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Renal Disease in Patients with Infective Endocarditis and Antineutrophil Cytoplasmic Antibodies

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Abstract

Infective endocarditis triggers the development of multiple immunological reactions, including the formation of autoantibodies. Certain categories of autoantibodies triggered by endocarditis, for example, antineutrophil cytoplamic antibodies (ANCA), may cause secondary diseases that require special diagnostic approaches and at times special interventions. Formation of ANCA secondary to endocarditis has been linked to vasculitis and renal disease. To evaluate the characteristics of renal disease in patients with infective endocarditis developing ANCA, we reviewed the reports of this syndrome. Forty-eight patients with endocarditis and positive ANCA serology were identified. Renal manifestations, including hematuria, proteinuria, and various levels of decrease in glomerular filtration rate, were almost ubiquitous. Renal histology, available from percutaneous kidney biopsy or autopsy in 28 subjects, revealed various pictures, including tubular injury, acute interstitial nephritis, post-infectious glomerulonephritis, pauci-immune glomerulonephritis, and others. The histological characterization of the renal and other lesions, along with the clinical picture, influenced the methods of treatment. Treatment of the underlying infection with antibiotics was associated with substantial improvement of clinical and laboratory features in most patients. However, a small number of patients with ANCA-mediated renal disease required immunosuppressive medications (corticosteroids, cyclophosphamide) or plasma exchange, with prompt and sustained response to these treatments. Ten patients died as a consequence of the endocarditis and 20 patients had surgical cardiac interventions. Disease secondary to autoantibodies triggered by endocarditis may require immunosuppressive medications in addition to antibiotics. Use of immunosuppressives carries the risk of sepsis in a setting of established infection. Defining the histology of the renal lesion in patients with infective endocarditis, ANCA formation, and renal involvement is required to identify patients who can potentially profit from the addition of immunosuppressive medication to antibiotics.

Categories: Cardiology, Internal Medicine, Pathology
Keywords: infectious endocarditis, anca, postinfectious glomerulonephritis, pauci immune glomerulonephritis, vasculitis

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Introduction And Background

Renal dysfunction is frequent in patients with infective endocarditis [1-5] and, when present, increases the risk of poor surgical outcomes [6] and worsens the prognosis [7]. A variety of histological lesions is found in patients with endocarditis and renal disease. An analysis of renal histological specimens, 20 from renal biopsy and 42 from autopsy, from 62 patients with endocarditis [8], revealed the following findings: renal infarcts (19 specimens, all autopsy material), acute glomerulonephritis (16 specimens, both biopsy and autopsy material), acute tubular necrosis (12 specimens, both biopsy and autopsy material), acute interstitial nephritis (six specimens, all from biopsy material), cortical necrosis (six specimens, all from autopsy material), pre-existing glomerular pathology (five specimens, both biopsy and autopsy material), hydronephrosis (one specimen, autopsy material), and normal renal tissue (three specimens, all autopsy material).

Virchow first described systemic emboli in patients with endocarditis in 1858 [9]. Glomerular lesions have also been recognized for over a century [10]. The mechanism of glomerular involvement was initially thought to be infected micro-emboli [10]. It was subsequently recognized that post-infectious glomerulonephritis and other life-threatening diseases are caused by immune mechanisms triggered by infections. The pivotal observation by Williams and Kunkel that chronic bacterial endocarditis stimulates the development of abnormal laboratory tests that characterize specific immunological conditions [11] ushered the modern era of investigation of immunological complications of infections. Immune complex deposition in the glomerular filter was the first pathogenetic mechanism of glomerulonephritis in endocarditis to be identified [12-14]. Circulating immune complexes may also be present in this post-infectious glomerulonephritis setting [15].

It is now recognized that glomerulonephritis in the course of endocarditis may have more than one pathogenetic mechanism and histological manifestation. In the histological analysis of renal tissue in patients with endocarditis presented above [8], vasculitic glomerulonephritis was more common than the

post-infectious variety. An association between infective endocarditis, positive serology for anti-nuclear cytoplasmic antibodies (ANCA), and glomerulonephritis has also been established [16]. Subsequently, several case reports of infective endocarditis with positive ANCA serology and renal disease have appeared in print.

The development of ANCA and renal disease in a patient with endocarditis creates new and important diagnostic and management problems. In this review, we analyzed the reported cases. The focus of the review was on the clinical issues of the axis endocarditis, ANCA formation, and renal disease. Our aims were to analyze the clinical picture, etiology, treatment, and outcomes of the identified patients with ANCA formation during the course of endocarditis and to come to some conclusions, based on this analysis, on the specifics of diagnosis and treatment. The pathophysiology of ANCA formation during infections and of ANCA-mediated disease were outside the scope of this report and were not addressed.

Review

The literature search included PubMed searches under the topics “Endocarditis and ANCA” and “Endocarditis and Renal Disease”, plus review of the references in the articles found in the electronic search. Three authors conducted separate bibliographic searches. All publications found in this search were reviewed. The articles chosen for systematic review were those presenting documented cases of infective endocarditis with ANCA positive serology.

