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CASE REPORT

Julio A. Chirinos · Vicente F. Corrales-Medina · Santiago Garcia · Daniel M. Lichtstein · Alan L. Bisno · Simon Chakko

Endocarditis associated with antineutrophil cytoplasmic antibodies: a case report and review of the literature

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Abstract We report a case of subacute bacterial endocarditis associated with small vessel vasculitis and a strongly positive cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) test. It is important to recognize this cause of positive c-ANCA because infectious endocarditis may closely mimic the clinical manifestations of ANCA-associated vasculitides such as Wegener granulomatosis or microscopic polyangiitis. Furthermore, ANCA-associated vasculitis may result in noninfectious endocarditis, which may be confused with bacterial endocarditis. In this paper, we review reported cases of ANCA-positive bacterial endocarditis and compare them to the reported cases of ANCA-associated idiopathic vasculitis with endocardial compromise.

Keywords Antineutrophil cytoplasmic antibodies · Endocarditis · Wegener granulomatosis

Abbreviations ANCA: Antineutrophil cytoplasmic antibodies · c-ANCA: Cytoplasmic antineutrophil cytoplasmic antibodies · p-ANCA: Perinuclear antineutrophil cytoplasmic antibodies · SBE: Subacute bacterial endocarditis · SVV: Small vessel vasculitis

Julio A. Chirinos and Vicente F. Corrales-Medina contributed equally in the preparation of this manuscript

J. A. Chirinos (✉) · V. F. Corrales-Medina · S. Garcia · D. M. Lichtstein · A. L. Bisno · S. Chakko
Department of Medicine, University of Miami, School of Medicine and Veterans Affairs Medical Center, Miami, FL, USA
e-mail: jchirinos@med.miami.edu
Tel.: +1-305-2828300
Fax: +1-305-9935170

Present address:
J. A. Chirinos
VAMC-Cardiology (111-A)
1201 NW 16th Street,
Miami, Florida 33125, USA

Introduction

Subacute bacterial endocarditis (SBE) is often associated with peripheral manifestations secondary to septic emboli and its complications (end-organ ischemia, metastatic abscesses) and/or to immunologic phenomena triggered by the infection. Many of the immunologic manifestations in SBE, including glomerulonephritis and cutaneous purpura, result from small vessel vasculitis (SVV).

The primary systemic vasculitides comprise of a broad group of syndromes characterized by inflammation of blood vessel walls [1]. Vasculitides are currently classified according to the size of the vessels involved and characteristic clinical and histopathologic findings. Antineutrophil cytoplasmic antibodies (ANCA) that are directed against either proteinase-3 (PR3) or myeloperoxidase are associated with a limited group of small vessel vasculitic syndromes. Wegener granulomatosis, microscopic polyangiitis, and the Churg–Strauss syndrome are associated with ANCA and are commonly referred to as ANCA-associated vasculitides [2]. These conditions have a variety of presentations, including cutaneous purpura, glomerulonephritis, and other manifestations of small vessel compromise. ANCA testing is useful to investigate suspected SVV and for the monitoring of ANCA-associated idiopathic vasculitis.

A variety of infectious and noninfectious diseases result in false positive ANCA tests by immunofluorescence. Most of these conditions are associated with negative specific ELISA testing for anti-PR3 of anti-myeloperoxidase [3]. ELISA testing is therefore more specific for ANCA-associated idiopathic vasculitis. In particular, the presence of cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) directed against PR3 is thought to be highly specific for Wegener granulomatosis [4]. SBE is a notable concern because it may be associated with c-ANCA with positivity for anti-PR3 by ELISA, and because many of the manifestations of SBE overlap with those of the ANCA-associated idiopathic vasculitides. Furthermore, noninfectious endocardial involvement is part of the spectrum of manifestations of the ANCA-associated vasculitides. The misdiagnosis of SBE as

ANCA-associated SVV and vice-versa can result in inappropriate therapy with catastrophic consequences. Here, we report a case of enterococcal SBE associated with a strongly positive c-ANCA. We review reported cases of infectious endocarditis associated with ANCA and cases of endocardial involvement in idiopathic ANCA-associated vasculitis in an attempt to compare these subgroups of patients.

