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Non-infectious endocarditis in a patient with cANCA-associated small vessel vasculitis

Sir, ANCs are frequently associated with a limited group of small vessel vasculitic syndromes, referred to as ANCA-associated small vessel vasculitis (ANCA-associated SVV) [1]. ANCA-associated SVV is the most common primary systemic small vessel vasculitis in adults and includes three categories: WG, microscopic polyangiitis and Churg–Strauss syndrome [1].

Non-infectious cardiac involvement in ANCA-associated SVV is more frequent than it is thought [2]. However, both ANCA-associated SVV with endocardial compromise and subacute bacterial endocarditis (SBE) have the many overlapped clinical manifestations including detectable vegetations by cardioechography, inflammatory signs, renal involvement and constitutional symptoms. In addition, streptococcal SBE sometimes shows positive cANCA testing [3]. Here we report a case of non-infectious endocarditis with ANCA-associated SVV, which could be diagnosed in early stage by careful clinical observation as well as laboratory findings.

A 67-year-old woman presented a 1-month history of fever, polymyalgia and anorexia. Two weeks before admission, she visited the former hospital and subsequently received antibiotic therapies. As her symptoms continued, she was admitted to our hospital. On admission, her temperature was 38.5°C. Heart rate was 80/min and blood pressure was 130/80 mmHg. Lungs were normal. Auscultation of the heart revealed a systolic murmur over the aortic area. On laboratory data, white blood cell counts were 16,400/mm³, with 84% neutrophils. CRP was 5.2 mg/dl. ESR was 121 mm/h. Blood cultures were performed four times and were all negative. Plasma glucose was 103 mg/dl. Electrolytes, proteinogram, renal function and liver enzymes were all within the normal range. Urinalysis revealed that glucose was 100 mg/dl, proteinuria 30 mg/dl, microalbuminuria 3+ [20–29 red blood cells/high-power field (HPF)]. Complements were all within the normal range. ANA was negative. RF was 38.7 U/ml (<19). The cANCA and pANCA by ELISA were 8.9 U/ml (<3.5) and <1.3 U/ml (<9.0), respectively. Anti-SS-A antibody was positive. Other serological tests including anti-SS-B antibody, anti-ds-DNA antibody, anti-Sm antibody, anti-RNP antibody, anti-cardiolipin β2GPI antibody, LAC, hepatitis B virus antigen and hepatitis C virus antibody were all negative. Electrocardiography showed inverted T wave in III, aVF and V3–V6. Echocardiography revealed the vegetation on the aortic valve, consistent with endocarditis (Fig. 1), with moderate AR. Chest X-rays showed cardiomegaly and pleuritis with bilateral pleural effusion. Chest CT revealed the infiltration of the left upper lobe, the pleuritis with bilateral pleural effusion and pericardial effusion. Abdominal CT detected no remarkable findings including mass, ascites and splenomegaly.

The administration of 30 mg daily of oral prednisolone (PSL) was started. Her clinical manifestations, such as fever, polymyalgia and anorexia, were improved within 8 days. Fourteen days after the administration of steroid therapy, all laboratory data, including CRP (0.1 mg/dl), ESR (24 mm/h), cANCA (3.7 U/ml) and findings of imaging tests, including electrocardiography, X-rays and CT, were almost normalized. The dosage of PSL was tapered gradually, and finally decreased to 12.5 mg daily at discharge. Though the laboratory data concerning inflammation improved, she complained of acute onset dyspnoea and oedema at discharge.
We diagnosed the present case as WG according to the diagnostic criteria for WG defined by the ACR [4] and positive cANCA by ELISA testing. The disease may run a course that varies from indolence to one of rapid progression leading to life-threatening multiorgan failure [5]. Most patients with WG do not survive more than a year after diagnosis, if they are not treated correctly [6]. In patients with WG, the non-specific symptoms are experienced during the initial phase and the characteristic granuloma is difficult to identify by the biopsy specimen, leading to a delay in the diagnosis of WG [5]. It has been previously reported that the average time from onset of symptoms to diagnosis of WG is 15 months with a range of immediate to 15 years [5].

