Propylthiouracil-induced Anti-neutrophil Cytoplasmic Antibodies and Agranulocytosis together with Granulocyte Colony-stimulating Factor Induced Sweet’s Syndrome in a Patient with Graves’ Disease

Celik Ozlem¹, Buyuktas Deram¹, Sevinc Mustafa¹, Tascilar Koray², Demirkesen Cuyan³ and Tasan Ertugrul¹

Abstract

Propylthiouracil (PTU) is an antithyroid drug which is known to cause drug-induced vasculitis. PTU is implicated in 80-90% of cases of anti-neutrophil cytoplasm circulating antibody (ANCA)-associated vasculitis caused by anti-thyroid drugs which induce ANCA production. Sweet’s syndrome is characterized by fever, leucocytosis, neutrophilia and the sudden onset of painful skin lesions. The pathology of the disease is still unclear. Cytokine dysregulation including interleukin-6 and endogenous granulocyte colony-stimulating factor (G-CSF) are thought to play a role in the pathogenesis of Sweet’s syndrome. PTU and G-CSF are known to cause Sweet’s syndrome and other neutrophilic dermatosis. The presence of ANCA can have a diagnostic value in Sweet’s syndrome. Systemic corticosteroids are the first-line therapy for both diseases. Here we report a female patient with Graves’ disease who developed ANCA and Sweet’s syndrome after using PTU and G-CSF.

Key words: granulocyte colony stimulating factor, propylthiouracil, Sweet’s syndrome


Introduction

Propylthiouracil (PTU) is an important treatment option for hyperthyroidism but it has various side effects. It can cause hepatotoxicity, agranulocytosis, pancytopenia, drug rash, systemic and cutaneous vasculitis and neutrophilic dermatosis. PTU is widely known to cause drug-induced vasculitis. It is associated with ANCA-positive systemic vasculitis and induces ANCA production. Anti-neutrophil cytoplasmic antibodies are serological markers for small vessel vasculitis. They are classified into two groups: perinuclear pattern (P-ANCA), cytoplasmic pattern (C-ANCA). Myeloperoxidase (MPO), lactoferrin, human leucocyte elastase are target antigens for P-ANCA. Proteinase 3 (PR3) is the target for C-ANCA (1). G-CSF is a recombinant human growth factor which is widely used in the management of neutropenia in malignancies.

Sweet’s syndrome is an acute febrile neutrophilic dermatosis which is characterized by painful papules, erythematous plaques and nodules, fever, elevated neutrophil count and erythrocyte sedimentation rate, and infiltration of neutrophils into the dermis. Sweet’s syndrome can be classified into five groups: classical or idiopathic Sweet’s syndrome, paraneoplastic, parainflammatory, pregnancy associated, drug-induced Sweet’s syndrome. Infectious and inflammatory diseases, vasculitis, systemic diseases (lupus erythematosus, Behcet syndrome), neoplastic conditions, and reactive erythemas should be considered in differential diagnosis. The diagnostic criteria for drug-induced Sweet syndrome are: (a) acute onset of painful erythematous plaques or nodules, (b) histopathologic evidence of a dense neutrophilic in-
A 43-year-old woman who had thyrotoxicosis symptoms and signs was admitted to our hospital. Thyroid function tests were as follows: TSH: 0.003 m IU/L (0.4-4.2), FT4: 2.38 ng/dL (0.7-1.9). I-131 thyroid uptake was increased [after 2 hours: 34% (normal range: 10±3), after 24 hours: 99m in thyroid scintigraphy. She had been treated with PTU 300 mg daily for Graves’ disease for three weeks. The blood count was normal before the treatment. She suffered from fever, fatigue, and myalgias. She had fever (38°C) and no other abnormalities on physical examination. Her labs revealed pancytopenia (WBC: 1,670/mm³ Hb: 11.8 g/dL Plt: 9.8x10⁴) and a CRP level of 90.5 mg/dL (normal range <5). She had positive P-ANCA and MPO-ANCA (IgG) level was 64.5 EU/mL >25 is positive). PTU treatment was discontinued and oral β-blocker treatment was continued. The hepatic and renal functions and the urine analysis were normal. Blood and urine cultures were obtained and ceftriaxone therapy was initiated. The fever persisted and the treatment was changed to piperacillin tazobactam. A single injection of granulocyte colony-stimulating factor (filgrastim) 48 MU was given for management of the neutropenia. After two days, she developed bilateral erythematous, pruritic, painful, papular lesions on the dorsal hands, ankles, and legs (Fig. 1). Plasma CRP level increased to 216 mg/dL and she developed hematuria, dyspnea, and bilateral pleural effusion. The fever still persisted at 38°C and neutropenem treatment was started. Repeated blood and urine cultures were negative. A skin biopsy of the left ankle showed diffuse neutrophilic dermatosis, and dermal edema (Fig. 2). She was diagnosed with Sweet’s syndrome. Antibiotics were discontinued and treatment with prednisolone was initiated at a dose of 30 mg/day (84 kg, 164 cm, BMI: 31 kg/m²). There was a dramatic improvement in her skin lesions, and symptoms. Repeated urine analysis and chest X-ray were all normal. CRP level decreased to 7 mg/dL (Table 1). After thyroid nodule biopsy (which showed no atypical changes) 15 mCi radioactive iodine therapy was given and she was discharged.