Case report

A 47-year-old man presented with a 5-month history of weight loss, subjective fevers, chills, malaise, and a rash on the anterior aspect of both legs. He had a history of popliteal deep vein thrombosis 5 months earlier, for which he was being anticoagulated with warfarin (5 mg daily). His medical and surgical history was otherwise unremarkable. His family history was negative for thromboembolism or connective tissue disease. He had a history of heavy smoking and alcohol use and denied intravenous drug use or any recent dental procedures. Significant physical findings included a temperature of 103°F, an apical holosystolic murmur radiating to the axilla, a diastolic decrescendo murmur in the aortic area, and 3+ bilateral lower extremity edema. There was a purpuric rash on the anterior aspect of his legs. His neurologic exam was nonfocal and his abdominal exam was benign. Initial laboratory data revealed a white blood cell count of $6.0\times10^3/mm^3$, with 72.1% neutrophils, 16% lymphocytes, 10.3% monocytes, and 0.8% eosinophils. His hemoglobin was 9.3 g/dl and his platelet count was $158\times10^3/mm^3$. His biochemistry panel revealed a normal serum creatinine (1.1 mg/dl), total protein of 6.8 mg/dl, and albumin of 2.6 mg/dl. His prothrombin time international normalized ratio was 4.7; coumadin was held. A repeat duplex scan of the lower extremities revealed recanalization of his popliteal vein. C3 level was 33.8 mg/dl (normal: 79–152) and C4 was 11.7 mg/dl (normal: 16–38). CH50 was 16 U/ml (normal: 26–58 U/ml). Rheumatoid factor was positive at a high titer (>1:320, normal <20). He had a strongly positive c-ANCA test at a titer of 34 U/ml (normal <2). Urinalysis revealed 3–5 white blood cells/high-power field, hematuria (35–40 red blood cells/high-power field) and proteinuria. Erythrocyte sedimentation rate was 115 mm/h. Chest radiograph revealed blunting of the left costophrenic angle. A two-dimensional echocardiogram revealed vegetation on the aortic valve (Fig. 1a,b). Two days after admission, he complained of left upper quadrant pain and was found to have splenic infarctions and a splenic collection demonstrated by contrast-enhanced computed tomography. He underwent a prosthetic aortic valve replacement because of splenic embolization, and the splenic collection was drained percutaneously. The patient's blood, aortic valve, and splenic aspirate cultures were positive for ampicillin-sensitive *Enterococcus faecalis*. He was treated with ampicillin and gentamicin. He required a splenectomy due to nonresolving splenic infarctions and abscess. The urinary abnormalities and rash resolved with antibiotic therapy and the patient did well after splenectomy. A follow-up ANCA test was negative. Sixteen months later, the patient demonstrated no evidence of systemic vasculitis.

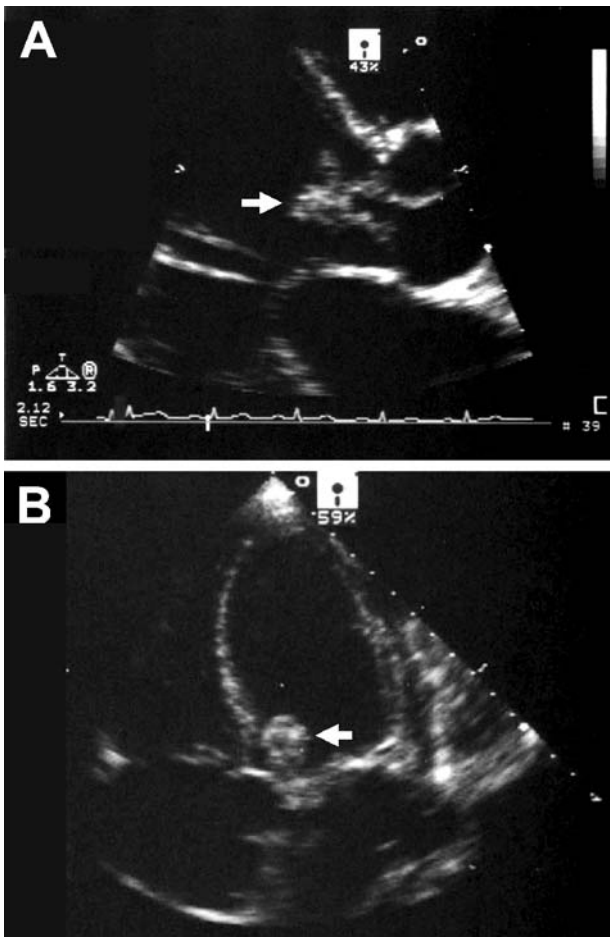

Fig. 1 Aortic valve vegetation as seen in the echocardiographic parasternal long axis view (**a**) and apical five-chamber view (**b**)

