CLINICAL RESEARCH STUDY

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Characteristics and Diagnostic Challenge of Antineutrophil Cytoplasmic Antibody Positive Infective Endocarditis

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ABSTRACT

OBJECTIVE: Antineutrophil cytoplasmic antibody (ANCA) has been reported in patients with infective endocarditis. Whether ANCA is associated with certain characteristics of infective endocarditis is unclear. The principal aim of this study is to investigate the clinical implications of ANCA in infective endocarditis and highlight the diagnostic challenge in ANCA-positive patients with infective endocarditis.

METHODS: A retrospective study was conducted in a tertiary hospital in China from August 2012 to December 2021. Patients with a diagnosis of infective endocarditis and available ANCA results were included in the study. The clinical and pathological characteristics were compared between ANCA-positive and ANCA-negative patients.

RESULTS: A total of 237 patients were included. Forty three (18.1%) were ANCA-positive, predominantly c-ANCA/anti-PR3. Compared to ANCA-negative patients, ANCA-positive patients had longer disease duration (P = .004), more frequent purpura (P = .015), macrohematuria (P = .002), proteinuria (P = .043), acute kidney injury (P = .004), and rapidly progressive glomerulonephritis (P = .010). Histologic findings of 8 patients with infective endocarditis-associated glomerulonephritis were reviewed. Two ANCA-positive patients with infective endocarditis presented with pauci-immune necrotizing and crescentic glomerulonephritis. A total of 18.6% of ANCA-positive patients with infective endocarditis were misdiagnosed as ANCA-associated vasculitis.

CONCLUSIONS: ANCA is detected in a substantial proportion of patients with infective endocarditis. The presence of ANCA in infective endocarditis is associated with longer disease duration, more frequent purpura, and kidney involvement. ANCA-positive infective endocarditis may mimic ANCA-associated vasculitis, and the differential diagnosis is challenging. Whether ANCA is pathogenic in infective endocarditis-associated small vessel vasculitis requires further study.

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KEYWORDS: ANCA; Diagnosis; Glomerulonephritis; Infective endocarditis

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA) is a well-known diagnostic marker for ANCA-associated vasculitis and is proven to be pathogenic in the disease.[1] However, it is suggested that ANCA may have clinical and pathogenic relevance in other diseases such as various autoimmune, infectious, and neoplastic diseases.[2]

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Serologic ANCA positivity has been detected in patients with a variety of chronic infections.[3] Previous studies showed that ANCA can be found in a substantial proportion (18%-33%) of patients with infective endocarditis.[4-8] The clinical implications of ANCA presence in infective endocarditis have been investigated by a few studies,[4-7] but no clear associations between characteristics of infective endocarditis and ANCA positivity were established, possibly due to small sample sizes (39-109 patients).

The presence of ANCA in infective endocarditis may complicate the differential diagnosis between infective endocarditis and ANCA-associated vasculitis. It has been noted in sporadic case reports that ANCA-positive infective endocarditis may closely mimic ANCA-associated vasculitis by the presence of ANCA and overlapping clinical and pathological manifestations such as cutaneous vasculitis and glomerulonephritis.[9,10] But the diagnostic challenge in ANCA-positive infective endocarditis has not been evaluated in studies with a substantial number of patients.

The principal aim of this study is to investigate the clinical implications of infective endocarditis-associated ANCA and highlight the diagnostic challenge in ANCA-positive infective endocarditis.

CLINICAL SIGNIFICANCE

- A total of 18.1% of the 237 patients with infective endocarditis were anti-neutrophil cytoplasmic antibody (ANCA)-positive.
- ANCA positivity in infective endocarditis was associated with longer disease duration, more frequent purpura, and kidney involvement. Pauci-immune necrotizing and crescentic glomerulonephritis was presented in 2 ANCA-positive patients with infective endocarditis.
- A total of 18.6% of ANCA-positive patients with infective endocarditis were initially misdiagnosed as ANCA-associated vasculitis, highlighting the diagnostic challenge.

