Crescentic Glomerulonephritis Associated with MPO-ANCA during Propylthiouracil Treatment: a Case report and Literatures Review

Nirut Suwan, M.D.*

Abstract: ANCA-related crescentic glomerulonephritis is an uncommon illness. It has become evident that ANCA, predominant of the p-ANCA type, can be detected in patients association with anti-thyroid (Propylthiouracil) therapy for Graves' disease. I described a case of crescentic glomerulonephritis and pulmonary hemorrhage associated with myeloperoxidase-antineurophil cytoplasmic antibodies (MPO-ANCA) during propylthiouracil (PTU) treatment. Although the serum creatinine level gradually decreased after cessation of PTU and immunosuppressive treatment, irreversible renal dysfunction persisted. Because of the widespread use of anti-thyroid medication, patients treated with PTU should be placed under vigilant observation by monitoring their urinalysis and serum creatinine level.

บทคัดย่อ ภาวะไตอักเสบชนิด Crescentic Glomerulonephritis ที่สัมพันธ์กับ MPO-ANCA ระหว่างการรักษาด้วยยาต้านไทรอยด์ Propylthiouracil: รายงานผู้ป่วย 1 รายและทบทวนวารสาร

นิรุธ สุวรรณ, พ.บ
กลุ่มงานอายุรกรรม โรงพยาบาลมหาราชนครราชสีมา นครราชสีมา 30000

เวชสารโรงพยาบาลมหาราชนครราชสีมา 2550; 31: 47-53.

ภาวะไตอักเสบชนิด Crescentic Glomerulonephritis ที่สัมพันธ์กับ MPO-ANCA เป็นภาวะที่พบได้น้อย และชนิด p-ANCA อาจมีความสัมพันธ์กับยาที่ใช้ในการรักษาภาวะไทรอยด์เป็นพิษ (Propylthiouracil) บทความนี้เป็นการนำเสนอผู้ป่วยที่ระหว่างได้รับยาเพื่อรักษาภาวะไทรอยด์เป็นพิษและเกิดภาวะไตวายชนิดรุนแรงร่วมกับภาวะเลือดออกในเนื้อปอดโดยมีผลการตรวจเลือดพบ myeloperoxidase-antineurophil cytoplasmic antibodies (MPO-ANCA) อย่างไรก็ตามแม้ว่าผลการตรวจระดับของซีรั่มครีเอตินินจะลดลงหลังจากหยุดยา Propylthiouracil ร่วมกับการให้ยากดภูมิคุ้มกันผู้ป่วยยังคงมีการดำเนินโรคเป็นภาวะไตวายเรื้อรังในที่สุด เนื่องจากยาเพื่อรักษาภาวะไทรอยด์เป็นพิษมีการใช้กันอย่างแพร่หลายผู้ป่วยที่ได้รับยาดังกล่าวจึงควรได้รับการตรวจปัสสาวะและซีรั่มครีเอตินินเพื่อการเฝ้าระวังภาวะดังกล่าว

* Renal Division, Department of Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima 30000

Introduction

Graves' disease is a common form of autoimmune thyroiditis which has been successfully treated with anti-thyroid drugs for more than a century. However these drugs may cause major complications including agranulocytosis, hepatotoxicity and immunological disturbances such as secondary systemic vasculitis[1]. Systemic vasculitides are a group of diseases characterized by inflammation and fibrinoid necrosis of the blood vessel wall. Antineutrophil cytoplasmic antibodies (ANCAs) are impotant serological diagnostic markers for such primary systemic small vasculitic disorders such as Wegener granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome. Pauci-immune necrotizing crescentic glomerulonephritis is the typical renal lesion. Furthermore, ANCA also can be detected in patients with a number of other vasculitic diseases, including drug-induced systemic vasculitis[2].

Anti-myeloperoxidase antineutrophil anticytoplasmic antibody (MPO-ANCA)-mediated crescentic glomerulonephritis in association with anti-thyroid therapy was firstly described in 1994[3]. Propylthiouracil (PTU)-associated ANCA-positive vasculitis has been received much attention, yet the kidney and lung are the organs commonly affected[4]. However, renal involvement of patients with PTU-associated ANCA-positive vasculitis has not yet been well characterized. Thus in this case report, I described a case of pulmonary hemorrhage and crescentic glomerulonephritis associated with MPO-ANCA during PTU treatment.

Case Report

A 28-year-old woman was admitted because of dyspnea and hemoptysis.