Literature search

Using a standard MEDLINE search (National Library of Medicine, Bethesda, MD, USA), we looked for reported cases of endocarditis associated with ANCA using the keywords: "endocarditis", "mitral", "aortic", "tricuspid", "pulmonary", "anti-neutrophil cytoplasmic antibodies", "ANCA", "Wegener's granulomatosis", "microscopic polyangiitis", "Churg–Strauss", and "cardiac" in different combinations. We complemented this search by cross-referencing published articles. We looked for two categories of reports. The first category included cases of endocarditis of infectious etiology associated with a positive ANCA test. The second category included cases of systemic ANCA-associated SVV with endocardial compromise in which no infectious etiology could be identified. For the first category of cases, we selected all reports in the English language that met all of the following criteria: (1) echocardiographic

findings consistent with endocarditis or histologic documentation of endocardial infection/inflammation in patients who underwent valve replacement or in whom a postmortem examination was performed; (2) identification of an organism by blood cultures, direct examination/cultures of the cardiac valves, or a clear response to antibiotic therapy without the use of immunosuppressive therapy; and (3) ANCA positivity by immunofluorescence (with either the cytoplasmic or the perinuclear pattern) and/or positivity for anti-myeloperoxidase or anti-PR3 antibodies by ELISA. For the second category, we selected reports that met all of the following criteria: (1) clinical findings consistent with the ANCA-associated systemic SVV (such as renal or pulmonary involvement, neuropathy, and upper airway disease); (2) presence of ANCA positivity by immunofluorescence, anti-myeloperoxidase or anti-PR3 antibodies by ELISA, or criteria for Wegener granulomatosis or Churg–Strauss syndrome as per the American College of Rheumatology classification system [5]; (3) histopathologic studies consistent with or diagnostic of any of the known ANCA-associated vasculitides; (4) endocardial compromise demonstrated by histopathologic or imaging studies; and (5) negative blood cultures and absence of histologic evidence of infection on microscopic valve tissue examination. Cases wherein immunosuppressive therapy and antibiotic therapy were administered simultaneously leading to uncertainty about the absence of underlying bacterial infection were excluded.

Infectious endocarditis associated with a positive ANCA test

We identified 11 case reports [6–12] of bacterial endocarditis associated with a positive ANCA test. After applying our selection criteria, we excluded three of them [6, 7] because no evidence of bacterial infection in blood cultures or histological examination of the valves was found.

Constitutional symptoms were reported in all patients. All cases had a subacute presentation; a more precise time course for symptoms before presentation was reported in seven cases and ranged from 4 weeks to >6 months. Skin manifestations were reported in seven cases, consisting usually of purpura (six cases). Splenomegaly demonstrated by computed tomography, ultrasound, or by physical exam was reported in three cases.

The erythrocyte sedimentation rate was elevated in all cases with values ranging between 35 and 115 mm/h; three cases were associated with values >100 mm/h. Anemia was reported in seven cases. The white blood cell count was elevated in only two cases. One case was associated with mild thrombocytopenia ($106\times10^3/mm^3$). Mild elevation of serum creatinine (up to 1.8 mg/dl) was reported in three cases. Urinalysis revealed active urinary sediment, with hematuria and/or proteinuria in all cases.

Seven cases had positive c-ANCA. All cases wherein ELISA testing was performed revealed positivity for anti-PR3 antibodies. The remaining case was positive for perinuclear ANCA (p-ANCA) but negative for anti-myeloperoxidase antibodies by ELISA. Interestingly, all cases were associated with at least one other positive autoantibody or elevated levels of circulating immune complexes. The most common positive autoantibody was rheumatoid factor (six cases); positive antinuclear antibody, cryoglobulins, and/or anticardiolipin antibodies were also reported. In addition, reported cases demonstrated some evidence of immune complex-mediated disease, such as low complement levels, vascular immune deposits, and/or elevated circulating immune complexes. Echocardiographic findings were reported for seven of the eight cases, revealing evidence of vegetations in five cases. Aortic involvement (with evidence by vegetations or significant aortic insufficiency) was present in three cases, mitral involvement in two, and concomitant aortic/mitral involvement in one case. One case corresponded to a pacemaker lead infection [8].