The following items from each selected report were reviewed separately by two authors: Demographic characteristics (age, gender, ethnicity), factors predisposing to endocarditis, presenting clinical manifestations, microbial etiology of endocarditis, echocardiographic, surgical, or autopsy findings in the cardiac valves, renal function tests, urinary findings (proteinuria, microscopy), hematological findings, serological tests, renal histology, management, and outcome, both of endocarditis and renal disease. Discrepancies between the two authors reviewing the same material were discussed and solved.

By the middle of February 2013, we found 36 publications [16-51] reporting 49 patients with infectious endocarditis and ANCA-positive serology. Two publications [45-46] reported varying aspects of the illness in the same patient. In addition, in the pathological series of Majumbar, et al. [8], one of five patients with infective endocarditis and vasculitic glomerulonephritis had a positive serum test for ANCA, but no other details were provided about this patient. Finally, we were unable to obtain one reference [51], which was not included in further analysis. Therefore, we will analyze 48 patients.

Clinical features

Among the 48 patients with infectious endocarditis and positive serologies for ANCA, eight (16.7%) were women and 40 (83.3%) were men. Age of the patients at presentation ranged between 24 and 87 years (Mean ± Standard Deviation 55.2±16.3 years). Ethnicity was not reported in a substantial number of patients.

Table *1* shows reported conditions predisposing to endocarditis. Among the 41 patients in whom a search was reported, only three had no predisposing conditions, 18 had one predisposing condition each, while 20 patients had two or more predisposing conditions each. Dental or gingival disease or procedures; preexisting abnormalities in native cardiac valves, primarily mitral valve prolapse (five patients) and aortic valve abnormalities (four patients); previous coronary artery surgery or cardiac instrumentation; and previous replacement of cardiac valve(s) were the four most common predisposing conditions. Typically, cardiac operations had been performed several years prior to the development of endocarditis.

Condition	Number of Patients	Percent of All Patients	Percent of Reported Problems[1]
Native heart valve abnormality	11	22.9	26.8
Dental/gingival disease/procedure	10	20.8	24.4
Previous coronary surgery-instrumentation	9	18.8	22
Implanted device (pacemaker, defibrillator)	4	8.3	9.8
Previous heart valve replacement	8	16.3	19.5
Recent corticosteroids/immunosuppressives	6	12.5	14.6
Cigarette smoking	6	12.5	14.6
Diabetes mellitus	6	12.5	14.6
Miscellaneous[2]	8	16.7	19.5
None found	3	6.3	7.5
Not reported	7	14.6	

TABLE 1: Conditions predisposing to infectious endocarditis in 48 patients with endocarditis and ANCA positivity.

(1) Case reports including information positive or negative on predisposing conditions; (2) Two exposures to kittens followed by Bartonella endocarditis. One each: recent previous infection outside the heart with the same microorganism; smoking crack cocaine, smoking marijuana, hepatitis C, non-alcoholic steatohepatitis, alcoholism.

Table 2 shows the infected valves and/or cardiac chambers. Aortic valve involvement was the most frequent, and mitral valve involvement, the second most frequent. Aortic or mitral valve involvement accounted for 89.6% of the cases. In 12.5% of the cases, two or more heart valves were infected. Six patients, five with documented aortic valve endocarditis, had previous aortic valve replacement. A fifth patient with three previous aortic valve replacements and one mitral valve replacement because of staphylococcal endocarditis had Staphylococcus aureus bacteremia but no vegetations in echocardiography [25]. This patient was not counted in the rows of total aortic and mitral valves involved in Table 2, but was counted in the rows of previously replaced aortic and mitral valves.

Valve	Number of Patients	Percent of All Ratients
Aortic, total	27	56.3
Previously replaced aortic valve	7	14.6
Mitral, total	16	33.3
Previously replaced mitral valve	3	6.3
Tricuspid	9	18.8
Pulmonic	2	4.2
Right atrium[1]	3	6.3
Two or more valves	6	12.5
Implanted devices	4	8.3

TABLE 2: Infected heart valves in 48 patients with infectious endocarditis and ANCA positivity.

1 Two patients with right atrial pacemaker wires, one patient with ventriculo-atrial shunt.

Thirty-seven patients (77.1%) had positive blood and/or tissue (removed valve) cultures. Five patients (10.4%) with positive blood cultures developed new murmurs. Typical histological features of infective endocarditis were found during surgical valve replacement in four patients (8.3%) and at autopsy in another two patients (4.2%). Echocardiography was the method for identifying the infected valve by demonstration of vegetations in 39 patients (81.3%). Surgical valve specimens confirmed the sonographic findings in 20 patients (41.7%).

Table *3* shows the microbial etiology of the infective endocarditis. Streptococcus species accounted for 33.3% of the cases and Staphylococcus species for 18.8%. These findings are not substantially different from those reported in studies of infectious endocarditis in the general population [52-57]. The identification of Bartonella species causing endocarditis was done by PCR analysis in four cases [18, 33, 35, 42], culture of the infected valve in one case [38], and high serum IgG antibody level in one case [45]. Culture-negative endocarditis in the setting of recent administration of antibiotics was diagnosed by characteristic echocardiographic findings and histological changes characteristic of infectious endocarditis in two surgically removed aortic valves [19, 24] and at autopsy in another case [37]. In three other reports [21-22, 50], culture-negative endocarditis was diagnosed in three patients who fulfilled the modified Duke criteria for infective endocarditis [58-59] and had appropriate responses to antibiotic treatment.