PATIENTS AND METHODS

This was a retrospective study. Between August 1, 2012, and December 28, 2021, all consecutive patients hospitalized for an acute episode of infective endocarditis at a tertiary hospital (Peking Union Medical College Hospital, Beijing, China) were retrieved. Patients with preinfective endocarditis end-stage renal disease, primary rheumatic disease, or incomplete data were excluded. Only patients tested for ANCA during the course of infective endocarditis were included in the study. Patients were classified as "ANCA-positive" or "ANCA-negative." For ANCA-positive patients, investigations to exclude the possibility of drug- or tumor-associated ANCA were carried out. Demographic, clinical, and laboratory data was collected from medical charts.

Cytoplasmic ANCA (c-ANCA) and perinuclear ANCA (p-ANCA) were detected by indirect immunofluorescence ([IIF] normal <1:10). Specific antibodies to proteinase 3 (anti-PR3) and myeloperoxidase (anti-MPO) were detected by enzyme-linked immunosorbent assay (ELISA, normal <20 RU/mL, before 2021) or chemiluminescence immunoassay ([CLIA] normal <16 RU/mL, after 2021). IIF combined with ELISA/CLIA were performed for every patient tested for ANCA.

The study complied with the Declaration of Helsinki. The study was approved by the institutional review board of Peking Union Medical College Hospital (S-K1956).

Definitions

Adult patients with definite or possible diagnosis of infective endocarditis based on the modified Duke criteria[11] and with available ANCA results were included in the study. ANCA results were classified as positive if any of the following was positive: cANCA, pANCA, anti-PR3, or anti-MPO. Acute kidney injury was defined according to the Kidney Disease: Improving Global Outcomes definition as an increase in serum creatinine by ≥0.3 mg/dL within 48 hours or to 1.5 times baseline within the prior 7 days.[12] Baseline serum creatinine was sought in each patient's medical records prior to the infection. When unavailable, the lowest serum creatinine during follow-up was used. Rapidly progressive glomerulonephritis (RPGN) was defined as rapid decline in kidney function accompanied by urinary findings of glomerulonephritis.[13] Disease duration was defined as the duration between the onset of symptoms to the diagnosis of infective endocarditis.

Statistical Analysis

Continuous variables were reported as mean ± standard deviation (SD) or median (interquartile range [IQR]) and were compared using Student's *t*-test or Mann-Whitney U tests based on the normality of data. Categorical variables were reported as n (%) and were compared by χ^2 test or Fisher exact test as appropriate. Two-sided *P* values of less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 26.

RESULTS

Prevalence of ANCA in Patients with Infective Endocarditis

A total of 564 patients hospitalized for an acute episode of infective endocarditis were retrieved after excluding 38 patients (7 had primary rheumatic disease, 15 had

Table 1 Prevalence of ANCA in Patients with Infective Endocarditis

ANCA results	Number of cases (N = 237)
ANCA by IIF or ELISA/CLIA	43 (18.1%)
ANCA by IIF	26 (10.9%)
cANCA	19 (8.0%)
pANCA	7 (2.9%)
ANCA by ELISA/CLIA	35 (14.7%)
Anti-PR3	34 (14.3%)
Titer of anti-PR3	87 (57-169)
Anti-MPO	6 (2.5%)
Titer of anti-MPO	37 (29-82)
Anti-PR3 + anti-MPO	5 (2.1%)

ANCA = antineutrophil cytoplasmic antibody; Anti-MPO = antibodies to myeloperoxidase; Anti-PR3 = antibodies to proteinase 3; cANCA = cytoplasmic ANCA; CLIA = chemiluminescence immunoassay; ELISA = enzyme-linked immunosorbent assay; IIF = indirect immunofluorescence; pANCA = perinuclear ANCA.

preinfective endocarditis end-stage renal disease, 16 had incomplete files). Among the 564 patients, ANCA was tested in 237 patients among whom 43 (18.1%) were ANCA-positive. Drug- or tumor-associated ANCA was ruled out. As shown in Table 1, infective endocarditis-associated ANCA were predominantly c-ANCA (8.0%, 19 out of 237) and anti-PR3 (14.3%, 34 out of 237). P-ANCA and anti-MPO were present in 2.9% (7 out of 237) and 2.5% (6 out of 237) of patients, respectively. Dual positivity of anti-PR3 and anti-MPO was observed in 2.1% (5 out of 237) of patients.

