



## C-ANCA-positive glomerulonephritis associated with subacute infective endocarditis caused by *Bartonella* infection

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Glomerulonephritis (GN) is sometimes associated with infective endocarditis (IE). *Bartonella* endocarditis is difficult to diagnose because it is rare and cannot be detected by blood culture. This is the first report of cytoplasmic anti-neutrophil cytoplasmic antibody-positive subacute endocarditis-associated GN caused by *Bartonella* infection in South Korea. A 67-year-old man was hospitalized due to azotemia. He complained of weight loss and anorexia for 6 months. A diagnosis of IE was made based upon echocardiographic detection of vegetations on the mitral and aortic valves and a *Bartonella* antibody titer of 1:2,048. Renal histology identified focal crescentic GN. Azotemia and proteinuria improved after doxycycline and rifampin treatment combining with steroid therapy.

**Keywords:** ANCA-associated glomerulonephritis; *Bartonella*; Infectious endocarditis

### INTRODUCTION

Infective endocarditis (IE) is a life-threatening disease caused by an infection of the heart tissues. Isolation of the causative organism from blood culture is critical for accurate diagnosis and treatment. When culture results of three independent blood samples are negative, the putative diagnosis indicates blood culture-negative endocarditis (BCNE) [1]. The incidence of BCNE ranges from 5% to 15% in patients with endocarditis, depending on the country [2]. BCNE is associated with infection by a number of pathogens, including *Granulicatella*, *Abiotrophia*, HACEK organisms, *Coxiella burnetii*, and *Bartonella* spp. [3]. Diagnostic tests for BCNE include

special extended-culture techniques, molecular techniques, and histopathologic evaluation.

Approximately 40-50% of IE cases have an associated kidney disease such as glomerulonephritis (GN) [4]. Crescentic GN is the most common renal pathology, which can be derived from anti-neutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitis. The presence of ANCAs against proteinase-3 or myeloperoxidase is a key diagnostic marker [5].

*Bartonella* spp. were first described as a cause of endocarditis in 1993 [6]. Bacteria belonging to the *Bartonella* genus are facultative intracellular gram-negative rods that infect erythrocytes or endothelial cells [7]. Most reports of *Bartonella* IE have involved adult patients and more than 70% of cases were men [8]. The clinical manifestation of *Bartonella* IE is similar to that of other subacute IE [9]. A diagnosis of *Bartonella* IE, however, often requires diagnostic tests other than blood culture to identify the infectious agent (as is the case for other BCNE). In most cases, antibiotic treatment of *Bartonella*-caused IE is effective. If renal function deteriorates despite appropriate antibiotic therapy, other treatments

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may be considered; these include corticosteroids, immunosuppressive agents, plasmapheresis, or valve replacement.

*Bartonella* IE is rare in South Korea [10], and kidney involvement has never been reported. This is the first report of cytoplasmic-ANCA (C-ANCA)-positive GN associated with subacute endocarditis caused by *Bartonella* infection in South Korea.

## CASE

A 67-year-old man was transferred from a private clinic because of his azotemia. He complained of weight loss (7 kg) and anorexia over the previous 6 months. He did not have any underlying disease nor had he undergone surgery in the previous 6 months. Physical examination at the time of admission revealed a blood pressure of 120/50 mmHg, a heart rate of 68 beats/min, a respiratory rate of 20 breaths/min, and a body temperature of 36.4°C. Laboratory studies revealed a white blood cell count of 7,880/mm<sup>3</sup>, a hemoglobin level of 6.7 g/dL, and a platelet count of 206,000/mm<sup>3</sup>. His blood urea nitrogen level was elevated to 53.8 mg/dL and his serum creatinine (sCr) was 4.35 mg/dL. His serum potassium level was elevated to 7.0 mEq/L. C-reactive protein was slightly elevated to 11.4 mg/dL. Diagnostics indicated that his blood albumin/globulin (A/G) ratio was reversed (total protein was 9.1 g/dL, serum albumin was 2.8 g/dL). Urinalysis with microscopy revealed protein (+) and red blood cell > 100/high-power field. The protein-to-creatinine ratio in a