The patient had been well until 3 months before admission, she had significant weight lost, palpitation, excessive sweating and fatigue for several weeks. A diagnosis of hyperthyroidism was made on the basis of abnormal thyroid function test. PTU was given and her symptoms were resolved. A few weeks later, polyarthralgia developed the patient came to this hospital while she was taking 300 mg of PTU daily.

At the arthritis clinic one week before admission, examination showed slightly swelling of proximal interphalangeal joints of both hands and right elbow. Treatment with ibuprofen (400 mg three times a day) was begun. Three days later she returned to the hospital because of dyspnea, generalized edema, and hematemesis. She had no history suggesting autoimmune disease or drugs allergy.

On physical examination she was afebrile, the pulse was 120 beats per minite, the respiratory rate was 30 beats per minite and the blood pressure was 190/110 mm Hg. There was no rash or oculopathy but generalized non-pitting edema of both legs. The weight of the thyroid gland was estimated to be 60 gm and no bruit. There were gereralized wheezes in both lungs. Examination of the joints and neurological manifestation revealed no abnormalities.

Haematology revealed a normochromic, normocytic anemia with haemoglobin of 8.4 g/dL, white cell count of 13.4 x 10^9/L and neutrophilia, platelet count of 147 x 10^9/L and erythrocyte sedimentation rate of 30 mm/h. Liver function test including alkaline phosphatase and alanine transferase were slightly increase. Plasma albumin was 2.7 g/dL. Measurement of complement showed normal both C3 and C4 level. Selorogical investigations show no hepatitis C and hepatitis B

infection and ANA was negative.

Radiography of chest revealed bilaterally diffuse alveolar infiltration with suggested diffuse alveolar hemorrhage (DASH) interpreted by pulmonologist. Urinary analysis showed blood 3+ with red blood cell cast and protein 3+ without eosinophiluria was detected. Blood test showed severe renal insufficiency with blood urea nitrogen of 104 mg/dL and creatinine of 12.2 mg/dL.

An initial diagnosis of systemic vasculitis was made and because of the temporal relation of symptoms to the commencement of PTU, this drug was stopped.

A test for ANCA was positive, with a perinuclear pattern of staining (p-ANCA); the titer of anti-myeloperoxidase antibody was 1:600.

The ultrasonography of both kidneys revealed normal size of both kidneys and slightly increased renal parenchymal echoes of both kidneys was observed. Despite intensive therapy with immunosuppressive agents, discontinuation of PTU, and gradually decreased serum creetnien level, irreversible renal dysfunction persisted.

Renal biopsy result

Renal biopsy revealed features of fibrocellular, crescentic glomerulonephritis in seven of nine glomeruli. The other two glomeruli exhibited global sclerotic changes. In addition, there were severe chronic tuberointerstitial alterations with diffuse interstitial fibrosis and tubular atrophy but no arterial lesions. Direct immunofluorescence showed no evidence of significant immunoglobulin or complement deposition. Electron microscopy confirmed the absence of immune complex deposited.

In view of the severity of the alveolar hemorrhage and renal involvement, the patient was commenced on pulse-methylprednisolone and oral cyclophosphamide 100 mg daily. The patient became more unwell with progressive nausea, anorexia. Because of severely impaired renal function, hemodialysis was initiated. The alveolar hemorrhage improved after cessation of PTU and immunosuppressive treatment. Unfortunately, she remained dialysis-dependent 6 months after diagnosis.

Discussion

This report documents the occurrence of severe alveolar hemorrhage and severe ANCA-related crescentic glomerulonephritis supposed to be secondary to PTU therapy.

The detection of ANCAs was firstly reported 30 years ago in patients with segmental necrotizing glomerulonephritis[5] and shortly afterward in patients with systemic vasculitis[6]. With the use of indirect immunofluorescence techniques and ethanol-fixation neutrophils, two major patterns of staining were identified: a diffuse, granular, cytoplasmic pattern (c-ANCA) which has been found to be a specific marker for Wegener' granulomatosis[7] and the p-ANCA pattern, seen in patients with necrotizing glomerulonephritis and microscopic polyangiitis[8]. The major target antigen for c-ANCA has been identified as proteinase 3; for p-ANCA, it is myloperoxidase[9].

