Case Report

Fatal cardiac small vessel involvement in ANCA-associated vasculitis: an autopsy case report

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Abstract

An 80-year-old Japanese man, who had fever and generalized fatigue not improved by antibiotics, was admitted to our hospital. Laboratory data indicative of renal dysfunction and anti-neutrophil cytoplasmic antibody (ANCA) in the serum led to the consideration of ANCA-associated vasculitis as a differential diagnosis. However, before the diagnostic confirmation, he was found dead on the bed. Autopsy revealed necrotizing crescentic glomerulonephritis in the kidneys. In addition, necrotizing granulomatous vasculitis with infiltration of multinucleated giant cells and neutrophils but not eosinophils was present in multiple organs. The direct cause of death was presumed as cardiac arrest by lethal arrhythmia because vasculitic lesions were distributed widely in the cardiac walls, acute congestion was observed in the systemic organs, and other causes of death were ruled out. This report presents the unusual manifestation of cardiac small vessel involvement in ANCA-associated vasculitis related to sudden death.

Key words: ANCA-associated vasculitis, cardiac small vessel involvement, sudden death, autopsy

1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA; Wegener), and eosinophilic granulomatosis with polyangiitis (EGPA; Churg-Strauss). MPA is a necrotizing vasculitis that preferentially affects the renal glomeruli with few immune deposits. In Japan, the majority of patients with MPA are positive for serum myeloperoxidase (MPO)-ANCA [1]. Inflammation that is not centered on the vessels, including granulomatous inflammation, is generally absent. On the other hand, GPA is a necrotizing granulomatous inflammation that usually involves the respiratory tract and simultaneously develops necrotizing small vessel vasculitis. Pauci-immune type necrotizing crescentic glomerulonephritis is common in GPA, as well as MPA. In the Japanese cohort, 54.6% of the patients with GPA are positive for serum MPO-ANCA with frequency noted to be higher than in western countries [1]. Lastly, EGPA is an eosinophil-rich and necrotizing granulomatous vasculitis that predominantly affects small to medium-sized vessels. This disease is associated with asthma or allergic sinusitis. The prominence of eosinophils in the blood and affected tissues is an essential feature.

Although all of these diseases can involve the systemic organs, including the central nervous system, cardiac involvement is relatively rare except for EGPA [2]. The frequency of cardiac involvement in EGPA is shown as 48% in the French study [3]. On the other hand, that in GPA varies from 4% to 44% among reports [4]. Contrary to EGPA and GPA, cardiac involvement in MPA is much rarer. The frequency is reported as approximately 10% in the European study [5] and 7.7% in the Japanese study [1]. The major cardiac manifestations of ANCA-associated vasculitis include myocarditis, valvular lesions, and coronary arteritis.

2. Clinical history

An 80-year-old Japanese man visited a physician with complaints of fever and generalized fatigue. Since antibiotic therapy did not improve the symptoms, he was then introduced to our hospital. He had been diagnosed with hypopharyngeal carcinoma two years ago and received chemoradiotherapy. At that time, he was in the disease- and drug-free state.

On admission, vital signs revealed body temperature of 38.8 ºC, blood pressure of 157/76 mmHg, and pulse rate of 86 per minute. The white blood cell count was 12300/μl with 2.0% eosinophils, red blood cell count was 328×10^4/μl, and platelet count was 44.3×10^4/μl. The following values indicated renal dysfunction; blood urea nitrogen: 46.8 mg/dl, creatinine: 3.67 mg/dl, and estimated glomerular filtration rate: 13.3%. In the serum, C-reactive protein was 14.87 mg/dl and MPO-ANCA was 130.0 IU/ml. On the other hand, proteinase 3-ANCA and other autoantibodies were negative.

The renal dysfunction with serum MPO-ANCA suggested MPA or GPA as differential diagnosis. EGPA could be ruled out because of the absence of asthma and related allergic diseases and eosinophilia. Before the confirmation of diagnosis, he died suddenly on the 7^{th} hospital day. Postmortem imaging of the central nervous system revealed only isolated lacunar infarctions but no subarachnoid hemorrhage. Autopsy of the thoracic and abdominal organs was performed at 6 hours later.

3. Pathological findings

The left and right kidneys had tiny cysts on the surface and weighed 210 g and 220 g, respectively. The heart showed mild dilatation and weighed 480 g. There was no remarkable macroscopic finding in the epicardial coronary arteries or scar in the myocardium.