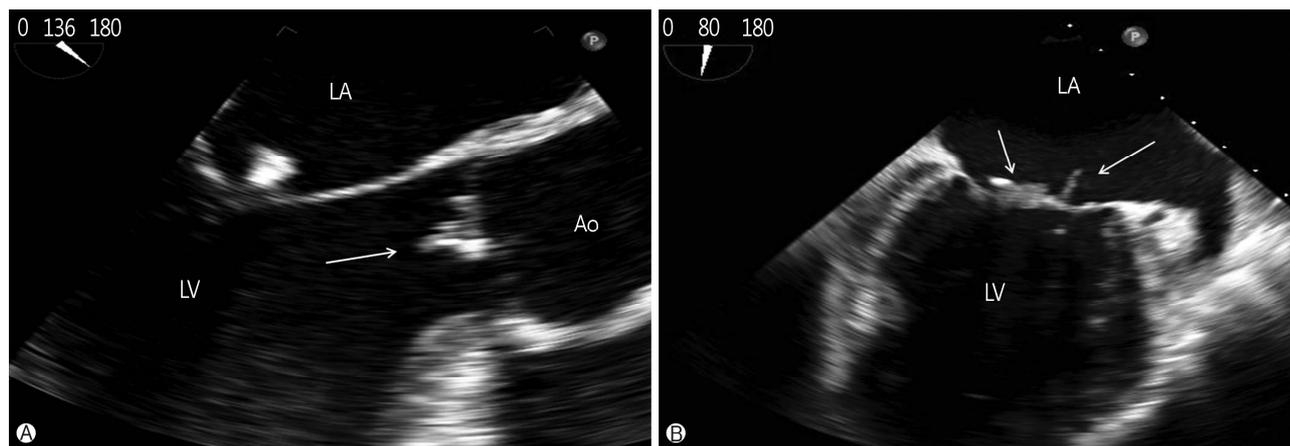
spot urine test was 1.1 g/g. The level of serum C3 was decreased to 43.9 mg/dL (range, 90-180 mg/mL), and the test for C-ANCA was positive. The size of the kidney was in the normal range on abdominal computed tomography.

Initially, we suspected multiple myeloma with kidney involvement due to A/G reverse and azotemia. However, serum and urine protein electrophoresis with immunoelectrophoresis were consistent with polyclonal gammopathy. Transesophageal echocardiography revealed two vegetations on the mitral valve with moderate mitral regurgitation and one vegetation on the aortic valve with minimal aortic regurgitation (Fig. 1). At this time, we suspected subacute IE even though cultures of two blood samples were negative.

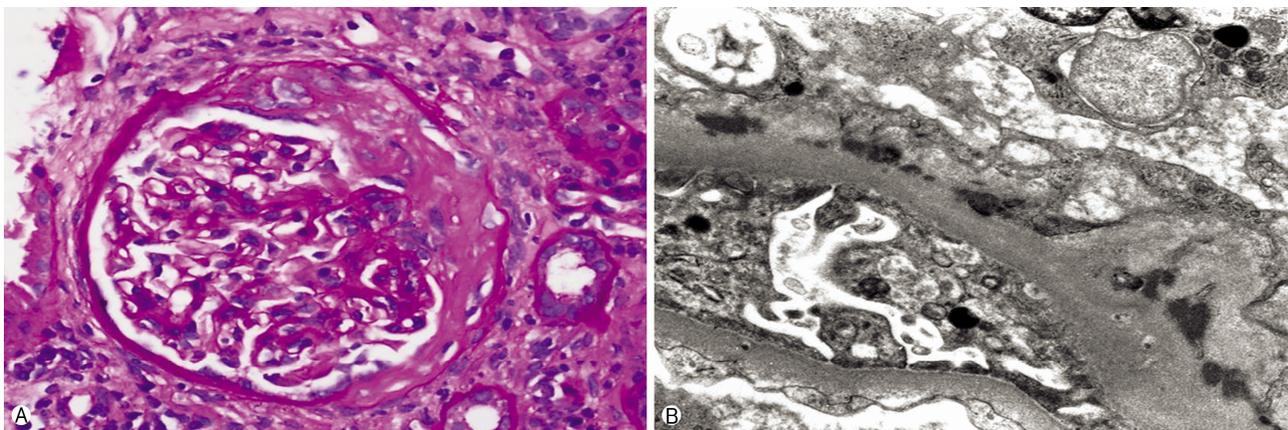
Renal histology revealed global sclerosis (4/28 glomeruli), mesangial proliferation (8/28), fibrotic crescent formation (7/28), diffuse glomerular capillary walls thickened due to deposition of C3, immunoglobulin M (IgM), and C1q (detected by immunofluorescent staining), and endothelial deposits (detected by electron microscopy) (Fig. 2).

We suspected GN associated with BCNE and so requested serological tests for Q fever, Legionella, and *Bartonella* from the Korean Centers for Disease Control and Prevention. We recommended assays for zoonotic organisms because the patient indicated that he had pets on his deer farm in the country.