Discussion

PTU is implicated in 80-90% cases of ANCA-associated vasculitis (AAV) caused by anti-thyroid drugs. The prevalence of ANCA in patients who receive PTU varies from 20 to 64% (1). Patients with PTU-induced AAV have a high titer of MPO-ANCA. They present with clinical features like fever, arthralgia, myalgia, weight loss, glomerulonephritis, intraalveolar hemorrhage, sensorineural hearing loss, peri-carditis, pyoderma gangrenosum, central nervous system vasculitis, and cerebral pachyplemomingitis. They also show laboratory abnormalities like anemia, hematuria, prote-inuria, elevated acute phase reactans (1). PTU is known to induce MPO-ANCA in 20-30% of patients with Graves’ disease in whom ANCA development is not otherwise observed (2, 3). Cin at al showed that PTU can induce asymptomatic production of ANCA in patients with Graves’ disease (3). Noh et al (10) analyzed 92 Graves’ patients who had MPO-ANCA associated vasculitis as a side effect to anti-thyroid drugs; 23 were taking methimazole (MMI), 68 were taking PTU. Organs involved were: kidneys, respiratory organs, skin, joints, eyes, muscles, gastrointestinal tract,
brain and nerves, and ears. Ulcers, purpura, and rash were the symptoms associated with skin involvement; dyspnea and hemoptysis were the symptoms associated with respiratory involvement; and hematuria, proteinuria were the signs of kidney involvement. They discussed that MPO-ANCA-associated vasculitis can occur at low doses of antithyroid treatment and it is more common with the use of PTU compared to MMI. They did not find any characteristic time of onset of MPO-ANCA-associated vasculitis (10).

Granulocyte colony-stimulating factor and PTU are known to cause Sweet’s syndrome and other neutrophilic dermatoses (6-9). Sweet’s syndrome can occur in patients with Hashimoto’s thyroiditis and rarely in patients with Graves’ disease (11). Extra-cutaneous manifestations of Sweet’s syndrome can present in the ocular mucosa and mouth, also in the bone, central nervous system, kidneys, intestines, liver, heart, lungs, muscles and spleen. The severity of the associated systemic disease and the presence of extracutaneous manifestations are the markers of prognosis (5). Kemmett et al (12) showed antibodies to neutrophil cytoplasmic antibodies at a serum dilution of at least 1 : 20 in the serum of six of the seven patients which were diagnosed clinically and histologically with Sweet’s syndrome. The presence of circulating neutrophil cytoplasm antibodies can have a diagnostic value in Sweet’s syndrome (12). Systemic corticosteroids are the gold standard for the treatment. Topical and intralesional corticosteroids, oral therapy with potassium iodide or colchicine, indomethacin, clofazimine, dapsoine, cyclosporine, intravenous immunoglobulin, and methotrexate are other therapeutic agents for the management (5, 13).