Clinical Characteristics and Laboratory Studies

The clinical characteristics of the 237 patients tested for ANCA are summarized in Table 2. There was a male predominance with a median age of 48 years. A total of 92% of patients had definite infective endocarditis and 84.4% had echo-documented vegetation. *Streptococcus viridans* were the most common microorganisms (42.2%), followed by *Staphylococcus aureus* (11.0%). Fever, embolism, and heart failure were common, which occurred in 98.7%, 55.3%, and 28.7% of patients, respectively. Rash was present in 31.6% of patients, including purpura, Janeway lesion, and Osler nodule. Hematuria and proteinuria were present in 58.8% and 35.5% of patients, respectively. Among the 134 patients with hematuria, 91 patients had urine sediment analysis that revealed a predominance of dysmorphic erythrocytes in 83.5% of patients, suggesting glomerulonephritis. Acute kidney injury was present in 24.9% of patients at admission. A total of 19 patients had clinical manifestations of RPGN.

We compared the clinical characteristics between ANCA-positive and ANCA-negative patients with infective endocarditis. No significant difference was observed in demographic, comorbidity, microorganism, or valvular involvement between the 2 groups. Clinical manifestations including fever, heart failure, shock, embolism, and arthralgia were not significantly different. However, compared to ANCA-negative patients, ANCA-positive patients had longer disease duration (4.0 vs 2.5 months, $P = .004$). In addition, ANCA-positive patients more frequently presented with purpura ($P = .015$) and kidney involvement including hematuria 3+ ($P = .001$), macrohematuria ($P = .002$), proteinuria ($P = .043$), acute kidney injury ($P = .004$), and RPGN ($P = .010$).

Moreover, ANCA-positive patients more frequently had other serologic abnormalities including hypocomplementemia ($P < .001$) and the presence of antinuclear antibody ($P = .024$) and rheumatoid factor ($P < .001$). The frequency of antiphospholipid antibodies was not significantly different, but only a half of patients were tested for antiphospholipid antibodies.

Renal Histology

Six ANCA-negative patients during the study period underwent renal biopsies that revealed glomerulonephritis in 5 and acute interstitial nephritis in 1. Three additional patients with biopsy-proven infective endocarditis-associated glomerulonephritis beyond the study period (from 2004 to 2011) were retrieved from our biopsy database, and all of them were positive for c-ANCA and anti-PR3. All the 8 patients (5 ANCA-negative, 3 ANCA-positive) with biopsy-proven infective endocarditis-associated glomerulonephritis had clinical manifestations of RPGN. The histologic findings of the 8 patients were previously summarized in our study on infective endocarditis-associated RPGN.[14] On light microscopy, all the 8 patients presented with mesangial or endothelial hypercellularity with extensive crescents formation in 7 patients. Fibrinoid necrosis was observed in 2 of the 3 ANCA-positive patients but none of the 5 ANCA-negative patients. On immunofluorescence, immune deposits were observed in 6 patients, predominantly C3. Two ANCA-positive patients had no significant deposition of immunoglobulin or complement. Two ANCA-positive patients presented with pauci-immune necrotizing and crescentic glomerulonephritis (Figure), closely mimicking the histologic features of ANCA-associated vasculitis.

