>Dyspnoea, haemoptysis, Arthralgia, malaise</td>
<td>PTU</td>
<td>11 months</td>
<td>C, P</td>
<td>Resolution</td>
</tr>
<tr>
<td>Ito</td>
<td>F</td>
<td>82</td>
<td>Epistaxis, arthralgia, Fever, ARF</td>
<td>PTU</td>
<td>?</td>
<td>Stopped carbim</td>
<td>Resolution</td>
</tr>
<tr>
<td>Kudo</td>
<td>F</td>
<td>52</td>
<td>Scleritis, rash</td>
<td>PTU</td>
<td>?</td>
<td>P</td>
<td>Resolution</td>
</tr>
<tr>
<td>Toda</td>
<td>F</td>
<td>54</td>
<td>Rash, impaired renal function</td>
<td>PTU</td>
<td>84 months</td>
<td>Stopped PTU</td>
<td>Resolution</td>
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<tr>
<td>M</td>
<td></td>
<td></td>
<td>Rash, fever, arthralgia</td>
<td>PTU</td>
<td>4 years</td>
<td>P</td>
<td>Stopped PTU</td>
</tr>
</tbody>
</table>

F, female; M, male; ARF, acute renal failure; PTU, propylthiouracil; carbim, carbimazole; P, prednisolone; C, cyclophosphamide; resolution, resolution of presenting symptoms and improvement in renal function.

Possible pathogenic mechanisms

It has been suggested that myeloperoxidase, which is involved in the formation of reactive metabolites from propylthiouracil, may bind covalently to one of these metabolites [18]. The myeloperoxidase may be modified, forming an immunogenic conjugate with the metabolite acting as a hapten. When studied the ANCA binding site did not involve the propylthiouracil metabolites, though this does not preclude the drug metabolites acting as a hapten. It is possible that the mechanism suggested for the development of ANCA may also occur in idiopathic ANCA associated vasculitis. However many of the patients reported had several ANCA specificities detected (anti-PR3, anti-MPO and anti-leucocyte elastase) which is uncommon in the idiopathic disease and may therefore represent a different pathogenic mechanism for the development of autoantibody [19]. The mechanism behind ANCA development is further complicated by the fact that anti-neutrophil antibodies are not uncommonly seen in patients with Graves’ disease, this may be a result of the similarities between thyroid peroxidase and myeloperoxidase. Development of ANCA may occur with other drugs including hydralazine and penicillamine though their occurrence with these drugs is strongly HLA-DR3 linked [20]. The HLA status of patients developing ANCA associated with propylthiouracil has not been studied.

It is unclear whether the altered state of self tolerance present in these patients contributes to the development of ANCA or whether there is an interaction between myeloperoxidase and propylthiouracil, resulting in an immunogenic compound. At present no good animal model of ANCA associated systemic vasculitis exists. Thyrotoxic cats were treated with propylthiouracil, two of five of these cats developed a lupus like syndrome with ANCA [21]. The development of these antibodies supports the concept that metabolites of propylthiouracil binding to myeloperoxidase are capable of inducing antibody production and that these antibodies were involved in the pathogenesis of the syndrome. Unfortunately, when the experiments were repeated the cats did not develop vasculitis, though this may have been due to a change in diet rendering these cats less susceptible to immune disease.

The association between propylthiouracil and ANCA associated vasculitis is an important, although rare side-effect of this widely used drug. As in our patient, it can cause life-threatening pulmonary-renal syndrome which has a high morbidity and mortality. Occurrence of symptoms of vasculitis should necessitate immediate withdrawal of the drug. The need for treatment with immunosuppressive therapy is less clear, although it is probable that aggressive disease should be treated with immunosuppressive regimes.
References


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