Histological examination revealed necrotizing crescentic glomerulonephritis in the kidneys. Cellular crescent formation was evident in many glomeruli and sometimes with segmental fibrinoid necrosis (Figure 1a). Under the immunofluorescence microscopy, only fibrinogen was detected at the sites of segmental fibrinoid necrosis and crescents; thus, the glomerulonephritis was considered as pauci-immune type. Necrotizing vasculitis affecting interstitial small vessels was also found (Figures 1b and 1c). The perivascular infiltrate had a granulomatous appearance with vague palisading of macrophages adjacent to the necrosis.

In the heart, small vessels surrounded by myocardial bundles showed fibrinoid necrosis with palisading of macrophages, including multinucleated giant cells, and neutrophils but not eosinophils (Figures 2a-2c). Some CD3-positive T cells also infiltrated into the lesions (Figure 2d) but no amyloid deposition was detected by Congo red stain (Figure 2e). Affected vessels exhibited a transmural distribution in most parts of the left ventricle (Figure 2a). On the other hand, the vasculitic lesions did not involve surrounding myocardial bundles or the conduction system of the heart directly. The coronary arteries displayed only minimal atherosclerosis (Figure 2f). There was no evidence of acute myocardial infarction, myocarditis, marked myocyte hypertrophy, myocardial fibrosis, and valvular lesions. Slight atherosclerosis of the aorta was found but there was no aortitis.

Similar vasculitic lesions were evident in the prostate gland, right pleura,

spleen, liver, and adrenal glands. Marked acute congestion of the liver, lungs, and other organs was present, while there was no granulomatous inflammation in the respiratory tract.

4. Discussion

Although there is no necrotizing granuloma in the respiratory tract, GPA is a suggestive diagnosis of this patient. MPA cannot be definitely ruled out, whereas EGPA can be ruled out due to the absence of both asthma and related allergic condition in the clinical history and eosinophilic infiltration into the vasculitic lesions. Postmortem examinations, including the autopsy imaging, suggest the sudden occurrence of cardiac arrest, though the possibility of fatal vasculitic lesions in the brain remains. Since there is no evidence of acute myocardial infarction, the occurrence of fatal arrhythmia can be speculated as the direct cause of the sudden cardiac arrest. Ventricular tachycardia and fibrillation are regarded as the most popular arrhythmias leading to sudden cardiac arrest, and these arrhythmic attacks are prone to occur when pathologic lesions are present in the myocardium. Thus, it seems reasonable to consider that the prominent necrotizing vasculitis of the heart can be associated with the lethal arrhythmic attack in this patient. Although there are some cases of ANCA-associated vasculitis patients with sudden cardiac death caused by coronary arteritis in the literature [6], this is the first presentation of cardiac small vessel vasculitis related to sudden death in ANCA-associated vasculitis.

ANCA-associated vasculitis is now recognized as one of the popular diseases in elderly patients [7]. The effectiveness of novel therapeutics, such as retuximab, on elderly patients with this disease has been shown [8]. A positive outcome would be expected if the patient could receive such a promising treatment.

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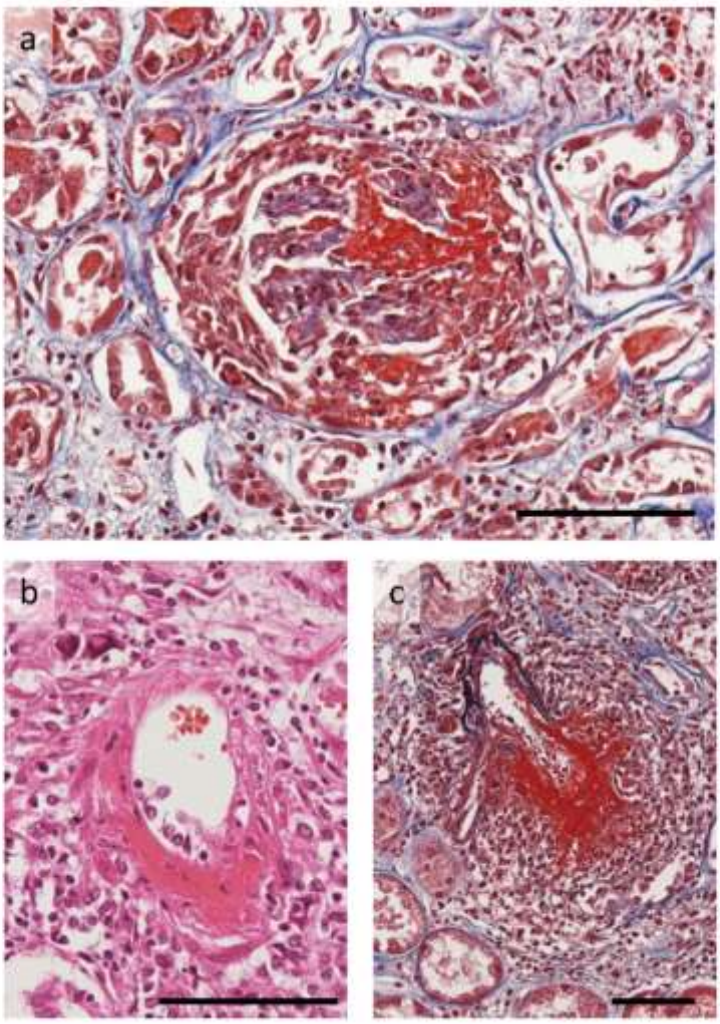

