Concomitant Drug- and Infection-Induced Antineutrophil Cytoplasmic Autoantibody (ANCA)-Associated Vasculitis with Multispecific ANCA

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Key Words
Antineutrophil cytoplasmic autoantibodies · Tuberculosis · Propylthiouracil · Drug-induced vasculitis · Bactericidal/permeability-increasing protein

Abstract
Objective: To report the first case of concomitant drug- and infection-induced antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) in a patient treated with propylthiouracil (PTU) and suffering from tuberculosis. Presentation and Intervention: A 28-year-old woman with PTU-treated hyperthyroidism presented with fever, purpura, pulmonary cavitations and ANCA to myeloperoxidase, bactericidal/permeability-increasing protein (BPI), proteinase-3 and elastase. Skin histopathology confirmed vasculitis. However, sputum examination revealed *Mycobacterium tuberculosis*. Remission was achieved after PTU withdrawal and treatment with antituberculosis drugs. Conclusion: Our case confirmed that BPI-ANCA are elevated in active tuberculosis. Multispecific ANCA were helpful for the diagnosis of concomitant PTU- and *M. tuberculosis*-induced AAV.

Introduction
Antineutrophil cytoplasmic antibodies (ANCA) are a group of autoantibodies associated with various diseases. Idiopathic ANCA-associated vasculitides (AAV) include granulomatosis with polyangiitis, microscopic polyangiitis and Churg-Strauss syndrome [1]. Also, ANCA can be detected in drug-induced vasculitides (DIV) and connective tissue diseases. ANCA-associated DIV are most frequently induced by propylthiouracil (PTU) [2]. Furthermore, ANCA are not uncommon among patients with *Mycobacterium tuberculosis* infection and in patients with nontuberculous mycobacterial diseases [3, 4].

We describe a rare case of concomitant drug- and infection-induced AAV in a patient treated with PTU and suffering from pulmonary tuberculosis at the same time.

Case Report
A 28-year-old woman was admitted with cough, fever, weight loss, fatigue and sweats. Her symptoms started 2 months before admission. Treatment with antibiotics was ineffective. Graves' disease was diagnosed at the age of 12 years. Initially, she was treated with methimazole, but after 4 years PTU was introduced. PTU was interrupted and reintroduced several times. PTU dose before admission was 300 mg/day.
On admission, the patient was febrile (39°C), cachectic (BMI 15.4 kg/m²), tachycardic (160/min), with purpuric macules and papules on lower legs (fig. 1a). Auscultation revealed rhonchi in the right lung. Blood analyses showed ESR 98 mm/h; anemia (hemoglobin 96 g/l, RBC 3.61 × 10⁶), leukopenia 2.3 × 10⁹/l with lymphopenia 0.5 × 10⁹/l; high CRP 73 (<5 mg/l) and fibrinogen 5.1 (2–4 g/l). Anti-HIV, anti-HCV antibodies, HBsAg and hemocultures were negative. Thyroxin was 205 (58–140 nmol/l), TSH was low, <0.01 (0.27–4.2 mIU/l). Because of the hypermetabolic state, the PTU dose was increased to 600 mg/day.

Chest radiography revealed fibrothorax on the right side with bilateral nonhomogeneous infiltrates, predominant on the right side (fig. 1b). Computed tomography revealed multiple nodular shadows, predominantly in the right lung, with irregular wall cavities (fig. 1c). Arterial blood gases were normal. Pulmonary function tests revealed restriction: FVC 47%, FEV₁/VC 85%, TLC 62%, with reduced diffusion capacity 38%, KCO 65%. Immunological profile is shown in table 1. Histopathology of a purpuric papule confirmed leukocytoclastic vasculitis. The clinical picture and serological profile were compatible with PTU-induced AAV [5] and PTU was replaced with thiamazole 20 mg/day.

However, the direct sputum analysis revealed acid-fast bacilli. Löwenstein culture confirmed M. tuberculosis. Antituberculous drugs were introduced: isoniazid 300 mg/day (with vitamin B₆) and rifampin 450 mg/day (given for 6 months); together with ethambutol 800 mg/day and pyrazinamide 1,000 mg/day (given for the first 2 months). Two months after the introduction of antituberculosis drugs, the patient’s symptoms disappeared, cutaneous vasculitis resolved. ESR decreased to 62, complete blood count normalized, but computed tomography showed slower regression of infiltrates. Six months after completion of antituberculosis drugs, ANA, aCL and ANCA to all target antigens disappeared, except myeloperoxidase (MPO)-ANCA (table 1). Computed tomography showed persistence of fibrothorax, while pulmonary function tests revealed restrictive syndrome.

**Discussion**

This was a case of concomitant drug- and infection-induced AAV in a patient treated with PTU and suffering from pulmonary tuberculosis at the same time. Systemic symptoms, cough, hemoptysis, dyspnea and nodular infiltrates can be present in both drug-induced AAV and pulmonary tuberculosis as was in this case. There is considerable overlap between clinical/serological profiles in patients with idiopathic, drug- and infection-induced ANCA-associated diseases [3]. ANCA are specific for various proteases such are proteinase 3 (PR3), MPO, elastase, or cationic proteins such as bactericidal/permeability-increasing (BPI) protein [6].

