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Case Report

Unexpected Evolution of Multiple Aneurysms as a Complication of p-ANCA Exchanged Vasculitis with Prednisolone Therapy: A Case Report and Review of the Literature

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Abstract

Background: ANCA-associated vasculitis (AAV) is a rare and potentially fatal systemic autoimmune disease characterized by inflammation and fibrinoid necrosis of the vascular wall, primarily triggering small-vessel pauci-immune vasculitis. Coronary artery aneurysms (CAAs) are an extremely uncommon finding though medium-size vessels can sometimes be involved, here we describe a case of multiple medium-size vessel impairment of AAV. To our knowledge, this is the first documented case of unexpected evolution of multiple vasculature involvement as a complication in a patient of plasma p-ANCA exchanged from positive to negative after tapering of Prednisolone (PSL) therapy.

Case Report: A 59-year-old Chinese male whose previous chief complain was chest pain and dizzy with history of MPO-ANCA-associated glomerulonephritis was referred to our hospital because of angina. On admission, laboratory data showed sedimentation rate of red cells was 18mm/H and immunoglobulin G was 20.79 g/L, while other specific antibodies and blood tests were negative. His angiography demonstrated vasculitis with multiple vessel wall irregularities, abrupt terminations, and giant aneurysms typically found in carotid arteries, cerebral arteries as well as coronary arteries, which indicating medium-size vessels impairment. More importantly, we have noted that his vascular impairment relapsed insidiously after tapering of Prednisolone (PSL). The diagnosis of ANCA-associated vasculitis was confirmed on the basis of the clinical presentation in the end, however, we missed the therapeutic opportunity to reverse his vascular impairment with initial misdiagnosis.

Discussion: The pathogenesis of AAV is multifaceted and numerous factors may be involved except ANCA-induced activation of cytokine-primed neutrophils and the formation of neutrophils extracellular traps. Once kidney and lung are involved, the fatality rate is high and the prognosis is poor. Therefore, healthcare providers should be aware of vascular lesions complications either in clinical or imageological examination and mechanism of these diseases including plasma ANCA exchanged AAV, of which mechanistic insights may have potential to open new therapeutic strategies for them.

Keywords: p-ANCA Exchanged Vasculitis; Angina; Multiple Aneurysms; Prednisolone

Background

ANCA-associated vasculitis (AAV) is a rare and potentially fatal systemic autoimmune disease characterized by necrotizing inflammation of small blood vessels and the presence of circulating pathogenic ANCA, which induced activation of primed neutrophils and monocytes leading to destructive vascular necrosis, always affecting small vessels (capillaries, venules, arterioles), but medium-size vessels can sometimes be involved [1,2]. To date, several subtypes of AAVs have been identified including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and

eosinophilic GPA (EGPA), etc [3]. Indirect immunofluorescence reveals two types of ANCA targeting myeloperoxidase (MPO) in perinuclear area (p-ANCA) and protease 3 (PR3) in cytoplasm (c-ANCA) [4]. Here we describe a case of vasculitis in which plasma p-ANCA exchanged after prednisolone therapy, however, the vascular lesions continued to trigger insidiously, resulting in multiple arteries impairment, especially the occurrence of a giant aneurysmal lesions in the right coronary artery. To our knowledge, this is the first documented case of unexpected evolution of multiple aneurysms as a complication in a patient with plasma p-ANCA exchanged after tapering of Prednisolone (PSL). In addition, we provide a comprehensive overview of the autoimmune mechanism of ANCA exchanged AAVs by reviewing the literature. Our findings emphasized the other possible pathogenesis concepts of AAV as well as the autoimmune mechanisms such as LAMP- 2 and IgG4-related immune regulation in the pathogenesis of AAV, of which mechanistic insights may have potential to open new therapeutic strategies of vasculopathy for currently medication of AAV.