Proteinase-3-ANCA (PR3-ANCA) is well known to be a specific marker of WG, which has a sensitivity and specificity of >90% [7]. Furthermore, it was less likely to detect other diseases and the results of positive cANCA only in ELISA shows to have a specificity of 98% [8]. It is recognized worldwide that ELISA testing against ANCA is superior to the IF method in the diagnosis of ANCA-associated SVV [8]. On the other hand, it is well known that a variety of infectious and non-infectious diseases could sometimes result in false positive ANCA tests by IF, associated with negative specific ELISA testing for anti-PR3 or anti-MPO [8]. Moreover, it has been reported that even if used by ELISA, there are the exclusive cases which could not be diagnosed as ANCA-associated SVV and that cANCA tests by IF and PR3-ANCA by ELISA are positive in some patients with SBE [3]. Therefore, it has been emphasized that the differences of clinical symptoms are important to differentiate those cases [9].

Cardiac involvement in WG is more common than generally thought, ranging from 6 to 44% of patients [2] and includes coronary arteritis, pericarditis, myocarditis, valvulitis/endocarditis, conduction system granuloma, sinus node arteritis, AV node arteritis, myocardial infarction and epicarditis [10]. In the present case, the findings of electrocardiography showed myocardial injury possibly caused by coronary arteritis, valvulitis or myocardial infarction, suggesting autoimmune cardiac involvement in WG. We assume that the autoimmune myocardial injury could be improved by steroid therapy, as the findings of electrocardiography were normalized after treatment. ANCA-associated SVV with endocardial compromise and ANCA-positive SBE have overlapping clinical and laboratory manifestations. ANCA-associated SVV with endocardial compromise involved almost exclusively the aortic valve and was associated with skin, renal, respiratory involvement, normal complement levels and the absence of splenomegaly [9]. In particular, echocardiographic findings had been documented to be able to detect aortic valve thickening including discrete vegetations and aortic insufficiency with or without aortic root dilatation. Discrete large vegetations seen on echocardiography suggest SBE; however, small discrete vegetations have also been sometimes reported in ANCA-associated SVV with endocardial compromise [9]. Therefore, the echocardiographic findings could not make definite diagnosis. We diagnosed the present case as the early stage of systemic ANCA-associated SVV associated with endocardial compromise but not SBE even though she had high fever and her echocardiogram revealed the vegetation on the aortic valve. The diagnosis could be reached by detailed observation of her clinical manifestations as well as positive cANCA testing and finally proved by pathohistological findings. Early diagnosis subsequently could start prompt steroid therapy, leading to the improvement of clinical and symptomatic manifestations as ANCA-associated SVV responds to immunosuppressive therapies, including the usage of steroids, cyclophosphamide or AZA, but does not respond to antibiotic therapies. In contrast, SBE responds to appropriate antibiotic therapies and adding immunosuppressive therapy is not effective and not recommended. Therefore, to avoid the unrequited and no effective treatments, we emphasize the importance for differentiating the non-infectious endocarditis with cANCA-associated SVV from infectious endocarditis in the early stage by careful clinical observations.

Rheumatology key message

- In ANCA-positive patients, it is important to differentiate non-infectious endocarditis from infectious endocarditis.

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Patients with anti-SRP antibodies have a clinical pattern typical of PM (typically developing rapidly progressive, severe, proximal muscle weakness with frequent occurrence of muscle atrophy) [2–4]. In general, patients have extremely high CK levels at presentation. The histological appearance of muscle biopsy specimens in anti-SRP myopathy is of sparse inflammatory infiltrate but significant muscle necrosis [2, 4].

In general, patients with anti-SRP antibodies have a good initial response to high-dose steroid therapy but the myopathy relapses with dose reduction leading to the requirement for very high cumulative doses of steroids [4]. Both of our patients failed AZA, MTX and mycophenolate mofetil prior to B-cell depletion therapy as is typical in these patients [3].

Anti-SRP myopathy is felt to be the disease primarily of the humoral immune system [5] and anti-SRP antibodies have been shown to inhibit the function of signal recognition proteins by inhibiting the binding of SRP to the SRP receptor [6], supporting a role for B-cell depletion in the treatment of the disease.

Rituximab has been used on a number of occasions for the treatment of refractory myositis [7–9] and good results have been reported in the treatment of anti-SRP myopathy with the use of rituximab following plasma exchange [5]. In our experience, whereas both patients had a rapid biochemical response the clinical response was not as impressive as previously reported. This may be due to the fact that some SRP-positive patients have been noted to have a paucity of hypertrophic fibres on muscle biopsy suggesting that the persistent weakness may be due to a lack of compensatory muscle hypertrophy [3].

In summary, we have reported our experience of treating two patients with anti-SRP myopathy, with aggressive B-cell depletion. Both patients had a poor clinical response, which is in contrast to the only other report of the use of rituximab in this patient population.

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