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**Fig. 1.**

a Palpable purpura on the leg.
b Chest X-ray: bilateral nonhomogeneous infiltrates predominant on the right side (arrow).
c Chest CT: multiple nodular shadows, predominant in the right lung, with irregular wall cavities (arrows).
d Strong fluorescence of perinuclear ANCA (indirect immunofluorescence, human neutrophils fixed in ethanol). ×400.
PR3-ANCA has high specificity (99%) for the newly diagnosed granulomatosis with polyangiitis, while MPO-ANCA is present in 70% of patients with microscopic polyangiitis [1].

In contrast to granulomatosis with polyangiitis and microscopic polyangiitis that have monospecific ANCA, our patient had multispecific ANCA, frequently found in patients with DIV and infections [2, 7]. In our patient, not only the long-term use, but also repeated PTU cycles provoked DIV. PTU-induced AAV may be mild or severe with alveolar hemorrhage, respiratory distress syndrome and pulmonary-renal syndrome [5]. Cutaneous lesions are the most frequent manifestations of PTU-induced AAV [8]. They vary from palpable purpura, vesicles and bullae to cutaneous necroses [8]. Our patient had typical clinical (arthralgia, fever, cutaneous vasculitis), laboratory (bicytopenia, low complement) and serological markers (high MPO-ANCA with low PR3-ANCA, elastase-ANCA, ANA and aCL) for PTU-induced AAV. In contrast to idiopathic AAV, hypocomplementemia, found in our patient, is typical for drug- and infection-induced AAV [2]. High MPO-ANCA, present in our patient, are the most specific serological markers for PTU-induced AAV [2, 5]. On the other hand, asymmetric pulmonary infiltrates with cavitations and elevated BPI-ANCA were not typical of PTU-induced AAV [5, 8]. BPI-ANCA are most frequently present in patients with tuberculosis or chronic pulmonary infections, especially with *Pseudomonas aeruginosa* [2, 9].

Bacterial permeability increasing protein has high affinity for lipopolysaccharide present in Gram-negative bacteria and participates in the phagocytosis of microorganisms. Lipopolysaccharide and lipoarabinomannan, a lipid glycoprotein in the cell wall of *M. tuberculosis*, have similar structures [9]. Suppression of antimicrobial function of BPI by BPI-ANCA could impair the elimination of *M. tuberculosis*, sustaining the inflammation. On the other hand, *M. tuberculosis* induces high production of tumor necrosis factor-α, important for expression of several antigens on neutrophils, activation and release of oxygen species [10]. Simultaneous presence of various auto-antibodies suggests that apoptotic blebs on neutrophils could be a source of autoantigens in our ANCA-positive patient with DIV and tuberculosis.

In our patient, both PTU, after 12 years of therapy, and *M. tuberculosis* contributed to the break of tolerance and production of multispecific ANCA. Solely PTU discontinuation, without immunosuppressants, may often result in regression of vasculitis [7]. Our case confirmed previous experience [5, 7] that after PTU withdrawal and disappearance of cutaneous vasculitis, low MPO-ANCA concentrations persist for a long time. Contrary to some findings, we found that BPI-ANCA concentration decreased after initiation of antituberculosis treatment and disappeared after successful recovery from tuberculosis [9].

### Conclusions

This case confirmed that BPI was the target antigen of ANCA in active tuberculosis. ANCA specific to BPI, MPO, PR3 and elastase, associated with ANA, aCL and complement consumption, were helpful markers for the diagnosis of concomitant drug- and infection-induced vasculitis in our patient treated with PTU and suffering from pulmonary tuberculosis at the same time.

### Acknowledgment

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<table>
<thead>
<tr>
<th>Antibodies</th>
<th>At presentation</th>
<th>After 1 year</th>
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<tr>
<td>Perinuclear ANCA (IIF)</td>
<td>1:2,560</td>
<td>1:160</td>
</tr>
<tr>
<td>ANCA (ELISA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPO (&lt;5 U/ml)</td>
<td>&gt;100</td>
<td>10.5</td>
</tr>
<tr>
<td>PR3 (&lt;5 U/ml)</td>
<td>27.6</td>
<td>2.3</td>
</tr>
<tr>
<td>BPI (&lt;10 U/ml)</td>
<td>44.6</td>
<td>9</td>
</tr>
<tr>
<td>Elastase (&lt;10 U/ml)</td>
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<td>2</td>
</tr>
<tr>
<td>ANA (HEp-2 cells)</td>
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<td>Ø</td>
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<tr>
<td>aCL IgG (&lt;10 GPLU/ml)</td>
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<tr>
<td>C3 (0.9–2.1 g/l)</td>
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<tr>
<td>C4 (0.1–0.4 g/l)</td>
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<td>0.11</td>
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Antibodies to cathepsin G, lactoferrin, histone, nucleosome, DNA, and β2-glycoprotein I were negative. IIF = Indirect immunofluorescence.
References