Microbial Agent	Number of Patients	Percent of All Patients	Reference
Streptococcus species	16	33.3	
Streptococcus viridans	9	18.1	16, 23[1,2],26,34[1],361
Streptococcus bovis	2	4.2	17,272
Streptococcus sanguis	1	2.1	23
Streptococcus parasanguis	1	2.1	28
Streptococcus oralis	1	2.1	31
Streptococcus mutans	1	2.1	48
a-Streptococcus	1	2.1	29
Staphylococcus species	9	18.8	
Staphylococcus aureus	5	10.4	24,32,40,43,44[1]
Staphylococcus coagulase negative	3	6.3	361
Staphylococcus lugdunensis	1	2.1	221
Enterococcus species	6	12.5	
Enterococcus faecalis	5	10.4	30,39,42,441,49
Enterococcus	1	2.1	361
Bartonella species	6	12.5	
Bartonella henselae	4	8.3	18,33,38,45
Bartonella quintana	2	4.2	35,421
Gemella species	2	4.2	
Gemella morbillorum	1	2.1	421
Gemella hemolysans	1	2.1	441
Actinobacillus actinomycetemcomitans	1	2.1	20
Neisseria flava	1	2.1	272
Propionibacterium acnes	1	2.1	421
Trophyrema whipplei	1	2.1	47

TABLE 3: Infectious agents causing endocarditis in 48 patients with ANCA positivity.

1 Two or more patients reported in the same reference. 2 Two microbial species cultured in the same blood.

Table *4* shows the presenting complaints and their frequency. The duration of symptoms prior to the diagnosis was longer than one month (up to one year) in 90.3% of the patients in whom duration of symptoms was reported. General symptoms of chronic disease, including anorexia, weight loss, weakness, fatigue, and malaise, were the most common symptoms, while among rheumatologic symptoms, arthralgias were the most common. In addition to the symptoms presented in Table *4*, several patients complained of skin rash or leg swelling.

Symptom	Number of Patients	Percent of All Patients	Percent of Reported Symptoms[1]
Duration until diagnosis	31	64.6	
Duration[2] 1 month	28	58.3	90.3
Anorexia, weight loss	18	37.5	58.1
Weight loss > 10 kg	7	14.6	70.02
Weakness, fatigue	15	31.3	48.4
Arthralgias	14	29.2	45.2
Malaise	13	27.1	41.9
Chills, sweating[3]	10	20.8	32.3
Dyspnea	9	18.8	29
Cough	7	14.6	21.9
Nausea, vomiting, abdominal pain	4	10.4	16.1
Myalgia	5	10.4	16.1
Epistaxis	2	4.2	6.5
Syncope/cerebrovascular accident	2	4.2	6.5

TABLE 4: Presenting complaints in 48 patients with infectious endocarditis and ANCA positivity.

1 Several reports did not contain any presenting symptoms. 2 The amount of weight loss was specified in 10 of the 18 patients with reported weight loss. 3 In all but two cases, night sweats were reported.

Table 5 shows objective clinical findings and their frequency. Fever, murmurs, skin rashes with predominance of purpura, renal manifestations, edematous states, central and peripheral neurological manifestations, splenomegaly, and hepatomegaly were reported with varying frequencies. Of note is that several reports contained limited information on clinical manifestations and only a few reports stated that the rest of clinical examination was normal.

Clinical Finding	Number of Patients	Percent of All Patients	Percent of Reported Patients[1]
Fever[2]	36	75	87.8
Murmur[2]	31	64.6	88.6
Rash	23	47.9	65.7
Purpura/splinter hemorrhage	19	39.6	54.3
Abnormal renal manifestations	45	94.1	95.7
Peripheral edema	16	33.3	42.1
Pulmonary congestion	8	16.7	21.6
Pleural effusion	8	16.7	21.6
Neurological manifestations[3]	16	33.3	41
Peripheral nervous system	10	20.8	25.6
Central nervous system	10	20.8	25.6
Splenomegaly	15	31.3	39.5
Hepatomegaly	7	14.6	18.4
Lung nodules, atelectasis, infiltrates	10	20.8	27.8
Miscellaneous[4]	5	10.4	14.3

TABLE 5: Objective clinical findings in 48 patients with infectious endocarditis and ANCA positivity.

1 Findings were missing in several reports. 2 A number of patients did not have fever or murmurs at presentation, but developed them after one or more days. 3 Three subjects had both central and peripheral neurological manifestations. 4 One each: ascites, esophageal varices, toe gangrene from infectious arterial emboli, occlusion of the left ulnar and radial artery without overt ischemic manifestations, and enlarged thoracic lymph nodes.

Nine patients with rashes had skin biopsies. Histology of these biopsies revealed leukocytoclastic vasculitis in five patients [23, 26-27, 31], no evidence of vasculitis or emboli without any other description in two [18, 39], necrotizing vasculitis of small and medium-sized arteries with fibrinoid necrosis and neutrophilic infiltrates in one [32], and suppurative inflammation suggesting septic embolism in one patient [44]. One patient with peripheral neuropathy had a sural nerve biopsy that revealed necrotizing vasculitis of small arteries without immune deposits, but with atrophy of the nerve fibers [25].