One case demonstrated negative bacterial cultures in blood and valve tissue, but there was evidence of bacterial colonies in the histopathology of the valve. The remaining seven cases had positive blood cultures for viridans streptococci (*Staphylococcuslugdunensis*, *Streptococcusbovis*, *Streptococcussanguis*), and our case had growth of *E. faecalis* from blood cultures (as well as valve tissue and from splenic collection material). Response to antibiotic treatment was good for the majority of cases, but one patient died from a ruptured mycotic aneurysm in the brain soon after initiation of therapy. Follow up of ANCA was reported in five cases, revealing a decrease or normalization of the titers after resolution of the SBE.

Systemic ANCA-associated SVV associated with endocardial compromise

We identified 17 cases of ANCA-associated idiopathic vasculitis with endocardial compromise [13–28]. Five cases were excluded after we applied our selection criteria, mainly because an underlying infectious etiology could not be ruled out with certainty [13–17]. One case was eliminated due to paucity of clinical data [18].

Constitutional symptoms were reported in most cases. The time course for symptoms before presentation for this condition ranged from 1 week to more than 11 months. In two cases, symptoms related to valvular dysfunction became apparent after more than 12 months of apparently successful immunosuppressive therapy with steroids and cyclophosphamide and remission of the ANCA-related SVV. Skin manifestations were reported in eight cases, purpura being the most common finding (six cases). Splenomegaly was not reported in any case. Elevated erythrocyte sedimentation rate was reported in five cases, with values ranging between 38 and 130 mm/h (with two cases >100 mm/h). Anemia was reported in seven cases. White blood cell counts were reported in nine cases, seven of which were abnormally elevated ($13–16\times10^3/mm^3$).

The presence of ANCA, anti-proteinase antibodies, or anti-myeloperoxidase antibodies was reported in nine cases. Seven had c-ANCA (with PR3 specificity by ELISA in the three tested cases), one had anti-PR3 antibodies with a negative immunofluorescence test, and in one

case the pattern of ANCA was not described. There was one report of positive antinuclear antibodies, one report of positive cryoagglutinins, and one report of a positive anticardiolipin test. Complement levels were reported in five cases. C3 levels were normal or high in all of them; C4 levels were normal in all but one case.

All patients were treated with combination therapy with steroids and cyclophosphamide or azathioprine. One patient died 1 day after initiation of treatment. Nine of the remaining ten cases demonstrated good clinical response to therapy, as judged by the manifestations of SVV. Of note, despite the fact that in most patients the SVV improved, nine out of ten cases required valve replacement, in some cases as late as 12 months after initiation of immunosuppressant therapy. Only one case showed resolution of valvular defects with immunosuppressant therapy.

The most common echocardiographic findings were aortic valve thickening and aortic insufficiency with or without aortic root dilatation. Evidence of discrete vegetations was reported in only three cases. Mitral valve involvement was reported in two cases. Interestingly, inflammatory granulomatous lesions suggestive of Wegener granulomatosis of the aortic valve were reported in only one case, the remaining cases showing myxoid or fibrinoid degeneration.

Discussion

The association of skin purpura, glomerulonephritis and constitutional symptoms suggests the diagnosis of SVV and frequently leads to the determination of ANCA in clinical practice. Cytoplasmic ANCA with anti-PR3 specificity is thought to be highly specific for idiopathic ANCA-associated vasculitis [4]. Nevertheless, these clinical manifestations may all result from SBE, which may also result in positive ANCA tests with anti-PR3 specificity, potentially leading to misdiagnosis and inappropriate therapy [6, 16]. Furthermore, ANCA-associated SVV can masquerade as SBE, resulting in a delay in potential organ-saving and lifesaving treatment.

