Methimazole-induced Pulmonary Hemorrhage Associated with Antimyeloperoxidase-Antineutrophil Cytoplasmic Antibody: A Case Report

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Abstract: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis has been recently recognized in Graves’ disease patients treated with antithyroid drugs. We describe the case of an 18-year-old girl who developed antimyeloperoxidase ANCA (MPO-ANCA)-positive vasculitis manifesting as a skin lesion and hemoptysis with hypoxic respiratory failure after taking methimazole. An open lung biopsy was consistent with acute capillaritis. Both skin and sural nerve biopsy showed lymphocytic vasculitis. Administration of steroid and plasmapheresis produced a good clinical response.

Case Report

This 18-year-old girl had received PTU on and off for 2 years after hyperthyroidism was diagnosed in June 1998. On June 15, 2000, general malaise, tremor, and palpitation developed. Methimazole and propranolol were prescribed at a local hospital. One week later, she noted right leg weakness when climbing stairs. Later that same week, she developed generalized skin itching and a rash. On June 29, 2000, shortness of breath and hemoptysis developed. She went to the local hospital where anemia (hemoglobin, Hb, 60 g/L) was noted. Chest roentgenogram showed diffuse bilateral ground-glass haziness. Pulmonary hemorrhage was suspected, and she was referred to our hospital for further management on July 5, 2000.

Antineutrophil cytoplasmic antibody (ANCA) is an important marker in systemic vasculitic disorders that include Wegener’s granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, and necrotizing crescentic glomerulonephritis [1, 2]. ANCA is classified into two types, cytoplasmic pattern (c-ANCA) and perinuclear pattern (p-ANCA), by indirect immunofluorescence [3]. p-ANCA is directed primarily against myeloperoxidase (MPO), but is also directed against lactoferrin, elastase, cathepsin G, lysozyme, and enolase, as shown by enzyme-linked immunosorbent assay (ELISA). The triggers for ANCA-positive vasculitis are still unknown. However, there have been reports of ANCA-positive vasculitis associated with certain medications. The two most commonly associated drugs are hydralazine and propylthiouracil (PTU) [4]. PTU-induced p-ANCA-positive vasculitis was first described by Dolman et al [5]. The clinical manifestations include nephritis, alveolar vasculitis, cutaneous leukocytoclasmic vasculitis, and migratory polyarthritides. Alveolar vasculitis with hemorrhage has been reported in patients treated with PTU [6, 7]. The thionamide antithyroid drugs methimazole and carbimazole also cause ANCA-positive vasculitis, although much less frequently than PTU [8, 9]. Here, we report a case of methimazole-induced systemic vasculitis presenting as alveolar hemorrhage and skin papulomacular lesion.
On physical examination, she had tachypnea, and was pale with apyrexia. Her blood pressure was 160/90 mmHg and pulse rate 84 per minute. Enlargement of the thyroid gland was apparent. On chest auscultation, diffuse coarse crackles were noted. Papulomacular skin lesions were visible on both lower extremities (Fig. 1). Laboratory data after admission were as follows: Hb 94 g/L, hematocrit 29.9%, white blood cell count 8,930/µL, platelet count 442 x 10^3/µL, blood urea nitrogen 5.7 mmol/L, and creatinine 44.2 µmol/L. Serum thyroid function parameters were as follows: free thyroxine (T4) 6.84 pmol/L (normal range 7.74–22.58 pmol/L), and thyroid-stimulating hormone (TSH) 0.272 mU/L (normal range 0.4–4.0 mU/L). The test for ANCA was performed by ELISA, and gave the following results: anti-MPO 62 EU/mL and anti-protease 3 (PR3) 4 EU/mL (positive > 15 EU/mL). Antinuclear antibody was at a titer of 1:80, featuring a speckled pattern, and anti-dsDNA antibodies had a titer of 24.3 IU/mL (normal < 12 IU/mL). Antimicrosomal antibody (≥ 1:20,480) and antithyroglobulin antibody (1:20,480) were both positive. The complement concentrations decreased (C3, 0.357 g/L; C4, 0.063 g/L). Anti-glomerular basement membrane (GBM) antibody and anticardiolipin antibody were negative, although antiphospholipid antibody was positive (33.95 IU/mL; positive criteria > 15 IU/mL).

Chest roentgenography revealed diffuse infiltration over both upper and lower lung fields (Fig. 2). Arterial blood gas showed near hypoxemia (PaO₂ 75 mmHg) under high flow delivery of oxygen (O₂ mask 10 L/min, 60%). Endotracheal intubation was performed 2 days later because of hypoxic respiratory failure. Open lung biopsy showed a patchy neutrophil infiltrate within alveolar septa, and adjacent airspace contained proteinaceous exudates with erythrocytes and necrotic neutrophils. Histiocytes were also present. Acute capillaritis was diagnosed. There was associated intraalveolar hemorrhage and occasional hemosiderin deposition (Fig. 3). Skin biopsy over the papulomacular lesion revealed lymphocytic vasculitis. Plasmapheresis and steroid pulse therapy (methylprednisolone 1 g/day) were given for 3 days (July 11–13). Her condition improved gradually and she was extubated on July 29. However, during the next 3 weeks, thyrotoxic status was noted with persistent muscle weakness, progressive weight loss, hand tremor, and increased free T4 (29.80 pmol/L). Electromyograph showed asymmetric polyneuropathy, and muscle biopsy showed a decreased ATPase stain and a mild degree of muscle atrophy, especially type II. Acute quadriplegic myopathy was suspected by a consulting neurologist. Sural nerve biopsy also showed lymphocytic vasculitis. She received corticosteroid, two courses of plasmapheresis, and I¹³¹ treatment for her hyperthyroidism from then on. The follow-up clinical course was excellent. Anti-MPO ANCA test repeated 6 months after discharge was less than 2 EU/mL.