Diagnostic Challenge in ANCA-Positive Patients with Infective Endocarditis

It is of note that 18 (41.9%) of the 43 ANCA-positive patients with infective endocarditis were initially misdiagnosed as autoimmune diseases, leading to commencement of immunosuppressive therapy in 11 patients before the diagnosis of infective endocarditis. Specifically, 8 (18.6%) patients were initially considered to have ANCA-associated vasculitis, highlighting the diagnostic challenge in ANCA-positive infective endocarditis.

Treatment and Outcome

All of the 237 patients received antibiotic therapy. Cardiac surgery was performed in 170 (71.7%) patients, and this did

Table 2 Characteristics of ANCA-Positive and ANCA-Negative Patients with Infective Endocarditis

	All patients (N = 237)	ANCA (+)(n = 43)	ANCA (−)(n = 194)	*P* Value
Demographic data				
Age (years)	48 (32-59)	46 (28-56)	48 (34-60)	.110
Male gender	161 (67.9%)	26 (60.5%)	135 (69.6%)	.246
Comorbidities				
Chronic kidney disease	3 (1.3%)	0%	3 (1.5%)	>.999
Hypertension	53 (22.4%)	8 (18.6%)	45 (23.2%)	.513
Diabetes mellitus	18 (7.6%)	4 (9.3%)	14 (7.2%)	.749
IE characteristics				
Definite IE	218 (92.0%)	40 (93.0%)	178 (91.8%)	>.999
Prosthetic valve	15 (6.3%)	3 (7.0%)	12 (6.2%)	.739
Multiple valve involvement	31 (13.1%)	9 (20.9%)	22 (11.3%)	.092
Echo-documented vegetation	200 (84.4%)	38 (88.4%)	162 (83.5%)	.426
Microorganisms				
Staphylococcus. aureus	26 (11.0%)	4 (9.3%)	22 (11.3%)	>.999
Streptococcus viridans	100 (42.2%)	18 (41.9%)	82 (42.3%)	.961
Culture negative	61 (25.7%)	9 (20.9%)	52 (26.8%)	.425
Clinical manifestations				
Disease duration (months)	3.0 (1.0-4.8)	4.0 (1.5-7.5)	2.5 (1.0-4.0)	.004
Fever	234 (98.7%)	41 (95.3%)	193 (99.5%)	.086
Embolic events*	131 (55.3%)	28 (65.1%)	103 (53.1%)	.151
Heart failure	68 (28.7%)	17 (39.5%)	51 (26.3%)	.082
Shock	19 (8.0%)	4 (9.3%)	15 (7.7%)	.757
Arthralgia	53 (22.4%)	13 (30.2%)	40 (20.6%)	.171
Skin	75 (31.6%)	20 (46.5%)	55 (28.4%)	.021
Purpura	29 (12.2%)	10 (23.3%)	19 (9.8%)	.015
Janeway lesion	31 (13.1%)	6 (14.0%)	25 (12.9%)	.851
Osler nodule	25 (10.5%)	6 (14.0%)	19 (9.8%)	.416
Kidney				
AKI at admission	59 (24.9%)	18 (41.9%)	41 (21.1%)	.004
RPGN	19 (8.0%)	8 (18.6%)	11 (5.7%)	.010
Macrohematuria	15 (6.3%)	8 (18.6%)	7 (3.6%)	.002
Hematuria	134/228 (58.8%)	29/43 (67.4%)	105/185 (56.8%)	.200
Hematuria 3+	74/228 (32.5%)	23/43 (53.5%)	51/185 (27.6%)	.001
Proteinuria	81/228 (35.5%)	21/43 (48.8%)	60/185 (32.4%)	.043
Serological abnormalities				
Antinuclear antibody	52/219 (23.7%)	15/40 (37.5%)	37/179 (20.7%)	.024
Anti-double-stranded DNA	8/218 (3.7%)	3/40 (7.5%)	5/178 (2.8%)	.164
Anticardiolipin	27/106 (25.5%)	6/29 (20.7%)	21/77 (27.3%)	.488
Anti-β2 glycoprotein-1	28/103 (27.2%)	6/28 (21.4%)	22/75 (29.3%)	.422
Rheumatoid factor	87/185 (47.0%)	26/33 (78.8%)	61/152 (40.1%)	<.001
Hypocomplementemia	61/187 (32.6%)	21/36 (58.3%)	40/151 (26.5%)	<.001

AKI = acute kidney injury; ANCA = antineutrophil cytoplasmic antibody; IE = infective endocarditis; RPGN = rapidly progressive glomerulonephritis.
*Renal embolism was presented in 5 patients who were all ANCA-negative.

