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

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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 ที่เกิดขึ้นกับ MPO-ANCA ระหว่างการรักษาด้วยยาทรอดร้า Propylthiouracil: รายงานผู้ป่วย 1 รายและบทความวารสาร

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ภาวะไตอักเสบชนิด Crescentic Glomerulonephritis ที่เกิดขึ้นกับ MPO-ANCA เป็นภาวะที่พบได้น้อยและชนิด p-ANCA อาจเป็นภาวะดื้อยาที่ใช้ในการรักษาภาวะไทอยด์เป็นพิษ (Propylthiouracil) บางครั้งนี้เป็นภาวะที่พบได้ในผู้ป่วยมีภาวะไทอยด์เป็นพิษและเกิดภาวะไตอักเสบชนิดขุนร่นร่วมกับภาวะเลือดออกในเนื้อปอดได้เป็นภาวะทางเลือดของ myeloperoxidase-antineurophil cytoplasmic antibodies (MPO-ANCA) อย่างไรก็ตามโดยทั่วไปการตรวจเลือดพบ myeloperoxidase-antineurophil cytoplasmic antibodies (MPO-ANCA) อย่างไรก็ตามแม้ว่าการตรวจระดับของชุนร่นร่นจะลดลงหลังจากหยุดยาPropylthiouracil รวมถึงการให้ยาอื่นๆกุม

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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 (ANCA) are important 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 cytoplasmic 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 hemaatemesis. She had no history suggesting autoimmune disease or drugs allergy.

On physical examination she was afebrile, the pulse was 120 beats per minute, the respiratory rate was 30 beats per minute 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 generalized 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\(^3\)/L and neutrophilia, platelet count of 147 x 10\(^3\)/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. Selerogical 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 antimeseloperoxidase 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 creatinine 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 tubulointerstitial 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 ANCs was firstly reported 30 years ago in patients with segmental necrotizing glomerulonephritis and shortly afterward in patients with systemic vasculitis. 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’s granulomatosis and the p-ANCA pattern, seen in patients with necrotizing glomerulonephritis and microscopic polyangiitis. The major target antigen for c-ANCA has been identified as proteinase 3; for p-ANCA, it is myeloperoxidase.

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. 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 granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, Henoch-Schönlein purpura, essential cryoglobulinemic vasculitis and cutaneous leukocytoclastic 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. The renal and pulmonary findings can differentiate it from classic polyarteritis nodosa; 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.

The cause of vasculitis is hardly discerned. There are some exceptions i.e., 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). 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. More than half of these have been described, 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.

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 antmyeloperoxidase antibodies, as did my case. After the discontinuation of PTU, two of the patients were treated with systemic glucocorticoids and one received cyclo-phosphamide therapy.

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.

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 lactoferrin, 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.

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