Figure 1. Glomerulus showing a segmental fuchsinophilic fibrinoid necrosis with circumferential cellular crescent formation (Masson trichome stain, **a**). Necrotizing arteritis affecting the renal interlobular arteries with granulomatous inflammation containing multinucleated giant cells. The fibrinoid necrosis is deeply acidophilic in hematoxylin and eosin stain **(b)** and fuchsinophilic in Masson trichrome stain **(c)**. Bar: 100 µm.

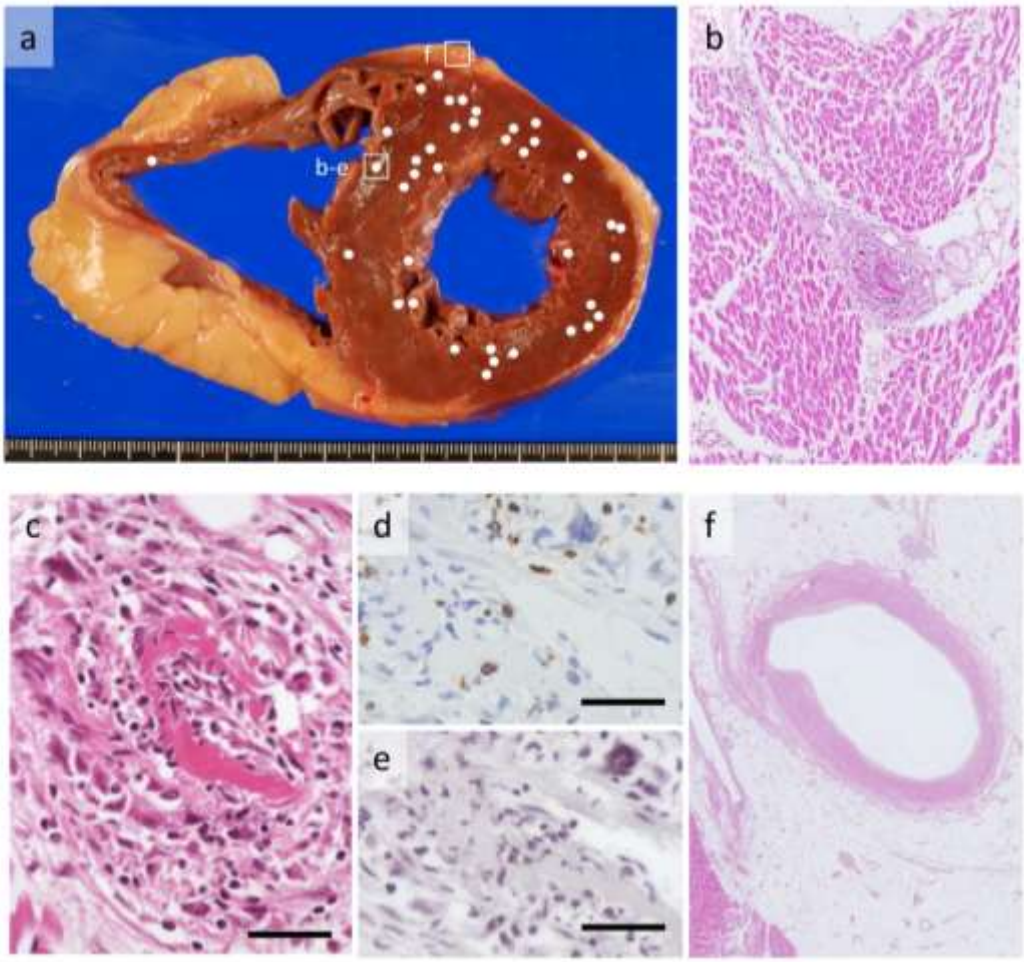

Figure 2. Necrotizing arteritis affecting small arteries surrounded by the cardiac muscle bundles with granulomatous inflammation containing multinucleated giant cells. Macroscopic view of the heart (**a**). White spots indicate the fields where vasculitic lesions are observed. Hematoxylin and eosin stain [low power field of view (**b**) and high power field of view (**c**)], CD3 immunostain (**d**), and Congo red stain (**e**). Bar: 100 μm. Hematoxylin and eosin stain of pericardial coronary artery showing no vasculitic change.