Anti-Thyroid Drug-Induced ANCA-Associated Vasculitis: A Case Report and Review of the Literature

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Abstract. We report a case of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis induced by propylthiouracil (PTU), and review the literature concerning to anti-thyroid drug-induced ANCA-associated vasculitis.

A 45-year-old man treated with PTU developed fever and arthralgia without pulmonary, skin or eye involvement. These symptoms persisted for a long period without specific symptom, sign or laboratory data of other arthritis. Laboratory findings of urine and blood were normal, except for positive MPO-ANCA (191EU) and PR3-ANCA (37EU) findings. After PTU was discontinued without steroids or immune modulating drugs, both symptoms disappeared. Our patient had a high titer of MPO-ANCA. Moreover, titers of ANCA fell in correlation with the course of symptoms after the cessation of PTU, and we diagnosed PTU-induced ANCA-associated vasculitis. Most patients with pulmonary renal syndrome receive anti-thyroid drugs over a prolonged period, but the duration of our case was shorter than those of these patients. It is suggested that our patient was diagnosed at an early stage of ANCA-associated vasculitis before the start of pulmonary or renal involvement.

Key words: Anti-thyroid drug, PTU, ANCA, Vasculitis

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sham) and less than 0.1 pIU/ml (Axsym TSH Dainapack, Abbott Laboratories, USA), respectively. Serum TSH receptor-antibody was positive (40.0%). On 99 mTc-thyroid scintigram, diffuse and high uptake in the thyroid gland was noted. Therefore, he was diagnosed with Graves’ disease. We did not measure MPO-ANCA or ANA before treatment with anti-thyroid drug. As he had itching caused by thiamazole, PTU was started in March 1998. While he was in the euthyroid state using 150 mg (3 tablets)/day of PTU in February 1999, general arthralgia, especially in both shoulders and knees, and low grade fever appeared. There was no respiratory, intestinal or urinary infection suggesting reactive arthritis. There was no specific symptom or sign of rheumatic diseases, and LE cell, immune complex, rheumatoid factor, anti-dsDNA or anti-ssDNA antibodies (Mesacup DNA-II ds or ss test, Medical and Biological Laboratories (MBL), Japan) were negative, although ANA (Fluoro HEPANA test, MBL) was positive (20 ×, diffuse type). Degree and distribution of arthralgia and degree of fever gradually progressed over more than 2 months without pulmonary, skin or eye involvement. Laboratory findings of urine and blood were normal, except for positive MPO-ANCA (191EU; NephroScholar MPO-ANC, Nissho Co., Japan) and PR3-ANCA findings (37EU; NephroScholar C-ANC, Euro-Diagnostica AB Co., Sweden). After PTU was discontinued without steroid or immune modulation drugs, both symptoms disappeared, following which serum levels of PR3-ANCA normalized rapidly, and those of MPO-ANCA decreased.

Discussion

Characteristic findings of anti-thyroid drug-induced ANCA-associated vasculitis are that 1) most patients were resistant to drug (mainly PTU) treatment of Graves’ disease [4-22]. They had received high doses of PTU (mean = about 5 tablets/day) usually over a prolonged period (mean = about 4 years) from the start of anti-thyroid drug until the onset of ANCA-associated vasculitis. 2) Most patients had high titers of MPO-ANCA (mean = about 250 EU/ml, two thirds of patients had more than 100 EU/ml). Moreover, clinical symptoms disappeared according to decreasing values of MPO-ANCA. Although there have been several reported ANCA-positive patients treated with anti-thyroid drug without clinical manifestations of vasculitis, their titers of MPO-ANCA were lower than those in most patients with vasculitis. Therefore, a high threshold titer of MPO-ANCA may be necessary to induce vasculitis, especially pulmonary renal syndrome, in most cases. 3) Positivity for anti-thyroid peroxidase (TPO) and anti-thyroglobulin antibodies was similar to that in untreated Graves’ patients. However, the incidence (about half of patients) and titers (20-2560 fold) of ANA were higher than those of untreated patients with Graves’ disease [23]. Moreover, ANA disappeared in some cases after the cessation of drug and treatment of vasculitis [5, 18]. 4) Comparison between Japanese cases and others showed a similar gender distribution, age at onset, anti-thyroid drug used, mean duration, drug dose, and pathological findings, treatment and prognosis of ANCA-associated vasculitis. The reason why anti-thyroid drug-induced ANCA-associated vasculitis mainly occurs in Japanese remains unclear. However, it may be that most patients with resistance to drug treatment in Japan hesitate to receive radioisotope therapy or thyroidec- tomy and have taken high doses of drugs over longer periods compared to those of patients in other countries. 5) Although prognosis was better than that of idiopathic ANCA-associated vasculitis, many patients had renal and/or pulmonary symptoms and received therapy with steroids and/or immunosuppressive drugs.

Arthralgia and fever are the most common involvements of anti-thyroid drug-induced ANCA-associated vasculitis. Our case had these symptoms for a long period without specific symptom, sign or laboratory data of other arthritis. Dolman et al. [14] reported mild cases of PTU-induced ANCA-associated vasculitis like ours. Many reports revealed that pathological findings of vasculitis were related to ANCA, and MPO-ANCA is thought to be a specific marker of anti-thyroid drug-induced ANCA-associated vasculitis. Our patient also had high titer of MPO-ANCA and PR3-ANCA, and titers of ANCA decreased in correlation with the course of symptoms after the cessation of PTU. Although we did not obtain pathological findings as the patient did not have renal, pulmonary or skin involvement for biopsy, we diagnosed that he was PTU-induced AN-
CA-associated vasculitis. Most cases of pulmonary renal syndrome had anti-thyroid drugs over a long period (usually several years). Some cases only demonstrated fever and/or arthralgia for a prolonged period before onset of pulmonary renal syndrome. The interval in our case was shorter than those in most patients. It is suggested that our case was diagnosed at an early stage of ANCA-associated vasculitis before the onset of pulmonary or renal involvement.

Although it was reported that aspecific (atypical) ANCA were detected by immunofluorescence in some patients with Graves' disease [24, 25], MPO-ANCA assessed by ELISA may not appear in untreated patients with Graves' disease [14, 24, 25]. There may be a specific reason why the anti-thyroid drug itself, especially PTU, can induce MPO-ANCA and ANCA-associated vasculitis. It was previously reported that PTU accumulates in neutrophils and binds to MPO [26, 27]. Lee et al. [27] reported that repeated administration of PTU altered the MPO structure surrounding the heme iron. It is suggested that changing the configuration of MPO may induce the antigenicity.

In summary, we reported a case of ANCA-associated vasculitis induced by PTU, and reviewed the literature. Anti-thyroid drug-induced ANCA-associated vasculitis usually happens to Graves' patients with resistance to drug treatment (mainly PTU, receiving high doses over a prolonged period) and with high titters of MPO-ANCA and ANA.

References