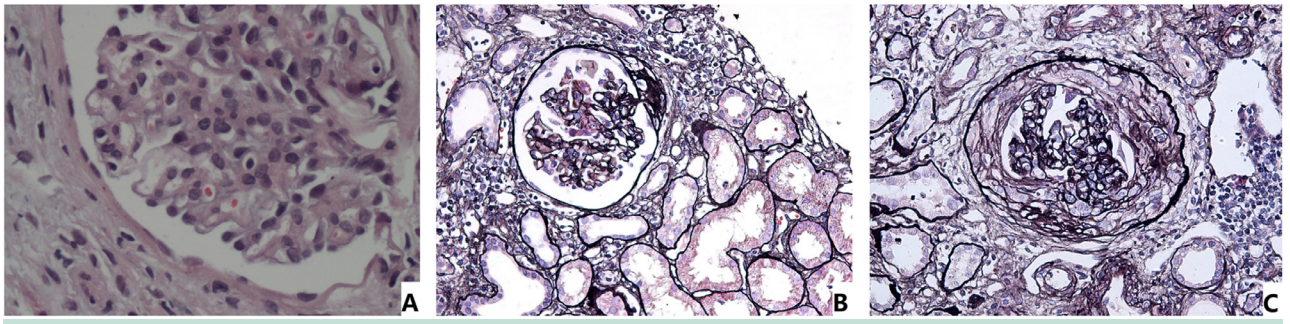

Figure **(A)** Endocapillary hypercellularity (HE × 400) **(B)** Focal glomerular necrosis (PASM × 200). **(C)** Crescent formation (PASM × 200). HE = hematoxylin and eosin; PASM = Periodic Schiff-Methenamine Silver.

not differ between patients with or without ANCA (79.1% vs 70.1%, $P = .237$). A total of 17 (7.2%) patients died during hospitalization. No significant difference regarding in-hospital death was observed between ANCA-positive and ANCA-negative patients (2.3% vs 8.2%, $P = .323$).

ANCA titers after treatment were followed up for 10 patients who were positive for anti-PR3, and the median time of follow-up was 3 months (IQR 1-10). ANCA titers turned negative in 4 patients and significantly decreased in another 5 patients after successful anti-infective treatment but without significant reduction in 1 patient in whom infective endocarditis was not in good control.

In our study, 8 patients had ANCA-positive infective endocarditis-associated RPGN. All the 8 patients received antibiotics and 7 underwent surgery. Four patients received immunosuppressive therapy during the course of anti-infective therapy. After a median follow-up of 11 months (IQR 5-18), all patients achieved recovery of renal function. At the last follow-up, 3 patients with immunosuppression and 3 patients without immunosuppression had serum creatinine <1.2 mg/dL. The other 2 patients had serum creatinine of 1.7 and 2.2 mg/dL, respectively.

DISCUSSION

This study investigated the prevalence and clinical significance of ANCA in infective endocarditis in the largest series of infective endocarditis to date. Among the 237 patients with infective endocarditis who had available ANCA results, 18.1% were ANCA positive. Compared with patients without ANCA, those with ANCA more frequently presented with purpura, severe hematuria, proteinuria, acute kidney injury, and RPGN. In all, 18.6% of ANCA-positive patients were initially misdiagnosed as ANCA-associated vasculitis, highlighting the diagnostic challenge.