Fig. 1. Papulomacular skin lesions on the right thigh as a manifestation of antimielyoperoxidase-antineutrophil cytoplasmic antibody-positive vasculitis in our 18-year-old female patient.

Fig. 2. Diffuse infiltration over both upper and lower lung fields on chest roentgenogram.

Fig. 3. Acute capillaritis with expansion of alveolar septa by an infiltrate of necrotic neutrophils and histiocytes (arrows). Extensive hemorrhage is also present in the alveolar space (Haematoxylin and eosin, x 66 original magnification).
Disc

Methimazole is a thionamide drug frequently used in the treatment of hyperthyroidism. It inhibits the oxidation and organification of iodide. Methimazole has rarely been linked to the development of systemic vasculitis. On the other hand, PTU has more often been associated with ANCA-positive vasculitis, commonly involving the skin, kidney, and lung [10, 11]; in renal involvement, glomerulonephritis is the most common manifestation. ANCA-associated vasculitis may cause variable constitutional symptoms, such as fever, myalgia, arthralgia, and flu-like syndrome [12]. It has also been suggested that previous reported cases of PTU-induced lupus syndrome could be reclassified as vasculitis [13]. Our patient developed methimazole-induced MPO-ANCA-positive vasculitis resulting in alveolar hemorrhage and respiratory failure. Lung, skin, and nerve biopsy all revealed small-vessel vasculitis. After withdrawal of the drug and treatment with steroid pulse therapy and plasmapheresis, her condition improved rapidly. The following clinical course was excellent.

The pathogenesis of methimazole-induced vasculitis is unknown. However, some mechanisms for PTU-induced ANCA-positive vasculitis have been proposed. Jiang et al reported that PTU exhibited high cytotoxicity in the presence of activated neutrophils. MPO was released from activated neutrophils, and transformed PTU into a cytotoxic product [14]. Lee et al speculated that PTU binds to MPO and changes the heme structure of the enzyme. This alteration in configuration may allow initiation of autoantibody formation [15]. Von Schmiedeberg et al proposed that PTU sulfonate, which is derived from PTU in the presence of MPO, is immunogenic for T cells; B cells are then activated by these T cells and mediate the vascular injury [16].

Alveolar hemorrhage is characterized by disruption of the alveolar septum with fibrinoid necrosis and capillary thrombosis. The loss of integrity of the capillary basement membrane results in alveolar hemorrhage. Immunologic disorders associated with alveolar hemorrhage have been classified into three categories: anti-GBM antibody mediated; immune-complex mediated; and ANCA-associated vasculitis [17]. In our patient, the absence of anti-GBM antibody and presence of MPO-ANCA strongly suggested that the alveolar hemorrhage was due to ANCA-associated vasculitis. If the alveolar hemorrhage is severe or life threatening, plasmapheresis should be considered in addition to steroids and/or cyclophosphamide therapy [18].

Antithyroid drug-induced vasculitis often occurs within weeks of treatment, but may develop months or even years later [10, 11]. It is important to recognize this rare side effect of this widely used drug. As in our patient, it can cause life-threatening pulmonary hemorrhage with high morbidity and mortality. The drug should be withdrawn immediately on the appearance of symptoms of vasculitis. Treatment with immunosuppressive therapy should be considered in patients with an aggressive disease course.

Although methimazole and PTU have similar structures containing a thionamide group, cross-sensitivity for vasculitis may not occur. Kudoh et al reported the case of a patient with a history of agranulocytosis with methimazole in previous years who developed PTU-induced rapid progressive glomerulonephritis with ANCA-positive vasculitis [19]. Our patient received PTU treatment for 2 years, on and off, before methimazole prescription. However, the safety of substituting one thionamide derivative for another is unpredictable. The ANCA concentration typically falls after withdrawal of the antithyroid drug, but may remain elevated in some cases. Other autoantibodies have also been detected with PTU hypersensitivity vasculitis, including antinuclear, anti-DNA, antimitochondrial, and anticardiolipin antibodies and lupus anticoagulant [4, 10].

In conclusion, we have described a rare case of MPO-ANCA-associated vasculitis with presenting symptoms of respiratory failure, alveolar hemorrhage, and skin papulomacular lesions after receiving methimazole. The importance of ANCA in the underlying pathogenesis of vasculitis remains unclear and needs further investigation.

References