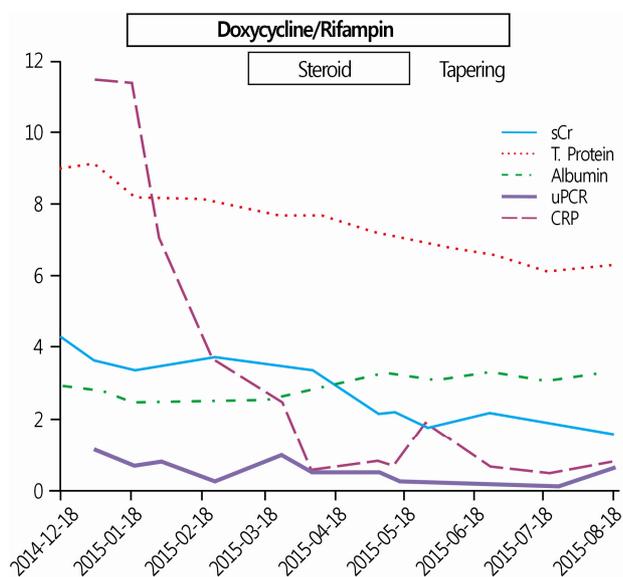
The serological tests showed that the patient's *Bartonella* IgG antibody titer was elevated to 1:2048. Although he was subsequently treated with the antibiotics doxycycline and ri-



**Fig. 1.** Transesophageal echocardiographic findings. There was one echogenic mass (9×9 mm; arrow A), with mild AR, on the aortic valve and two echogenic masses (8×5 and 9×9 mm; arrows B), with moderate MR, on the mitral valve. AR, aortic regurgitation; MR, mitral regurgitation; LA, left atrium; LV, left ventricle; Ao, aorta.



**Fig. 2.** Renal pathologic findings. (A) Periodic acid-Schiff staining under light microscopy ( $\times 400$ ). A glomerulus shows global mesangial expansion with mild thickening of the capillary wall and crescent formation. Tubulointerstitial lymphocytic infiltration and tubular atrophy are also present. (B) Electromicrograph showing some subendothelial electron dense deposits ( $\times 10,000$ ).



**Fig. 3.** Clinical course after admission. Serum creatinine and proteinuria improved after antibiotics were combined with steroid therapy. sCr, serum creatinine; CRP, C-reactive protein; uPCR, urine protein/creatinine ratio.

fampin for 8 weeks, his azotemia and proteinuria did not improve. After combining steroid therapy (0.5 mg/kg) with antibiotic treatment for another 6 weeks, his sCr improved to 2.10 mg/dL, his proteinuria disappeared (Fig. 3), and his complement C3 level returned to normal. Follow-up transthoracic echocardiography after 5 months showed that one of two vegetations on the mitral valve disappeared and the other decreased slightly from 9.0×9.0 mm to 9.3×7.6 mm with mild mitral regurgitation. The size of vegetation on the aortic

valve decreased markedly from 9.0×9.0 mm to 5.3×4.9 mm. He currently receives out-patient support for chronic kidney disease.

## DISCUSSION

The diagnosis of BCNE is difficult and uncommon in South Korea. Nevertheless, a rigorous approach is needed to identify the specific infectious causes of endocarditis and non-IE, including careful documentation of a case’s history and asking the patient and family about contact with animals in the case of a potential zoonosis and joint, gastrointestinal, and neurological symptoms [11]. Our patient’s self-reported history of animal contact was very helpful in our diagnosis.

Among the extra-cardiac manifestations associated with IE, renal involvement occurs in about 40-50% of patients [12]. The causes of kidney disease include acute pyelonephritis, abscess formation from septic emboli, immune complex-mediated GN, ANCA-associated GN, and acute tubular necrosis or acute interstitial nephritis arising from renal toxicity caused by antibiotic treatment [12].

Renal biopsy is the only method of diagnosing IE-associated GN. Key histopathologic findings include emboli, interstitial nephritis, crescentic GN, immune complex-mediated GN, and acute tubular necrosis [13]. Our patient exhibited focal crescentic GN with focal mesangial GN.

In this case, a diagnosis of IE was made due to the echocardiographic detection of vegetations on the mitral and aortic

valves, and a positive serologic test result for *Bartonella*. Some may argue that serologic testing is insufficient to diagnose bartonellosis because there is no definitive cut-off titer for diagnosis and because of the potential for cross-reaction with antibodies to *Chlamydia* spp. or *Coxiella burnetii*. However, Edouard et al. showed that an IgG titer greater than 1:800 (in an immunofluorescence antibody assay) or a positive western blot can be considered as major Duke criteria indicating *Bartonella* endocarditis [14].