Laboratory tests

Blood hemoglobin, reported in 25 patients, ranged between 4.2 and 12.0 g/dL (9.0±1.9 g/dL), with 18 patients (70.0%) having hemoglobin levels less than 10 g/dL. Microcytosis and hypochromia were reported in several cases. One patient [21] was reported to have “moderate anemia.” One other patient [41] had a “normal hemogram." Blood hematocrit, measured in 15 patients, ranged between 20.5% and 36.5% (29.1±5.6%). Eight patients (53.3%) had a hematocrit less than 30%.

White blood cell count, reported in 31 patients, ranged between 2.5 and 25.3 x10 ^{3}/mm^{3} (10.0±5.8 x10^{3}/mm^{3}). Among these subjects, eight (25.8%) had leukocytosis (^{3} 10x10^{3}/mm^{3}) and six (19.4%) had leukopenia (< 4x10^{3}/mm^{3}) at least in one blood sample. Among the 16 patients with reported differential examination of the white blood cells, 11 (68.8%) had a shift to the left (neutrophils > 75% or appearance of immature white cells). In addition, one patient [16] was reported to have “no leukocytosis”, another patient [18] had “normal white cell count with a left shift,” and a third patient [19] had “leukopenia.”

Platelet count, reported in 26 patients, ranged between 42 and 554 x10 ^{3}/mm^{3} (170±77 x10^{3}/mm^{3}). Among these patients, seven (26.9%) had thrombocytopenia (platelet count < 100x10^{3}/mm^{3}) in at least one blood count. In addition, one patient [20] was reported to have “thrombopenia” and another patient [43] had a “normal platelet count.”

Table 6 shows erythrocyte sedimentation rate and serological tests other than ANCA. Erythrocyte sedimentation rate was elevated in all patients tested. Most patients had multiple abnormalities in their immunological tests in addition to ANCA. Normal or negative results were reported for hepatitis B and C serology (14 patients), liver function tests (eight patients), HIV serology (eight patients), anti-streptococcal antibodies (two patients), and serum creatine phosphokinase (one patient).

Test	Positive	Percent of All Patients	Percent of Reported Tests
+ Erythrocyte sedimentation rate[1]	23	47.9	100
+ C-reactive protein	35	72.9	94.6
+ Rheumatoid factor	18	37.5	81.8
+ Gamma-globulins[2]	20	41.7	95.2
- C_3 complement	20	41.7	62.5
- C_4 complement	14	29.2	45.2
- C_{H50} complement	13	27.1	61.9
+ Antinuclear antibodies[3]	12	25	37.5
+ Antiphospholipid antibodies	7	14.6	63.6
+ Cryoglobulins	7	14.6	36.8
+ Circulating immune complexes	5	10.4	83.3
+ Lactate dehydrogenase	5	10.4	71.4
+ Ferritin	3	6.3	75
+ Anti-beta2 glycoprotein	3	6.3	42.9
+ Fibrinogen	2	4.2	66.7
Miscellaneous[4]	4	8.3	100

TABLE 6: Erythrocyte sedimentation rate and abnormal serological tests other than ANCA in 48 patients with infectious endocarditis and ANCA positivity.

+ Abnormally high level. - Abnormally low level. 1 range: 35-140mm/hr; Mean±Standard Deviation 75±33 mm/hr. 2 Diffuse hypergammaglobulinemia or elevated levels of IgG or IgM. 3 at times only specific antibodies (e.g. antidouble stranded DNA antibody) were positive. 4 One each, d-dimers, anti-smooth muscle antibody, anti-F-actin antibody, lupus anticoagulant.

Table 7 shows ANCA profile. The majority of the patients had positive c-ANCA and/or anti-PR3 serologies. Four patients had positive c-ANCA and elevated titers of both anti-PR3 and anti-MPO antibodies [36, 48]. Two patients had elevated titers of all four ANCA antibodies [34]. Two patients had elevated p-ANCA but normal anti-MPO titer [19, 40]. One patient had elevated c-ANCA and normal anti-PR3 titer [47]. One patient had normal c-ANCA and elevated anti-PR3 titer [49]. One patient had at presentation elevated p-ANCA and anti-PR3 titers. However, at the end of follow-up, c-ANCA and anti-PR3 were elevated [27]. Finally, all four ANCA antibody titers were in the normal range in a patient with endocarditis and pauci-immune glomerulonephritis [28]. This patient was reported as an association between infective endocarditis and vasculitic disease because up to 10% of the patients with granulomatosis with polyangiitis or with microscopic polyangiitis have negative assays for ANCA [28, 60].