Case Presentation

A 59-year-old Chinese male with a history of p-ANCA-associated glomerulonephritis for 5 years, was referred to our hospital because of chest pain and dizzy worsen for 1 month. Five years prior to the current presentation he reported an episode of microscopic hematuria, what' more he had suffered a transient asthma attack, and his blood results demonstrated the presence of myeloperoxidase (MPO) specific antineutrophil cytoplasmic antibodies (ANCA, titer 1/640), subsequent renal biopsy identified a pauci-immune focal segment lesion with small crescent body formation (Figure 1), thus he was diagnosed as p-ANCA-associated glomerulonephritis and received medication of PSL and his hematuria disappeared quickly, then he was discharged with advice of anther 12 months of PSL. 3 years later, he presented with a dizziness usually happened when he was turning around his head and neck, but left without further investigation for his daily life was not affected, however, He reported that he often had low fever and fatigue since then. Gradually, he began to feel dull pain in the anterior cardiac area accompanied by radiating pain in the inner side of his left elbow when he rode bike or went upstairs quickly, and the chest pain was relieved after stopping activities. He complained the above symptoms worsen recently. He had no history of hypertension or dyslipidemia, no smoking history, or any notable family history of coronary heart disease. Also the patient denied childhood history of Kawasaki disease. On admission, the sedimentation rate of red cells was 18 mm/h, and immunoglobulin G was 20.79 G/l. Urine routine, renal function, CRP, ANA, dsDNA, ANCA and complement were all within the normal range. His cervical ultrasound showed local thickening of the medial and medial membrane of the right carotid artery, tortuous dilation of the right vertebral artery, and severe stenosis of the left vertebral artery resulting in occlusion. Chest CT showed hemangiomatous dilatation of both lungs (Figure 2). Abdominal CT showed multiple tortuous vascular masses in hepatic hilum, lesser omental sac and splenic hilum (Figure 3). Echocardiography showed multiple neodymolar expansions of the coronary arteries which could not be explained by Kawasaki disease (Figure 4). Further angiography of the great arteries of the head and neck, cerebral arteries and coronary arteries (Figure 5, 6) showed multiple tumor-like dilatation of bilateral internal carotid arteries, tortuous and tumor-like dilatation of the whole right vertebral artery, severe stenosis of the initial segment of the left vertebral artery, multiple tumor-like dilatation of the left main coronary artery, anterior descending coronary artery and the right coronary artery. Combined with the previous history of MPO-ANCAAAV with kidney and systemic vascular involvement, hence, a diagnosis of ANCA-associated vasculitis was made, presenting as p-ANCA exchanged vasculitis. After symptomatic support treatment, his clinical symptoms remained improved, and his lab test including creatinine and C-reactive protein (CRP) levels have remained normalized as of his most recent follow-up after hospital discharge.

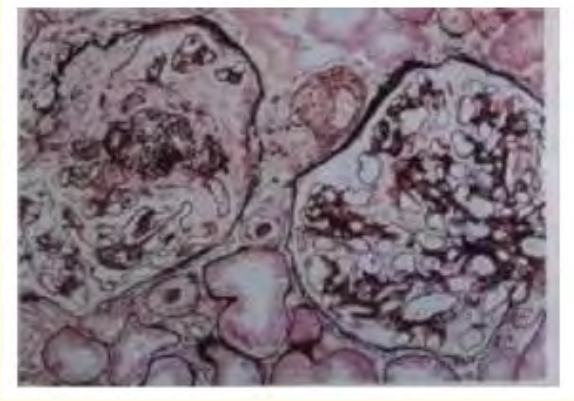

Figure 1: Renal biopsy showed a pauci-immune focal segment lesion with small crescent body formation.

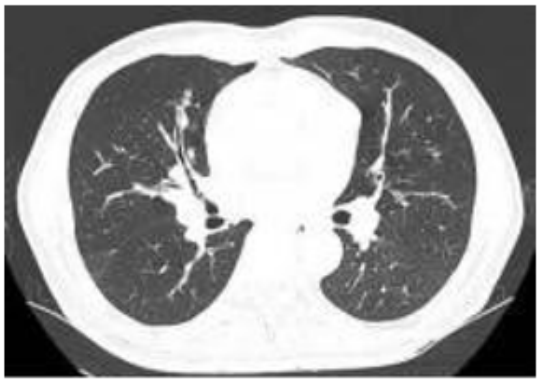

Figure 2: Chest CT showed hemangiomatous dilatation of bilateral lungs.