It has become evident that ANCA, predominant of the p-ANCA type, can be detected in patients with a wide range of non-vasculitic conditions, including inflammatory bowel disease, autoimmune liver disease, rheumatoid arthritis, cancer and certain infections[10]. The antibodies in these disorders are almost always directed

against neutrophil constituents other than proteinase 3 or myeloperoxidase[11]. Thus all serum samples that are positive for ANCA on direct immunofluorescence studies should be further characterized with the use of an antigen specific assay such as the enzyme-linked immunosorbent assay.

The main ANCA-positive disorders are the vasculitides, a heterogeneous group of clinical syndromes characterized by the inflammation and destruction of blood vessels[12]. These conditions can be broadly grouped on the basis of the predominant types of vessel affected. Involvement of the large vessels may be due to giant-cell arteritis or Takayasu's arteritis. Giant-cell arteritis occurs in patients older than 50 years of age and typically affects the extracranial arteries of the head and neck[13]. Takayasu's arteritis is usually seen in women younger than 40 years of age and mainly affects the proximal aorta and its branches[14]. Since either of these condition would have resulted in the loss of distal arterial pulses, her disorder was not presumed to be due to these conditions because her pulses were still intact. In addition, in patients with these disorders, the ANCA test is negative.

Polyarteritis nodosa is a vasculitis of the medium-sized vessels that may affect any organ; the skin, joints, peripheral nerves, bowel and kidneys which are most commonly involved. Some patients have positive tests for hepatitis B surface antigen but the test for ANCA is usually negative[12].

Small-vessel vasculitides consist of Wegener's granulo-matosis, Churg-Strauss syndrome, microscopic polyangiitis, Henoch-Schönlein purpura, essential cryoglobulinemic vasculitis and cutaneous leukocy-toclastic vasculitis. Wegener's granulomatosis is characterized by involvement of the upper and lower respiratory tracts along with renal disease which is generally a glomerulonephritis[15]. Disease that is more widespread can involve the skin, peripheral nerves, joints and heart. In this patient, joint pain, skin ulcers, renal findings and episode of pericarditis are consistent with this diagnosis. In addition, the ANCA test is positive in 70 to 90 percent of patients with active Wegener's granulomatosis; four-fifths of them have a c-ANCA pattern, with antibodies to proteinase 3, whereas the remainder have a p-ANCA pattern, with antibodies to myeloperoxidase[16, 17]. However, two of the features of this case unremarkable chest radiograph and her mild asthma, are not consistent with this diagnosis. Asthma is commonly seen in patients with the Churg–Strauss syndrome, as transient pulmonary infiltrates, disease of the upper respiratory tract, a history of atopy, and peripheral nerve involvement[18, 19]. Most patients with Churg-Strauss syndrome have a positive test for p-ANCA[20]. The hallmark laboratory feature is intense peripheral eosinophilia with infiltration of the involved tissues. The absence of most of these clinical features in this case leads me to rule out Churg-Strauss syndrome.

Henoch-Schönlein purpura is the most common systemic vasculitis in children although it is also seen in adults[21]. Purpura, arthralgias, and colicky abdominal pain are the most frequent manifestations; approximately half the patients have hematuria and proteinuria. Pathological specimens are characterized by vascular deposition of IgA-dominant immune complexes with an associated vasculitis; ANCA are not present. By definition, cutaneous leukocytoclastic vasculitis is confined to the skin[2]. Histologically, the lesions resemble those that occur in systemic small-vessel vasculitis and

the ANCA test is generally negative. I shall also excluded essential cryoglobulinemic vasculitis since cryoglobulins were not detected in this patient.

Microscopic polyangiitis is a systemic small-vessel vasculitis that is primarily associated with a pauci-immune necrotizing (and sometimes crescentic) glomerulonephritis, pulmonary capillaritis, cutaneous lesions and arthralgias[22, 23]. The renal and pulmonary findings can differentiate it from classic polyarteritis nodosa[23]: in contrast to the latter disease which is usually ANCA-negative, microscopic polyangiitis is strongly associated with a p-ANCA pattern of staining, specifically for antibodies to myeloperoxidase[22].

The cause of vasculitis is hardly discerned. There are some exceptions ie., polyarteritis nodosa from hepatitis B surface antigen and small vessel vasculitis from circulating cryoglobulins, hepatitis C antigen, or some drugs (such as penicillins, sulfonamides, hydralazine or PTU)[24]. In particular, hydralazine and PTU appear to cause vasculitis by inducing the development of ANCA.

