ANCA in Atheroembolism; Just a Coincidence or Bearing Cause and Effect?

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Much attention has been given to microscopic polyangiitis (MPA) characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) in the patients’ sera. Patients with MPA usually present with rapidly progressive renal failure along with peripheral neuropathy and pulmonary hemorrhage, which is sometimes fatal. The pathological hallmark of MPA is the involvement of small vessels such as glomeruli and alveolar capillaries. The number of such patients is increasing and it is a disease of the elderly; I have never seen patients younger than 50 in my clinic.

ANCA is dichotomized largely into two categories based on the immunofluorescence staining pattern of neutrophils: peri-nuclear (P-) and cytoplasmic (C-) ANCA. C-ANCA is directed against the protein antigen termed proteinase 3 in the azurophilic granules in neutrophils. On the other hand, the specificity of P-ANCA is relatively diverse and myeloperoxidase (MPO), which is also in the azurophilic granules, is the most frequent target. Thus, P-ANCA which reacts with MPO is called MPO-ANCA. P-ANCA and C-ANCA are quite useful diagnostic markers of MPA and Wegener’s granulomatosis, respectively, although its etiopathogenetic importance is still under debate. Classification of vasculitides was reorganized on the bases of the vascular size involved and the presence or absence of ANCA. Treatment of ANCA-related vasculitides is either glucocorticoid or immunosuppressant such as cyclophosphamide, or both.

Atheroembolism also known as cholesterol crystal embolism is a fairly rare condition compared to thromboembolism. It usually occurs after an intra-arterial procedure such as angiography, cardiac catheterization, and cardiac surgery, although it also occurs spontaneously. Floating atheromatous plaques in the aortic wall suddenly break down into small pieces and spread over the entire body. The result of such shower embolization is organ damage induced by multiple small artery occlusions. Constellation of blue toe, renal failure, livedo reticularis, and intestinal infarction is the typical clinical manifestation of atheroembolism. However, many cases of atheroembolism are unrecognized clinically. Treatment of atheroembolism is either medical or surgical. Medical treatment includes aspirin and statins as well as the correction of the underlying conditions such as high blood pressure, diabetes mellitus, and abstinence from smoking.

Although MPA and atheroembolism are distinct entities, their clinical manifestations are astonishingly similar; blue toe, renal failure, livedo reticularis, and intestinal infarction are typical manifestations of MPA as well. Inflammation measured by serum levels of C-reactive protein is increased and even eosinophilia is sometimes detected in atheroembolism.

A very interesting case is reported in this issue of Internal Medicine by Sugimoto et al (1). A 75-year-old man who had had compromised renal function probably due to arteriosclerosis and hypoperfusion of the kidneys underwent coronary angiography and emergency coronary bypass grafting. Acute renal insufficiency requiring hemodialysis developed 2 weeks after the surgery. In the meantime, the patient developed palpable purpura on his entire body and diffuse blue mottlings on his toes and soles. He was found to have high serum C-reactive protein, eosinophilia, and MPO-ANCA, in particular.

I believe most physicians who are informed of the above medical history would make a diagnosis of vasculitis, especially ANCA-related vasculitis. In the present case, the skin biopsy specimen revealed some degree of inflammation in and around an arteriole and biconvex clefts in the lumen suggesting cholesterol embolism. However, anti-coagulation with warfarin, atrovastatin, and LDL-apheresis did not show any beneficial effects. Therefore, the authors decided to use glucocorticoid on the basis of positive MPO-ANCA and an increasing eosinophilia. Glucocorticoid dramatically im-
proved the patient’s laboratory data, cutaneous lesions, and kidney function leading to the successful discontinuation of hemodialysis.

As the authors mentioned in the report, the correct diagnosis of cholesterol embolization syndrome was obtained only after the skin biopsy specimen was examined pathologically. The clinical diagnosis of MPA would have been placed on this patient if no pathological examination was performed or the pathological specimen lacked the bi-convex clefts in the arteriolar lumen, which are typical of cholesterol embolization syndrome.

Several cases of renal atheroembolism associated with ANCA have already been reported. Maeshima et al reported a 50-year-old man who showed systemic vasculitic syndrome with positive P-ANCA and C-ANCA along with acute deterioration of renal function (2). Although the pathological diagnosis was cholesterol embolism, they continued to treat him with glucocorticoid and cyclophosphamide with a favorable outcome. Aviles et al reported a case of cholesterol microemboli who also developed extracapillary glomerulonephritis in the presence of P-ANCA which is the hallmark of ANCA-related vasculitis (3). Delen et al reported a 65-year-old woman with systemic inflammatory signs and renovascular hypertension due to atherosclerotic narrowing of both renal arteries (4). A stent was placed in both renal arteries, which resulted in the normalization of blood pressure. ANCA was tested negative. However, systemic inflammation and renal function deteriorated as well as the appearance of pleuroperticarditis after two months. The patient became positive for P-ANCA and renal biopsy showed evidence of cholesterol embolism.

Although only a few cases have been reported to date, they indicate a very interesting implication between vascular insult of a portion of the body, i.e. renal arteries, and systemic spreading of the vascular inflammation. Cholesterol emboli elicit local vasculitis, activate leukocytes, and release inflammatory cytokines, which trigger systemic vasculitis. Activated neutrophils release enormous amounts of reactive oxygen radicals as well as myeloperoxidase against which the patients’ immune system produces the antibodies (ANCA) only as an effect (5); ANCA might not be a cause of vasculitis.

References


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