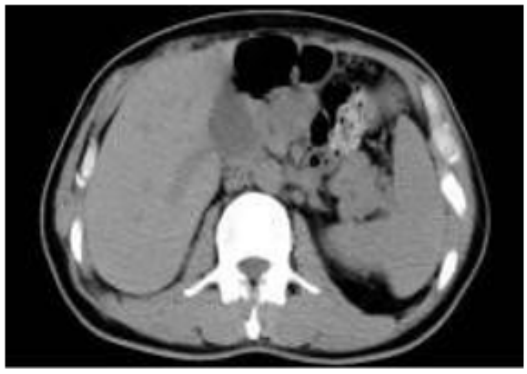

Figure 3: Abdominal CT showed multiple vasodilation in the hepatic hilar region.

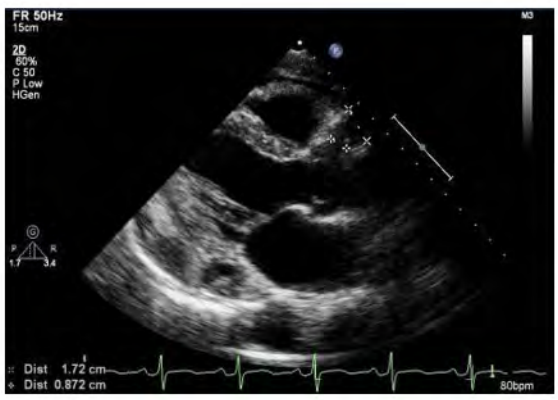

Figure 4: Echocardiography showed multiple neodymolar expansions of the coronary arteries.

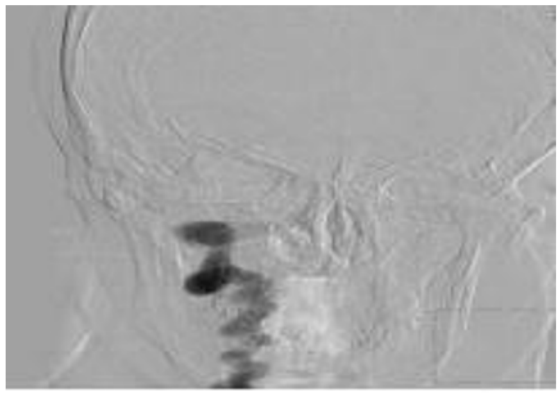

Figure 5: Angiography of the great arteries of the head and neck showed multiple tumor-like dilatation of bilateral internal carotid arteries.

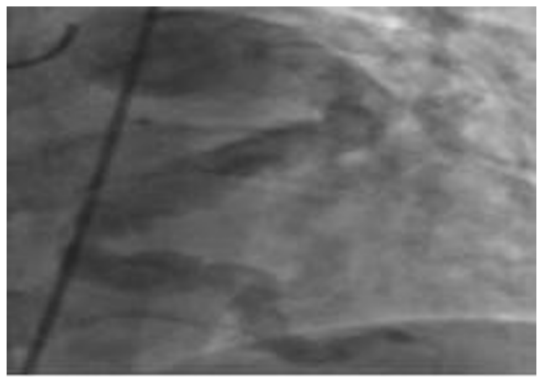

Figure 6: Angiography of the coronary arteries showed a giant aneurysmal lesions in the right coronary artery with multiple tumor-like dilatation

Discussion and Review of the Literature

Anti Neutrophil Cytoplasmic Antibody (ANCA) associated vasculitis (AAV) is an autoimmune disease characterized by inflammation of the small blood vessels [5,6]. Its clinical manifestations are complex, especially the early ANCA associated small vasculitis often lacks typical symptoms, easy to be misdiagnosed [7]. Once kidney and lung involvement occurs, the fatality rate is high and the prognosis is poor [8]. At present, the main therapeutic drugs for ANCA-related vasculitis include corticosteroid, cytotoxic drugs, immunosuppressive agents and new biological agents. The treatment mainly includes three stages:

induction and remission, maintenance and remission, and relapse treatment stage [9]. Once diagnosed, all patients should be treated with corticosteroid combined with immunosuppressants, single corticosteroid therapy is not very effective to delete the pathogenic autoimmunity and easily prone to relapse [10,11].