Cytokine dysregulation including interleukin-6 and endogenous G-CSF are thought to play a role in the pathogenesis of Sweet’s syndrome. Increased levels of G-CSF can explain leucocytosis, neutrophilic dermatosis and skin lesions, while increased levels of IL-6 are thought to be associated with fever and pain (14).

The present patient developed pancytopenia and fever after initiation of PTU. We considered it as an adverse effect of PTU and we used G-CSF to increase the neutrophil count. After the appearance of the skin lesions our first consideration was drug-induced vasculitis. MPO-ANCA (IgG) level was high. Hematuria was thought to indicate kidney involvement, pleural effusion was thought to be a sign of respiratory tract involvement of drug-induced anti-neutrophil-associated vasculitis. But the skin biopsy revealed Sweet’s syndrome. We had no tissue evidence of vasculitis in this patient.

In the present case PTU should have induced ANCA production. These circulating ANCAs upregulated the function of the neutrophils and induced the production of the cytokines (15). That could cause the migration of neutrophils in different tissues. High G-CSF levels by an unknown mechanism are known to trigger leucocytosis and neutrophilic dermatosis. The G-CSF which we gave our patient to manage the neutropenia could have contributed to this process. Cytokine dysregulation including interleukin-6 and endogenous G-CSF are thought to play a role in the pathogenesis of Sweet’s syndrome. It can be a disease of neutrophilic chemotaxis and phagocytosis or a hypersensitivity reaction. In the literature there are some reports on antibodies to neutrophil cytoplasmic antigens as a serologic marker for Sweet’s syndrome. The pathogenesis of both disorders (AAV and Sweet’s syndrome) are similar thus both G-CSF and PTU use may have caused this patient’s condition.

In conclusion PTU use is responsible for both AAV and Sweet’s syndrome and other neutrophilic dermatoses. Clinicians should be aware of these adverse effects of this drug

### Table 1. Clinical Characteristics and Inflammation Index during Follow-up of the Patient

<table>
<thead>
<tr>
<th>Day (after starting PTU)</th>
<th>16&lt;sup&gt;th&lt;/sup&gt; day</th>
<th>21&lt;sup&gt;st&lt;/sup&gt; day</th>
<th>25&lt;sup&gt;th&lt;/sup&gt; day</th>
<th>27&lt;sup&gt;th&lt;/sup&gt; day</th>
<th>30&lt;sup&gt;th&lt;/sup&gt; day</th>
<th>51&lt;sup&gt;st&lt;/sup&gt; day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>Fever</td>
<td>Fatigue</td>
<td>Myalgia</td>
<td>Admission</td>
<td>Neutropenia</td>
<td>Leukopenia</td>
</tr>
<tr>
<td>Treatment</td>
<td>PTU stopped</td>
<td>A single injection of G-CSF</td>
<td>Antibiotics stopped</td>
<td>Antibiotics stopped</td>
<td>Prednisolone started</td>
<td></td>
</tr>
<tr>
<td>Laboratory data</td>
<td>Leucocyte count</td>
<td>1670</td>
<td>1710</td>
<td>5290</td>
<td>5490</td>
<td>6340</td>
</tr>
<tr>
<td></td>
<td>(4130-10300/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Red blood cell</td>
<td>448×10&lt;sup&gt;4&lt;/sup&gt;</td>
<td>378×10&lt;sup&gt;4&lt;/sup&gt;</td>
<td>372×10&lt;sup&gt;4&lt;/sup&gt;</td>
<td>405×10&lt;sup&gt;4&lt;/sup&gt;</td>
<td>398×10&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>C-reactive protein</td>
<td>90.5</td>
<td>143</td>
<td>216</td>
<td>178</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>(0-5 mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
and should discontinue the treatment should symptoms appear. MMI seems to be more reasonable as the antithyroid drug of choice but cross-reaction between both antithyroid agents should be taken into consideration.

The authors state that they have no Conflict of Interest (COI).

References

© 2011 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html