Test	Positive	Percent of All Patients	Percent of Reported Tests
c-ANCA[1]	31	64.6	86.1
Anti-PR3[2]	36	75	83.7
p-ANCA[1]	11	22.9	28.2
Anti-MPO[2]	11	22.9	27.5

TABLE 7: Anti-neutrophil cytoplasmic antibodies in 48 patients with infectious endocarditis and ANCA positivity,

1 Measured by immuno-fluorescence. 2 Measured by ELISA

Renal manifestations

These manifestations are shown in Table *8*. Hematuria and proteinuria were almost ubiquitous. Proteinuria in the nephrotic range was reported in 17.9% of the patients. Pyuria was also reported in a minority of the patients. It is possible that the low percent of patients with dysmorphic red blood cells and red cell casts is an underestimate because of failure to perform urine microscopy by a trained observer. While the majority of the patients had some degree of renal functional impairment, hemodialysis or other renal replacement methods were applied in only 15.0% of the patients.

Feature	Number of Patients	Percent of All Patients	Percent of Reported Problems
Hematuria	35	72.9	92.1
Dysmorphic red cells, red cell casts	12	25	36.42
Pyuria	63	12.5	18.22
Proteinuria	29	60.4	78.4
Nephrotic proteinuria	5	10.4	17.9
Renal function			
Not reported	10	20.8	
Normal4	8	16.7	21.1
Abnormal5	306	62.56	78.96
Renal replacement therapy	8	16.7	
Renal biopsy or autopsy	28	58.3	

TABLE 8: Renal manifestations in 48 patients with infectious endocarditis and ANCA positivity.

1 Findings were missing in several reports. 2 Probable underestimation due to absence of manual performance of urinalysis. 3 One patient[40] had urinary tract infection, but urine findings were not reported. 4 Serum creatinine ≤ 1.2 mg/dL, glomerular filtration rate (GFR) ≥ 60 mL/min, “biochemical profile normal”. 5 Serum creatinine > 1.3 mg/dL, GFR < 60 mL/min, “acute renal failure”, progressive renal failure”. 6 One patient in whom serum creatinine or estimated glomerular filtration rate data were missing had history of chronic glomerulonephritis.

Histological evaluation of the kidneys was reported in 28 patients [16, 19-22, 24, 26-29, 31, 33, 36-37, 41-42, 44-45, 48]. Three patients (22, 31, 37) had autopsies, and the remaining 23 patients had percutaneous kidney biopsies. One patient had two kidney biopsies. The final pathological diagnosis without any specific histological findings was reported in eight patients [33, 36]. Light microscopy was reported in the remaining 20 patients. Immunofluorescence findings were reported in 19 patients. Electron microscopy findings were reported in only four patients [29, 44, 48, 50].

Table *9* shows the histological diagnoses of renal pathology. Several biopsies exhibited more than one

histological entity (for example, post-infectious glomerulonephritis and acute interstitial nephritis). Post-infectious glomerulonephritis was the most common renal histological picture. Pauci-immune glomerulonephritis or renal vasculitis was found in four biopsies. Of note is that all four patients with this histological picture received, in addition to antibiotics, corticosteroids and/or other immunosuppressive treatments (see below). No specific ANCA pattern or titer was identified in the patients with pauci-immune glomerulonephritis or vasculitis.

Diagnosis	Number of Patients	Percent of All Patients	Percent of Reported Problems
Post-infectious glomerulonephritis	15	31.3	53.6
Pauci-immune glomerulonephritis/vasculitis	4	8.3	14.3
Acute interstitial nephritis	7	14.6	25
Tubular injury	2	4.2	7.7
Other renal histology [1]	3	6.3	10.7
Not identifiable glomerulonephritis [2]	6	12.5	21.4

TABLE 9: Renal histology in 28 patients with infectious endocarditis and ANCA positivity.

1 One each, focal embolic glomerulonephritis, focal glomerulosclerosis, chronic sclerosing glomerulonephritis. 2 Differentiation between post-infectious and pauci-immune glomerulonephritis was not possible, primarily because of absence of immunofluorescence findings. Several patients had histological features characteristic of more than one lesion, for example glomerulonephritis plus interstitial nephritis.

Treatment and outcome

Antibiotics were administered to all patients. However, the type of antibiotic was not specified in 12 cases. Initial antibiotic treatment included beta-lactam antibiotics in 30 patients (ampicillin - eight, ceftriaxone - six, penicillin - five, amoxicillin - four, oxacillin/cloxacillin/flucloxacillin - four, cefazolin - two, and cefoxitin - one), aminoglycosides in 23 patients (gentamicin - 21, tobramycin - one, netilmicin - one), vancomycin in six patients, imipenem/cilastatin or doxycycline in two patients, and one each rifampin, daptomycin, and amphotericin. A combination of a beta-lactam and an aminoglycoside was the most common initial treatment. Antibiotic treatment was changed after the results of the blood cultures became available in several instances, and its duration was up to one year of doxycycline after excision of an aortic valve infected with Bartonella henselae [33].

Surgical heart repair was performed in 24 patients (50%). Eleven patients [18-19, 21, 24, 30, 35-36, 38, 42, 44, 47] had aortic valve replacement; four patients [26, 28, 34, 36] had mitral valve replacement; four patients [25, 31, 33, 43] had both aortic and mitral valve replacement; one patient [49] had aortic, mitral and tricuspid valve repair; one patient [29] had closure of a ventricular septal defect; and one patient [23] had replacement of an infected pacemaker. The type of valve replacement was not reported in one patient with right atrial endocarditis [36].