This case was initially diagnosed as "ANCA-related glomerulonephritis" because of microscopic hematuria 5 years ago, considered the toxicity of the use of cyclophosphamide, he received corticosteroid treatment only, his hematuria disappeared quickly and his plasma p-ANCA exchanged from positive to negative as well, however, the vasculature impairment continued to trigger without any awareness, resulting in multiple arteries involvement finally, especially the occurrence of a giant aneurysmal lesions in the right coronary artery, indicating the fact that some AAV patients with subsequently ANCA undetectable after tapering of PSL therapy may have many other autoimmune factors that still play a vital role in the progression of vasculopathy. Coincidentally, by reviewing the other cases reported in literature, we have noted that some patients with diagnosis of AAV sometimes combined with plasma ANCA switched from positive to negative. Lysosomal-associated membrane protein-2 (LAMP-2) is a highly glycosylated type I glycoprotein expressed on the membranes of neutrophils, endothelial cells and other cells, which are closely linked to subsets of systematic vasculitis [12]. Studies have shown that serum LAMP-2 could be expressed alone in AAV with ANCA- negative patients [13,14]. Some study conducted by Gibson and Kain., *et al*. displayed that LAMP-2 was considered as ANCA antigens, expressed on the surface of neutrophils and endothelial cells and circulating autoantibodies to human LAMP-2 (hLAMP-2) can be detected in most patients with AAVs [12,15]. Moreover, Peschel., *et al*. have identified autoantibodies to hLAMP-2 that bind native glomerular, suggesting hLAMP-2 play an important role of pathogenesis in ANCA-negative pauci-immune focal necrotising glomerulonephritis [16]. Gibson reported that ANCA against LAMP-2 that is expressed on the glomerular endothelium, are present in some adults with AAV-associated renal disease, indicating serum LAMP-2 can be used as a diagnostic biomarker of AAV specially when renal vessel impairment [12]. In this case, we have noted systemic small and medium vessel vasculitis after tapering of PSL therapy with previously diagnosis of p-ANCA-associated glomerulonephritis similar to Gibson's findings, then questions coming, if there was some abnormal expression of LAMP- 2 in the subsequently progression vasculature involvement in this case? What' more, it has been reported that AAV could overlap with IgG4-related disease sometime [17,18]. We have also noted that the immunoglobulin G was always keeping comprehensive high level during the whole progression of vasculopathy. If there was also IgG4-related autoimmune factors that played a vital role in the pathogenesis of systemic vasculitis mainly affecting small- or medium-sized vessels. In addition to ANCA-induced activation of cytokine-primed neutrophils, what else factors of immunopathological were involved in the progression of such vasculitis? All these questions are still unclear and needs to be further confirmed in clinical studies.

Review the process of the diagnosis and treatment of this case, we have awared that the clinical diagnosis and disease activity evaluation for p-ANCA exchanged AAV with insidious vascular damage is a challenge. Because of the laboratory, imaging, and other tests in common use have limited ability to help the clinician diagnose and evaluate the disease activity of such disease. Though the diagnosis of ANCA- associated vasculitis was made finally, the best therapeutic opportunity was unfortunately missed. For AAV with ANCA switched from positive to negative, there is still other autoimmune substances could participate in the immunopathological process of AAV. Therefore, there is need for the search of reliable biomarkers such as LAMP- 2 that may help to clinical diagnosis and evaluation of disease activity for p-ANCA changed AAV specially when renal involvement. Last but not the least, current normative treatment with corticosteroid combined with immunosuppressants, has the toxicity that contributes significantly to morbidity and mortality, moreover, prolonged use of cyclophosphamide is also associated with an increase rate of malignancy, therefore, future in-depth study on the mechanistic insights may have potential to open new therapeutic strategies of vasculopathy for currently medication of AAV.

Conclusions

In conclusion, we present a rare case of multiple medium-size vessel impairment as a insidious complication of AAV with serum antibodies against MPO that exchanged from positive to negative after tapering of PSL therapy. We propose that except ANCA-induced activation of cytokine-primed neutrophils, our findings emphasized the other possible pathogenesis concepts of AAV such as LAMP- 2 and IgG4-related immune regulation in the pathogenesis of AAV, and the possible diagnosis of AAV should be carefully considered when running into such middle-aged and

elderly male patients with multiple aneurysmal lesion. Moreover, the autoimmune mechanisms insights may have potential to open a new therapeutic strategies of vasculopathy of ANCA exchanged AAV in the future.

Consent

A written informed consent for publication of this case report has been obtained from the patient.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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