CASE REPORT

Severe Pulmonary Embolism, Thrombosis of Lower Extremity, Unexpected Mild Renal Disorder in MPO-ANCA Associated Vasculitis: A Case Report

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Key words: antineutrophil cytoplasmic antibody-associated vasculitis; myeloperoxidase; pulmonary embolism; arterial embolism

Abstract Myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) associated vasculitis is an autoimmune disease usually with severe multiple dysfunction syndrome, especially prominent acute renal failure. A 65-year-old woman was admitted with progressive dyspnoea for six months and fever, sputum with blood, pain of the lower extremities and intermittent claudication for two days, indicating multiple organ involvement (respiratory system, blood vessels). The renal involvement was relatively mild, presenting with microscopic haematuria. The chest computed tomography demonstrated multiple pulmonary embolisms. Ultrasound and computed tomography angiography for the lower extremity vessels showed venous and arterial thrombosis. Exclusion of other diseases that can cause multiple organ damage and thrombosis, the positive perinuclear ANCA and MPO-ANCA strongly support the diagnosis of MPO-ANCA-associated vasculitis. The patient's physical condition has been greatly improved by treatment with corticosteroids and anticoagulation.

MYELOPEROXIDASE antineutrophil cytoplasmic antibody (MPO-ANCA) associated vasculitis is subgroup of ANCA-associated vasculitis (AAV) characterized by the presence of circulating ANCAs that are principally

directed against MPO. The main clinical presentations are necrotizing glomerulonephritis and pulmonary capillaritis. The occurrence of kidney involvement is over 90%.^[1] Thrombosis could occur in variety of pathological and physiological conditions, such as hemostasis and inflammatory diseases. Although the risk of venous thrombosis is relatively increased in active AAV, multiple thrombosis involving venous and arterial systems has not been reported.^[2] Here we describe a 65-year-old woman with MPO-AAV who develop severe

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pulmonary lesion, thrombosis of lower extremity, and unexpected mild renal disorder. Written informed consent was obtained from her.

CASE DISCRIPTION

In October 2018, a 65-year-old woman was admitted to our hospital with progressive dyspnoea for six months and fever, sputum with blood, pain of the lower extremities and intermittent claudication for two days. Before her illness, she was relatively healthy. On admission, her vital signs were arterial blood pressure of 120/84 mm Hg, heart rate of 116 bpm, temperature 38.3 °C, respiratory rate of 26 bpm and 95% of oxygen saturation while breathing ambient air. A moist rale over the bilateral lower sides of the lung and weakened pulse of the right arteria dorsalis pedis were found. Laboratory data revealed elevated neutrophil count ($6.5 \times 10^9/L$), reduced lymphocyte count ($1.0 \times 10^9/L$), a serum albumin level of 28 g/L and a serum creatinine level of 62 $\mu\text{mol/L}$. Her haemoglobin level was 101 g/L. Erythrocyte sedimentation rate was 69 mm/h and C-reactive protein was 129.0 mg/L. Procalcitonin level was normal. Cholesterol [5.31 mmol/L (normal range <5.18 mmol/L)] only mildly increased and triglyceride was normal. CD55 and CD59 were negative. Perinuclear ANCAs and antibodies against MPO (122.04 U/ml) were positive. Antibodies against proteinase 3, nuclear antigens, double-stranded DNA, glomerular basement membrane, cardiolipin antigens, lupus anticoagulant, β_2 -glycoprotein were all negative. Urine analysis showed 23 dysmorphic red blood cells per ml of urine and no proteinuria. No signs of malignancy were observed. Other diseases causing secondary multiple organ dysfunction and thrombosis were excluded.

Renal and carotid artery ultrasound revealed no

abnormalities. A computed tomographic pulmonary angiography showed multiple bilateral pulmonary embolisms, interstitial pneumonia and hydropericardium (**Fig. 1**). An ultrasound of the lower limbs showed bilateral deep vein thrombi in the femoral vein. The computed tomography angiography for the lower extremity arteries showed complete occlusion of the right posterior tibial artery (**Fig. 2**). No obvious abnormality of renal function made our patient refuse kidney biopsy.

The above evidence and the positive perinuclear ANCA and MPO-ANCA strongly supported the diagnosis of MPO-AAV. Consequently, high-dose methylprednisolone (1 mg/kg·d), intravenous cyclophosphamide (0.5 g/m²) and low molecular weight heparin sodium anticoagulant (3200 U Q12h) were administered to induce remission of violent autoimmune inflammation. After 8 days, she was discharged for relieved symptoms. At the 3-month follow-up, the pulmonary embolisms were improved, and serum creatinine remained stable (72 $\mu\text{mol/L}$).