Corticosteroids were administered to 17 patients (35.4%) [19-20, 22, 25, 28-29, 31-33, 36-37, 42, 44-45, 48]. Cyclophosphamide was administered to six patients [12.5%]. The first patient [19], placed on cyclophosphamide because of the diagnosis of Type III mixed cryoglobulinemia before the diagnosis of infectious endocarditis was established, improved clinically after aortic valve replacement, discontinuation of cyclophosphamide, and placement on antibiotics. The second patient [20] had been diagnosed with p-ANCA positive systemic vasculitis and glomerulonephritis several months prior to the diagnosis of infective endocarditis. Antibiotic institution led to rapid defervescence. No other follow-up was provided for this patient.

The third patient [25] received cyclophosphamide after a sural nerve biopsy revealed necrotizing vasculitis. His clinical status, which had been deteriorating while on antibiotics, improved rapidly after the start of the immunosuppressive medication. The fourth patient [33] was initially treated with cyclophosphamide and corticosteroids. The immunosuppressive regime was discontinued after a renal biopsy, which revealed a crescentic glomerulonephritis without features of ANCA-mediated disease [33]. The fifth patient [45] was initially diagnosed with ANCA-mediated disease. Discontinuation of cyclophosphamide and treatment with appropriate antibiotics after the diagnoses of Bartonella endocarditis and post-infectious glomerulonephritis were established led to the cure of this patient. The sixth patient [48], diagnosed with pauci-immune glomerulonephritis and probable cerebral vasculitis, improved rapidly after institution of cyclophosphamide therapy, while he previously had been rapidly deteriorating on antibiotics for two weeks prior to the initiation of immunosuppressive medications.

The indications for the use of intravenous gamma-globulin in three patients [36, 42, 44] were not specified. All three patients had downhill courses and died in a short time. Finally, one patient with pauci-immune glomerulonephritis and anuria while on antibiotics [28], improved rapidly and was able to discontinue hemodialysis soon after the third session of plasma exchange.

Ten patients (20.8%) died. Nine patients died between eight days and 2.5 months after the diagnosis of infective endocarditis. The causes of death included intracerebral hemorrhages, probably from mycotic aneurysms, in two patients [17, 31], sepsis in two [37, 44], cardiac disorders, including cardiovascular arrest and cardiogenic shock, in two [22, 44], and cerebral infarct probably secondary to septic cerebral embolism in one [42], while no cause of death was given for two patients [36]. Finally, one patient [43] was lost to follow-up and was found dead at home some time later.

Among patients who survived, duration of follow-up and course after diagnosis were not reported in three patients [20, 39-40]. In the remaining 35 patients, duration of follow-up after the diagnosis for infective endocarditis was two to 84 months (18.4±17.2 months). Clinical manifestations improved or disappeared in all. Follow-up of renal function was not reported in 10 patients. In the remaining patients, renal function improved substantially or was normalized in 24, while one patient had end-stage renal disease after 2.5 years of follow-up [36]. ANCA remained positive throughout the follow-up period in this patient and in another seven patients [19, 23-24, 27, 36, 44-45], although its titer decreased in three. ANCA became negative in 22 patients. The longest reported time period for normalization of ANCA was one year [35]. Follow-up of ANCA tests was not done or not reported in five patients [23, 28, 33, 40, 47].

Summary of clinical findings

The majority of the patients were middle-aged men. Conditions predisposing to infective endocarditis were present in almost all. Constitutional symptoms were present for months before the diagnosis of infective endocarditis. Fever, murmurs, renal manifestations, skin rashes, fluid retention, central and peripheral neurological signs, and splenomegaly were the most common clinical findings. The aortic and, to a lesser extent, the mitral valve were the most common sites infected. The microorganisms responsible for infectious endocarditis were similar to those causing endocarditis in the general population. Streptococcus species were the most common and Staphylococcus species the next more common causative agents.

Anemia was frequent at presentation, while blood leukocyte counts varied. Both leukopenia and severe leukocytosis were encountered. A shift to the left was the most frequent leukocyte abnormality, but differential white blood cell counts were reported in a relatively small number of patients. Most platelet counts were normal, but a few patients exhibited thrombocytopenia. The most striking laboratory feature was the presence of multiple abnormalities of tests indicating inflammation (ESR, CRP) and serologic tests indicating disorders of autoimmunity (in addition to ANCA, elevated titers of rheumatoid factor, ANA, anti-phospholipid antibodies and cryoglobulins, plus low serum complement levels).

Treatment of the endocarditis was started with a usual regime of combination of beta-lactam antibiotics and aminoglycosides in most cases. Blood cultures and serologic or histochemistry findings changed the antibiotic regimen in several instances. Corticosteroids were used in a number of patients. Immunosuppressives were also used in a smaller number of patients. Three patients with histological findings consistent with ANCA-mediated disease and progressive deterioration of their clinical status while on antibiotics had rapid clinical improvement after addition of immunosuppressive regimens, including cyclophosphamide and corticosteroids in two patients and plasma exchange in the third patient.