The prevalence of ANCA in our study is consistent with previous studies,[4-8] which reported ANCA in 18%-33% of patients with infective endocarditis. Consistent with previous studies, ANCA associated with infective endocarditis were predominantly cANCA and anti-PR3. Dual positivity (anti-PR3 and anti-MPO) were detected in 5 patients, confirming previous observation.[5,8]

In the current study, a longer disease duration was observed in patients with ANCA than in those without ANCA. Langlois et al[5] also observed a longer disease duration in ANCA-positive patients. The longer disease duration in ANCA-positive infective endocarditis may be explained by the difficulty of early diagnosis in these patients. Another explanation could be that ANCA is usually associated with chronic infections with prolonged disease duration.[3] Therefore, ANCA is more likely to be present in infective endocarditis patients with prolonged disease duration.

The current study revealed a higher frequency of purpura in patients with ANCA than in those without ANCA. The association between ANCA and rash in patients with infective endocarditis were investigated in 2 previous studies that revealed a higher frequency of rash or purpura in ANCA-positive patients but lacked statistical significance,[5,6] possibly due to the small sample sizes.

Infective endocarditis-associated glomerulonephritis is well-recognized, but the exact prevalence of glomerulonephritis in infective endocarditis is unknown. In our study, hematuria and proteinuria were present in 58.8% and 35.5% of patients, respectively. A predominance of dysmorphic erythrocytes in most patients with hematuria suggested a high prevalence of infective endocarditis-associated glomerulonephritis in our cohort. In the current study, ANCA-positive patients more frequently presented with urine occult blood 3+ ($P = .001$), macrohematuria ($P = .002$), and proteinuria ($P = .043$), suggesting a higher frequency of glomerulonephritis in patients with ANCA. Moreover, the frequency of RPGN was significantly higher in ANCA-positive patients ($P = .010$). Acute kidney injury was present in 24.9% of patients at admission, and it was more frequent in patients with ANCA than those without ANCA ($P = .024$). Taken together, our study suggested an association between ANCA and kidney involvement in infective endocarditis, consistent with 2 previous studies that revealed more frequent renal failure and a higher level of serum creatinine in ANCA-positive patients compared with ANCA-negative patients.[4,5] We are aware of only 1 previous study exploring the association between ANCA and hematuria/proteinuria in patients with infective endocarditis. The study revealed no significant difference in the frequency of hematuria and proteinuria between patients with and without ANCA, but only 39 patients were included.[6]

Given that infective endocarditis-associated purpura and glomerulonephritis are primarily cutaneous vasculitis[15] and immune-mediated injury,[8] the higher frequencies of purpura and glomerulonephritis may reflect more frequent immune reactions in ANCA-positive patients with infective endocarditis. As revealed by our study (Table 2), antinuclear antibody, rheumatic factor, and complement consumption were more frequently observed in ANCA-positive patients compared with ANCA-negative patients. The assumption is also supported by the observation that ANCA is associated with more frequent occurrence of high immunoglobulin G (IgG) levels in patients with infective endocarditis.[4]

Does ANCA have a pathogenic role in the context of infective endocarditis-associated purpura or glomerulonephritis? The question has been raised by many previous authors who reported ANCA-positive infective endocarditis presenting with cutaneous vasculitis[16] or pauci-immune necrotizing and crescentic glomerulonephritis,[9,10] which is the typical histologic feature of ANCA-associated vasculitis.[17] Histologic studies may shed light on this question. On reviewing previous literature, pauci-immune glomerulonephritis accounted for 22.2% of the histologic patterns in renal specimens from patients with ANCA-positive infective endocarditis.[18] In the largest

series of infective endocarditis-associated glomerulonephritis, pauci-immune crescentic glomerulonephritis was observed in 22% of patients with or without ANCA.[8] However, previous studies did not compare the histologic features between patients with and without ANCA. In our study, immunofluorescence was negative in 2 of the 3 ANCA-positive patients, but none of the 5 ANCA-negative patients. Fibrinoid necrosis was present in 2 of the 3 ANCA-positive patients, but none of the 5 ANCA-negative patients. These differences may suggest a pathogenic role of ANCA in infective endocarditis-associated glomerulonephritis but needs to be confirmed by larger biopsy studies.