DISCUSSION

AAV is a systemic small vessel vasculitis characterized by episodes of destructive vascular and extravascular inflammation mainly affecting the respiratory tract and kidney. According to autoantibodies specific for antigens, AAV is classified by two clinical syndromes: proteinase 3 ANCA-associated vasculitis (PR3-AAV) and MPO-AAV. The respiratory tract involvement is usually found in PR3-AAV patients; MPO-AAV patients commonly have kidney involvement.^[3, 4] Over 90% MPO-AAV patients with kidney involvement mainly present with hematuria, proteinuria and progressive deterioration of renal function.^[1] In our case, she only

Figure 1. Computed tomography pulmonary angiography. CT angiogram of the chest showing an extensive filling defect in the pulmonary artery (arrow) after admission (A). CT angiograms of the chest showing improved pulmonary embolism (arrows) before discharge (B) and 3 months after treatment (C), respectively.

Figure 2. Computed tomography angiography of lower limb vessels. CT angiogram of the lower extremity arteries showing complete occlusion of the right posterior tibial artery (arrow). R: right; L: left; F: front; B: back.

had mild renal impairment with very few microscopic hematuria and normal serum creatinine during follow-up.

The patient was admitted to our hospital with prominent clinical manifestations of hemoptysis and progressive dyspnea. Computed tomographic pulmonary angiography revealed multiple embolisms over bilateral pulmonary arteries. Pulmonary involvement from both acute and chronic disease processes is common in AAV and has been reported in 25%–80% of cases.^[5] Peribronchial nodules, bronchiectasis, pulmonary hemorrhage, emphysema, cavitating lesions, necrotizing pneumonia, interstitial pneumonitis, parenchymal scarring and pulmonary venous congestion have been reported.^[6] The cumulative incidence at 10 years of AAV complicated with pulmonary embolism was reported about 4.8%.^[7] Our patient also had rare arterial occlusion of both lower extremities. As for arterial thrombosis, recent reports are mainly focused on coronary events and ischemic stroke, and report of the incidence rate of peripheral vascular disease in MPO-AAV is lesser-known.^[8]

The proposed pathophysiology of thrombosis in AAV is relevant to endothelial cell injury. As we all know, endothelial cells injury results in exposure of subendothelial collagen, subsequently providing platelet adhesion sites and activating coagulation system, which is a key to thrombosis. In AAV, ANCA bonds to the antigens (MPO and PR3) expressed on the surface of neutrophils and monocytes, leading to violent cellular activation. The activated cells release abundant reactive oxygen species, proteases, and neutrophil extracellular traps to injure the endothelium. Furthermore, the alternate pathway of complement is activated by activated neutrophils with generation of the anaphylatoxin C5a, involving inflammation amplification

loop and aggravating the damage on the endothelial cells.^[4, 9] Besides, our patient has abnormal coagulation system with hypercoagulable state. All mentioned above have promoted the development of multiple thrombosis.

For AAV patients, standard treatment regimens of glucocorticoid plus cyclophosphamide are keys to induce remission. Furthermore, opportune and continuous anticoagulation therapy is also essential to prevent clots from growing and new ones from forming. Adequate evidences indicate that sufficient anticoagulation therapy is important to reduce or eliminate thrombosis. However, finding a balance of coagulation system has been plaguing clinicians. A small number of AAV cases with pulmonary embolism has been reported to have bleeding tendency after using anticoagulant therapy.^[10, 11] Therefore, the management of thrombosis in AAV patients is challenging due to the increased baseline risk of pulmonary hemorrhage. As for our patient, we did not treat her with thrombolytic therapy. Anticoagulation therapy was based on steroid and cyclophosphamide therapy, which was effective for improvement of hemoptysis, anhelation and pulmonary embolism. Even though, currently careful monitor and prevention is effective means and a guideline for anticoagulation strategy of AAV is in need.

In conclusion, MPO-AAV can involve multiple organ systems, and the pulmonary and kidney systems are mainly affected. Arterial embolisms and mild renal disorder can be found in less common cases. Patients presenting with unexplained pulmonary embolisms should take AAV into consideration.

Conflicts of Interest Statement

The authors have no conflict of interests to declare.

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中文摘要

1 例严重肺及下肢血管栓塞并轻微肾损害的髓过氧化物酶阳性的抗中性粒细胞胞浆抗体相关性血管炎：病例报告

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摘要

髓过氧化物酶阳性的抗中性粒细胞胞浆抗体相关性血管炎 (myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitis, MPO-AAV) 是一类以严重的多器官损害为特征的自身免疫性疾病，尤以急性肾功能衰竭为突出表现。本文报道了 1 例 65 岁的老年女性，因 6 月来进展性的呼吸困难，发热、咯血痰、下肢疼痛并间歇性跛行 2 天入院。通过一系列详尽检查发现严重的肺动脉栓塞及动静脉血栓，肾脏损害相对轻微，核周型抗中性粒细胞胞浆抗体 (perinuclear antineutrophil cytoplasmic antibody, P-ANCA) 及抗髓过氧化物酶抗体 (myeloperoxidase antineutrophil cytoplasmic antibody, MPO-ANCA) 呈阳性。排除其他因素导致多器官损伤及血栓形成可能性，此患者被诊断为 MPO-AAV。给予糖皮质激素，环磷酰胺及抗凝治疗后，患者的临床症状及肺栓塞明显改善。

关键词：ANCA 相关性血管炎；髓过氧化物酶；肺栓塞；动脉栓塞