Although a great degree of overlap in clinical and laboratory manifestations occurs between ANCA-associated SVV with endocardial compromise and ANCA-positive SBE, important differences in clinical presentation do exist between these entities (Table 1). Under appropriate circumstances, serial blood cultures should easily allow the clinician to detect streptococcal or enterococcal SBE. In addition, ANCA-positive SBE was associated with skin or renal involvement, low complement levels, circulating immune complexes/immune complex deposits, and other positive autoantibodies likely resulting from polyclonal B-cell activation. ANCA-associated idiopathic vasculitis with endocardial compromise involved almost exclusively the aortic valve, was associated with skin, renal and respiratory involvement, normal complement levels, and the absence of circulating immune complexes/immune complex deposits. Although discrete large vegetations seen on echocardiography suggest SBE, small discrete vegetations have been rarely reported in ANCA-associated vasculitis with endocardial compromise. An increased white blood cell count does not support an infectious etiology, and was actually more often reported in ANCA-associated SVV with endocardial compromise. Finally, splenomegaly, relatively common in SBE, is rare in Wegener granulomatosis; splenic infarctions are extremely rare in Wegener granulomatosis, with only four reported cases in the literature [13, 29, 30].

Reported cases of ANCA-positive SBE demonstrated hypocomplementemia, increased circulating immune com-

Table 1 Clinical and laboratory findings in patients with ANCA-associated vasculitis with cardiac valve involvement and patients with SBE and positive ANCA

	ANCA-associated idiopathic vasculitis (n=11)	Subacute bacterial endocarditis (n=8)
Age in years, mean (range)	40.6 (17–77)	57.6 (26–79)
Male to female ratio	9:2	3:1
Time course	Usually subacute (63.6%)	Subacute (100%)
Constitutional symptoms	Frequent (72.7%)	Frequent (100%)
Erythrocyte sedimentation rate range (mm/h)	38–130	35–115
White blood cell count, range ($\times 10^3/mm^3$)	Normal-16.1	3.69–16.4
Active urine sediment	Yes (100%)	Yes (100%)
Organ involvement	May include skin, kidneys, lungs and peripheral nerves	Limited to skin and kidneys
Other autoantibodies	Rare (rheumatoid factor, cryoglobulins, and anticardiolipin antibodies have been described)	Frequent, (including rheumatoid factor, antinuclear antibodies, cryoglobulins, and anticardiolipin antibodies)
Abnormal complement levels or report of immune deposits	Rare	Frequent
Valve involved	Aortic 100% Mitral 18.2% Both 18.2%	Aortic 62.5% Mitral 37.5% Both 12.5%
Need for valve replacement	Almost always	Uncommon

plexes, and/or immune complex deposition in histological specimens indicating that small vessel involvement was due to immune complex-mediated complement deposition rather than the pauci-immune inflammation that occurs in the ANCA-associated idiopathic vasculitides.

Interestingly, the course (and response to therapy) of endocardial involvement in the ANCA-associated SVV did not parallel the response of the small vessel disease component and lead almost invariably to the need for valve replacement in the reported cases. Histologic examination of compromised valves revealed myxomatoid or fibroid degeneration of the valve tissue rather than granulomatous inflammation in most cases, explaining the lack of response to immunosuppressive therapy. This suggests that damage occurring during the initial valvulitis could lead to further valve distortion despite remission of the valvulitis with immunosuppressive therapy.

Reversion of c-ANCA to negative with clinical resolution of the infection has been well documented. Follow-up of several years has been reported in some patients, who remained free of any evidence of systemic vasculitis, confirming that the presence of ANCA was falsely positive. Although it has been suggested that immunosuppressive therapy would benefit patients with high titers of PR3 ANCA [7], this treatment clearly should not be recommended because there is no evidence that ANCA plays a role in the pathogenesis of small vessel disease in SBE. Appropriate antibiotic treatment of the underlying infection has resulted in resolution of SVV and normalization of ANCA titers in such patients.

Conclusions

SBE and ANCA-associated systemic SVV have overlapping clinical manifestations. These include fever, constitutional symptoms, cutaneous purpura, glomerulonephritis, and laboratory evidence of the acute phase response. Awareness of false positive ANCA tests in SBE and possible endocardial involvement in idiopathic ANCA-associated vasculitis is important. If the differential diagnosis is considered, the distinction should not be difficult. Small vessel compromise in ANCA-positive SBE does not seem to be mediated by ANCA; it responds to appropriate antibiotic therapy, and adding immunosuppressive therapy is not indicated. Endocardial involvement in ANCA-associated idiopathic SVV does not usually respond to immunosuppressive treatment and usually progresses to the point where valve replacement is necessary, which may occur despite improvement or resolution of the manifestations of small vessel inflammation.

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