The presence of ANCA in infective endocarditis is possibly more important in the context of differential diagnosis between ANCA-positive infective endocarditis and ANCA-associated vasculitis. Ying et al[6] identified 8 cases of ANCA-positive infective endocarditis who were misdiagnosed as ANCA-associated vasculitis in literature. The exact prevalence of misdiagnosis in patients with ANCA-positive infective endocarditis has not been evaluated previously. In our study, 18.6% of patients with ANCA-positive infective endocarditis were initially misdiagnosed with having ANCA-associated vasculitis, highlighting the diagnostic challenge. The overlapping clinical manifestations (ie, constitutional symptoms, purpura, glomerulonephritis) and the presence of ANCA can pose serious diagnostic pitfalls. In addition, the histologic features of infective endocarditis may occasionally mimic ANCA-associated vasculitis by presenting with pauci-immune necrotizing and crescentic glomerulonephritis,[9,10] which was observed in 2 ANCA-positive patients with infective endocarditis in our study. The differential diagnosis between infective endocarditis and vasculitis is of obvious importance, given the harmful consequence of immunosuppressive therapy in this scenario. Although there is no difference in the frequency of constitutional symptoms, skin and renal involvement between ANCA-associated vasculitis and ANCA-positive infective endocarditis,[19,20] positive blood cultures and valvular vegetation on echocardiography strongly support the diagnosis of infective endocarditis. In addition, dual ANCA, hypocomplementemia, multiple autoantibodies, endocapillary hypercellularity, and immune complex deposit favor the diagnosis of infective endocarditis over ANCA-associated vasculitis.[19,20]

Effective antibiotics are the cornerstone of treatment for infective endocarditis, and surgery is necessary in certain conditions. In our study, all patients received antibiotics, and 71.7% of patients underwent surgery. After successful treatment of infective endocarditis, ANCA titers significantly decreased, and most patients with ANCA-positive infective endocarditis had favorable outcomes, consistent with previous observation.[18,20] For patients with ANCA-positive infective endocarditis-associated RPGN, resolution of kidney disease by antibiotics alone was described in previous case reports.[21] In our study, 4 ANCA-positive patients with infective endocarditis-associated RPGN achieved renal recovery by anti-infective therapy alone, confirming the role of anti-infective therapy. The role of immunosuppressive therapy in infective endocarditis-associated RPGN was discussed in our previous study[14] and beyond the scope of the current study.

There are several limitations of this study. First, it was a retrospective study. Patients with infective endocarditis during the study period were not consecutively tested (42% tested) for ANCA. The decision to measure ANCA was made by referred clinicians. This might lead to selection bias in the study. We do not know if similar results would have been obtained if ANCA had been measured in the whole population of infective endocarditis. Furthermore, the patients were hospitalized in a tertiary center, which might represent a referral bias because patients with less severe disease were likely not referred to the tertiary center. Finally, only 8 cases of biopsy-proven infective endocarditis-associated glomerulonephritis were included in histologic studies. Biopsy studies with larger sample sizes are warranted to clarify the histologic features of ANCA-positive infective endocarditis-associated glomerulonephritis

CONCLUSIONS

Our findings suggested that ANCA was present in a substantial proportion of patients with infective endocarditis. Compared with ANCA-negative patients, ANCA-positive patients with infective endocarditis had longer disease duration, more frequent purpura, and kidney involvement. Clinicians should be vigilant against the diagnostic challenge posed by ANCA-positive infective endocarditis. Whether ANCA is involved in the pathogenesis of infective endocarditis-associated small vessel vasculitis or is merely a bystander of systemic hyperimmune reactions requires further study.

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