Half of the patients required cardiac surgery for valve replacement or other repairs. Approximately one-fifth of the patients died in a short time period after the diagnosis of infective endocarditis was made. The main causes of death were intracerebral hemorrhage or embolism, cardiac dysfunction, and sepsis. Antibiotic treatment, heart surgery, and in a few selected instances, addition to antibiotics of immunosuppressives and corticosteroids, was associated with great improvement of the clinical status in all survivors, and improvements in the renal function and the laboratory tests, including ANCA titers, in the majority of the survivors.

Differential diagnosis

The differential diagnosis is a critical aspect of infective endocarditis with ANCA positivity. The diagnostic difficulties are underlined by the facts that it took weeks to months to make the diagnosis in the majority of the cases and that several publications stressed the changing patterns of diagnosis and treatment as the clinical picture evolved. These difficulties are due to the lack of specificity of the presenting symptoms. A great variety of noxious entities, including infections, rheumatologic diseases, malignancies, metabolic diseases, and psychiatric diseases among others, can cause similar presentations.

Differentiating between a primary vasculitis and an infectious process associated with positive ANCA serology is the major diagnostic step initially. Constitutional symptoms, fever, and involvement of skin and kidneys are common in both entities, while splenomegaly, thrombocytopenia, hypocomplementemia, circulating immune complexes, and a multiplicity of serum autoantibodies are features suggesting chronic

infection [45]. In one study comparing 66 patients with primary ANCA-positive vasculitis and 17 patients with chronic infections (seven with infectious endocarditis) and positive ANCA serology, the only clinical differences between the two groups were higher frequencies of pulmonary and neurological manifestations in the patients with primary vasculitis and higher frequency of splenomegaly in the patients with endocarditis. Relapses were more frequent in the patients with primary vasculitis [36].

Although it has been suggested that elevated titers of specific ANCA are more common in primary vasculitic syndromes while low levels of multiple ANCA antibodies are usually seen in ANCA antibodies secondary to infections, the serum levels of various ANCA did not differ between patients with primary vasculitis and those with endocarditis [36]. Careful analysis of the evolution of the presenting picture, with emphasis on conditions predisposing to endocarditis, physical examination (murmurs, splenomegaly), echocardiographic findings, and repeated blood cultures can lead to the diagnosis of endocarditis. Specific histological findings in the cardiac valves are also useful.

A second major category of differential diagnosis is between infectious endocarditis and other conditions causing ANCA antibody formation. These conditions, the list of which is increasing, include other chronic infections [61], drugs including hydralazine, propylthiuracil, penicillamine, allopurinol, sulfasalazine [62], minocycline, procainamide, carbimazole, thiamazole, clozapine, phenytoin, and others, chronic inflammatory conditions, including systemic lupus erythematosus, rheumatoid arthritis [63], inflammatory bowel disease, primary sclerosing cholangitis, autoimmune hepatitis [64] and others, and various malignancies [65].

Renal manifestations are frequent in patients with endocarditis or primary vasculitis. The differential diagnosis of renal involvement in a patient with infective endocarditis and multiple autoantibodies involves several entities. Acute tubular injury can be the result of sepsis, hemodynamic disturbances caused by defective heart function, or antibiotics. Aminoglycosides, which are routinely used for the treatment of endocarditis, are an important cause of tubular injury. Treatments with newer antibiotics targeting specific microorganisms may have a lower incidence of tubular damage [66].

Septic emboli can cause renal disease. Acute interstitial nephritis is another part of the differential diagnosis of renal involvement. Antibiotics, particularly beta-lactam compounds, are a major cause of interstitial nephritis. However, it must be kept in mind that acute interstitial disease is part of the renal histology found in patients with primary ANCA-positive renal disease [67-68]. In acute interstitial nephritis, the cells infiltrating the renal interstitium are T-cells [69]. Cellular immunity has been proposed as a major mediator of ANCA-associated vasculitis [70].

The deposition of immune complexes, either circulating or formed in situ in the glomerular filter, may cause post-infectious glomerulonephritis. One other disease that can affect the kidneys and has been reported as a sequel of infectious endocarditis is Henoch-Schonlein purpura [71]. Finally, several autoantibodies triggered by infective endocarditis are markers of renal disease and may cause it. The association between lupus nephritis, high titers of specific ANA (for example, anti-double-stranded DNA, which has been reported in some patients with infective endocarditis and ANCA positivity), and low serum complement levels is well-known. The renal manifestations of antiphospholipid syndrome include proteinuria, hypertension, renal failure, and glomerular histological lesions, suggesting hemolytic-uremic syndrome [72-74]. Renal disease (vasculitis or pauci-immune glomerulonephritis) is a frequent manifestation of primary ANCA vasculitis. Animal experiments have provided evidence that ANCA causes renal disease [75].

The first step in identifying the type of renal disease in a patient with infective endocarditis and renal manifestations is an examination of the urinary sediment by an experienced observer. The finding of many brown casts suggests acute tubular injury. White cells and white cell casts are indicators of interstitial nephritis, while dysmorphic red blood cells and red cell casts are seen in glomerulonephritis. Usually serum complement levels are low in lupus nephritis or in post-infectious glomerulonephritis and not affected by ANCA-associated disease. The finding of circulating immune complexes may assist the diagnosis of a chronic infection, but cannot be used to differentiate between various types of renal disease.