In approximate 20 percent of patients treated with PTU, the ANCA test becomes positive during the course of therapy and in a small percentage of these patients, features of vasculitis develop[25, 26]. More than half of these have been described[27, 28], in patients with Graves' disease. In descending order of frequency, the clinical feature include arthralgia, skin lesions, hematuria or proteinuria, fever, alveolar hemorrhage and serositis. Examination of renal biopsy has most commonly revealed pauci-immune necrotizing or crescentic glomerulonephritis[27].

A previous study at the hospital showed that patients with ANCA-positive vasculitis associated with drugs, especially hydralazine and PTU, often had very high titer of antimyeloperoxidase antibodies, as did my case[28]. After the discontinuation of PTU, two of the patients were treated with systemic glucocorticoids and one received cyclo-phosphamide therapy[24].

The mechanism of PTU-induced, ANCA-positive vasculitis is unknown. Some authors have speculated that myeloperoxidase released from activated neutrophils convertes PTU into cytotoxic or immunogenic products[29-31].

How can the diagnosis of a drug-induced, ANCA-positive vasculitis be confirmed? In addition to a test for antibodies to myeloperoxidase, test for other ANCA that target neutrophil antigens, such as elastase or lactoferin, may be helpful.

In the current case because of clinically rapid progressive glomerulonephritis, a renal biopsy, a more invasive procedure, should be considered and the cause of severe crescentic glomerulonephritis in our patient is presumably due to PTU-related vasculitis.

An ANCA-positive vasculitis associated with PTU is increasingly recognized. It has recently been identified that the patients taking anti-thyroid medication have a higher prevalence of circulating ANCA and it has been proposed that there may be some merit in testing for the present of ANCA in patients on such medication. And treatment will be held if ANCA is present in order to prevent the future development of vasculitic complications[34].

In summary, I report the case of a 28-year-old woman who developed a florid diffuse alveolar hemorrhage and severe ANCA related vasculitis, rapid progressive glomerulonephritis secondary shortly after commencing treatment with PTU. Because of the

temporal relationship with the commencement of PTU and the presence of ANCA, it is proposed that the alveolar hemorrhage and ANCA- related glomerulonephritis were caused by acute drug reaction. This response used to be reported previously. Because of the widespread use of anti-thyroid medication, it is an important potential side effect.

Therefore, hyperthyroidism patients treated with PTU should be placed under vigilant observation by monitoring their urinalysis and serum creatinine level.

References

1. Cooper DS. Drug Therapy: Antithyroid Drugs. N Engl J Med 2005; 352: 905-17.
2. Jennette JC, Falk RJ. Small vessel vasculitis. N Engl J Med 1997; 337: 1512-23.
3. Vogt BA, Youngi K, Jennette JC, Falk RJ, Burke BA. Sinaiko A. Anti-neutrophil cytoplasmic autoantibody-positive cresentic glomerulonephritis as a complication of treatment with propylthiouracil in children. J Pediatr 1994; 124: 986-8.
4. Dolman KM, Gans ROB, Vervaat TJ, Zevenbergen G, Maingay D, Kikkels RE, et al. Vasculitis and antineutrophil cytoplasmic autoantibodies associated with propylthiouracil therapy. Lancet 1993; 342: 651-2.
5. Davies DJ, Moran JE, Niall JF, Ryan GB. Segmental necrotising glomerulonephritis with antineutrophil antibody: possible arbovirus aetiology? Br Med J 1982; 285: 606.
6. Hall JB, Wadham BM, Wood CJ, Ashton V, Adam WR. Vasculitis and glomerulonephritis: a subgroup with an antineutrophil cytoplasmic antibody. Aust N Z J Med 1984; 14: 277-8.
7. Van der Woude, FJ, Rasmussen N, Lobatto S, Wiik A, Permin H, Van Es, et al. Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. Lancet 1985; 1: 425-9.
8. Falk RJ, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. N Engl J Med 1988; 318: 1651-7.
9. Hoffman GS, Specks U. Antineutrophil cytoplasmic antibodies. Arthritis Rheum 1998; 41: 1521-37.
10. Franssen CFM, Stegeman CA, Kallenberg CGM, Gans ROB, de Jong PE, Hoorntje SJ, et al. Antiproteinase 3- and antimyeloperoxidase-associated vasculitis. Kidney Int 2000; 57: 2195-206.
11. Gross WL, Schmitt WH, Csernok E. ANCA and associated diseases: immunodiagnostic and pathogenetic aspects. Clin Exp Immunol 1993; 91: 1-12.
12. Jennette JC, Falk RJ. Small-vessel vasculitis. N Engl J Med 1997; 337: 1512-23.
13. Lie JT. Aortic and extracranial large vessel giant cell arteritis: a review of 72 cases with histopathologic documentation. Semin Arthritis Rheum 1995; 24: 422-31.
14. Gail SK, Claire WH, Joseph G, Randi YL, Anthony SF, Menachem R, et al. Ann Intern Med 1994; 120: 919-29.
15. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener's granulomatosis: an analysis of 158 patients. Ann Intern Med 1992; 116: 488-98.
16. Hoffman GS, Specks U. Antineutrophil cytoplasmic antibodies. Arthritis Rheum 1998; 41: 1521-37.
17. Niles JL, Pan GL, Collins AB, Shannon T, Skates S, Fienberg R, et al. Antigen-specific radioimmunoassays for anti-neutrophil cytoplasmic antibodies in the diagnosis of rapidly progressive glomerulonephritis. J Am Soc Nephrol 1991; 2: 27-36.
18. Guillevin L, Cohen P, Gayraud M, Lhofe F, Jarrouse B, Casassus P. Churg-Strauss syndrome: clinical study and long-term follow-up of 96 patients. Medicine 1999; 78: 26-37.

19. Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg- Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990; 33: 1094-100.
20. Tervaert JW, Kallenberg CGM. Anti-myeloperoxidase antibodies in Churg-Strauss syndrome. J Neurol 1993; 240: 449-50.
21. Dillon MJ, Ansell BM. Vasculitis in children and adolescents. Rheum Dis Clin North Am 1995; 21: 1115-36.
22. Irvine AD, Bruce IN, Walsh MY, Bingham EA. Microscopic polyangiitis: delineation of a cutaneous-limited variant associated with antimyeloperoxidase auto antibody. Arch Dermatol 1997; 133: 474-7.
23. Langford CA. Treatment of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: where do we stand? Arthritis Rheum 2001; 44: 508-12.
24. Choi HK, Merkel PA, Walker AM, Niles JL. Drug-associated neutrophil cytoplasmic antibody-positive vasculitis: prevalence among patients with high titers of antimyeloperoxidase antibodies. Arthritis Rheum 2000; 43: 405-13.
25. Dolman KM, Gans ROB, Vervaat TJ, Zevenberger G,. Maingay D, Nikkels RE, et al. Vasculitis and antineutrophil cytoplasmic autoantibodies associated with propylthiouracil therapy. Lancet 1993; 342: 651-2.
26. Gunton JE, Stiel J, Clifton-Bligh P, Wilmshurst E, McElduff A. Prevalence of positive anti-neutrophil cytoplasmic antibody (ANCA) in patients receiving anti-thyroid medication. Eur J Endocrinol 2000; 142: 587.
27. Otsuka S, Kinebuchi A, Tabata H, Yamakage A, Yamazaki S. Myeloperoxidase-antineutrophil cytoplasmic antibody-associated vasculitis following propylthiouracil therapy. Br J Dermatol 2000; 142: 828-30.
28. Carrasco MD, Riera C, Clotet B, Grifol M, Foz M. Cutaneous vasculitis associated with propylthiouracil therapy. Arch Intern Med 1987; 147: 1677.
29. Jiang X, Khursigara G, Rubin RL. Transformation of lupus-inducing drugs to cytotoxic products by activated neutrophils. Science 1994; 266: 810-3.
30. von Schmiedeberg S, Goebel C, Gleichmann E, Uetrecht J. Neutrophils and drug metabolism. Science 1995; 268: 585-6.
31. Lee E, Katsura H, Miki Y, Kariya K. Mechanism of inactivation of myeloperoxidase by propylthiouracil. Biochem Pharmacol 1990; 39: 1467-71.
32. Yu F, Chen M, Gao Y, Wang Sx, Zou Wz. Clinical and Pathological Features of Renal Involvement in Propylthiouracil-Associated ANCA-Positive Vasculitis 2007: 49: 607-14.
33. Faical J, Mohamed A, Richard J. Myeloperoxidase-antineutrophil cytoplasmic antibody-positive crescentic glomerulonephritis associated with benzylthiouracil therapy. Nephrol Dial Transplant 2003; 2421-3.
34. Jennette JC, Falk RJ. Small-Vessel Vasculitis. N Engl J Med 1997; 337: 1512-23.