Imaging methods that can be of help in the diagnosis of the type of renal disease include gallium scan, which may be of help in cases of interstitial nephritis [76], and fusion of a renal perfusion nuclear scan with computer tomography can help in the diagnosis of renal infarcts either from antiphospholipid syndrome [77] or from septic emboli. However, the most important step in the diagnosis of the renal disease is the performance of a kidney biopsy, which should be considered as imperative in this case, in view of the various mechanisms that can potentially cause renal disease, the presence of multiple autoantibodies, and the lack of specificity of ANCA findings in endocarditis.

So far, examination of renal tissue in patients with infectious endocarditis and ANCA positivity has not revealed lupus-like or antiphospholipid-mediated disease. The main question addressed by renal histology is the differentiation between post-infectious glomerulonephritis and ANCA-mediated disease. This differentiation may affect the treatment. Post-infectious glomerulonephritis usually responds to treatment of infective endocarditis with antibiotics. Some reports have suggested that addition of corticosteroids may

be of help [78-79]. The pediatric literature provided evidence that the development of ANCA (p-ANCA) does not affect the course of post-infectious glomerulonephritis [80]. The course of several patients with endocarditis, ANCA positivity, and post-infectious glomerulonephritis supports this contention. In addition to the kidneys, vasculitic manifestations in other organs (skin, nerves) constitute an indication for biopsy of these organs, which may change the treatment pattern.

The question raised by the findings of ANCA-associated pathology is whether specific treatment is needed for ANCA-associated disease. Of note is that there are instances when renal pathology suggests ANCA-associated disease in patients with infectious endocarditis and negative ANCA [81]. Much more important is the fact that ANCA-associated disease can cause endocarditis with echocardiographic findings very similar to those of infective endocarditis [82-95]. This causes major diagnostic difficulties, particularly in patients with negative blood cultures. Further, infectious endocarditis can develop on a valve with ANCA-associated disease [96]. At least one of the patients analyzed in this report [20] may also be an example of this sequence.

Finding ANCA-associated disease in a patient with infective endocarditis raises the question of treatment with immunosuppressives. This treatment is imperative if an infectious cause for endocarditis is ruled out in a patient with positive ANCA and echocardiographic findings suggesting endocarditis. However, cyclophosphamide and corticosteroids constitute major risks for infections in patients with ANCA-associated disease [97]. Immunosuppressive medications administered to patients with severe active infections may impair control of active bacterial infections [98]. Among the patients analyzed in this chapter, a small number (three) with a histological pictures of ANCA-associated disease and deterioration of the clinical status while on antibiotics only, had dramatic and sustained improvement after addition of immunosuppressives to their therapeutic regimen. Although this experience is limited, it appears that antibiotics alone may not be sufficient in treating some patients with infectious endocarditis and ANCA-associated disease. Identifying patients who have ANCA-associated endocarditis and those who have infectious endocarditis causing ANCA generation and ANCA-associated manifestations requiring addition of immunosuppressives to the antibiotics is the final great challenge in the differential diagnosis.

Conclusions

Certain types of infective endocarditis have acquired new prominence recently, and their complications may become more frequent. Specifically, Staphylococcus aureus bacteremia and endocarditis are increasing in frequency and have been characterized as “consequence of medical progress” [99]. For example, the increasing use of automatic implanted cardioverter defibrillators (AICDs) has led to an increase in infections, many from Staphylococcus aureus, related to these devices [100-101]. One of the complications of infective endocarditis is development of ANCA. The development of ANCA during the course of infective endocarditis is associated with multiple other serological abnormalities and with some clinical manifestations typically associated with ANCA. Currently there is no agreement about the effect of ANCA formation on the severity of post-infectious glomerulonephritis [80, 102], and more importantly, no specific ANCA findings pointing towards the diagnosis of pauci-immune glomerulonephritis versus other renal histology have been reported [36, 61]. The definitive diagnosis of the type of renal disease in a patient with endocarditis, multiple autoantibodies, and urinary findings suggesting glomerulonephritis requires performance of kidney biopsy.

Treatment of endocarditis using only antibiotics leads to disappearance of both serological abnormalities and clinical manifestations of ANCA-associated disease in many patients. However, infective endocarditis with ANCA-associated manifestations creates diagnostic difficulties and is a cause of morbidity and mortality. A few patients with ANCA triggered by endocarditis require immunosuppressive medications in addition to the antibiotics. Identifying these patients, as well as patients with endocarditis caused not by infectious agents but by granulomatosis with polyangiitis, constitutes a major diagnostic challenge.

Future developments will need to address several issues including: (a) Completion of the identification of the clinical picture by using a uniform methodology of description addressing appropriately the cardiologic, infectious, nephrologic, pathologic, rheumatologic, and surgical dimensions of the disease. Current bibliography suffers at times from emphasis on aspects interesting one subspecialty and ignoring other aspects; (b) Improvement of diagnostic methodologies. In this regard, a major question that can prove fruitful is whether a specific ANCA generated as a result of an infection can be identified and used clinically; (c) Investigation of the factors (genetic, environmental, others) that can lead to ANCA-associated disease triggered by infections and elucidation of the mechanism by which the interplay of these factors causes disease; and (d) Investigation of novel treatments based on the developments in the previous three categories.

Additional Information

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