The appropriate antibiotic treatment for *Bartonella* endocarditis is a 6-week course of amoxicillin, ceftriaxone, or doxycycline in combination with aminoglycosides for 2-4 weeks [15]. Surgical treatment is recommended if the condition is accompanied by heart failure, high embolic risk, and persistent sepsis [16]. Therefore, we did not remove the vegetations and initially prescribed doxycycline with rifampin rather than gentamicin due to the patient's azotemia.

There are four case reports of IE associated with GN in

**Table 1.** Characteristics of infective endocarditis with glomerulonephritis in Korea

Case No. (year of report)	1 (1990)	2 (1999)	3 (2004)	4 (2009)	5 (present)
Sex/age	M/53	M/24	M/28	F/59	M/67
Organism	No growth	<i>S. viridans</i>	<i>S. sanguis</i>	<i>E. faecalis</i>	<i>Bartonella</i> spp.
Laboratory findings					
CRP (mg/dL)	9.9	NR	8.5	206.5	11.4
Total protein (g/dL)	7.3	5.8	5.2	5.2	9.1
Serum albumin (g/dL)	2.4	2.1	2.4	2.4	2.8
Serum Cr (mg/dL)	7.0	16.2	3.46	3.2	4.35
Proteinuria	2.0 g/day	(+++)	1.5 g/day	3.0 g/day	1.1 g/day
Serum IgG (mg/dL)	NR	NR	2,090.85	NR	4,080.2
Serum C3	Decreased	Decreased	Decreased	Decreased	Decreased
ANA titer	-	1:40	-	-	1:40
ANCA	NR	NR	-	-	+
Cryoglobulin	+	-	-	-	-
Anti-GBM Ab	NR	NR	+	NR	-
LM					
Crescent	29%	100%	21%	54%	25%
Global sclerosis	8%	-	71%	-	14%
Segmental sclerosis	-	-	7%	-	-
Mesangial proliferation	Almost	-	-	-	29%
IF					
C3/C1q/IgM	(+ / + / +)	(+ / - / +)	(+ / + / +)	(+ / - / +)	(+ / + / +)
Mesangial/capillary	(+ / +)	(+ / +)	(+ / -)	(+ / +)	(- / +)
EM (EDD)					
Subepithelial	NR	+	-	NR	-
Subendothelial	NR	+	+	NR	+
Mesangial	NR	-	+	NR	+
Treatment					
Antibiotics	+	+	+	+	+
Surgery	TVR	MVR	VSD repair	Not done	Not done
Renal therapy	HD	Steroid+HD	PCX	Not done	Steroid
Outcome	Died	CAPD	CKD	CKD	CKD

CRP, C-reactive protein; Cr, creatinine; IgG, immunoglobulin G; ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; GBM Ab, glomerular basement membrane antibody; NR, not reported; LM, light microscopy; IF, immunofluorescence stain; EM, electron microscopy; EDD, electron dense deposits; TVR, tricuspid valve replacement; MV, mitral valve; VSD, ventricular septal defect; HD, hemodialysis, CAPD, continuous ambulatory peritoneal dialysis; PCX, plasma exchange; CKD, chronic kidney disease.

Korea [17-20]. We summarized the characteristics of each in Table 1. Their clinical manifestations and course of infection were not different from cases reported elsewhere. Serological markers varied: cryoglobulin in case 1, anti-GBM antibody in case 3 [19], and ANCA in our case. Interestingly, all exhibited a reversed A/G ratio, which initially led us to suspect multiple myeloma. We believe that the elevated IgG levels in cases 1 and 5 are related to polyclonal gammopathy and reveal the chronic inflammation associated with IE. All cases reported hypocomplementemia, azotemia, and mild proteinuria. The patient in case 1 died [17] and the other patients developed chronic kidney disease. The renal function of our patient was improving under treatment, but did not recover completely, although his proteinuria disappeared after combined steroid and antibiotic therapy. Follow-up echocardiography showed an improvement, but he still developed chronic kidney disease.

Diagnosis was delayed because the patient's chief complaint and his initial clinical findings were vague, and his condition was not rapidly progressive. Interestingly, the symptoms were very similar to those in a case reported by Van Haare Heijmeijer et al. [12]. However, this patient diagnosed to *Bartonella* IE lately after steroid and cyclophosphamide therapy for idiopathic ANCA-associated GN without antibiotics. They summarized the renal pathology and therapy for ten cases of *Bartonella*-caused endocarditis-associated GN. In most cases, their renal pathologies were either focal or diffuse crescentic GN. Moreover, as for our patient, seven of the patients displayed a positive ANCA result.

In conclusion, it is necessary to carefully evaluate the case history, conduct a thorough physical examination, and perform serologic tests to identify BCNE. In addition, if azotemia presents with proteinuria, a renal biopsy is considered to rule out GN-associated endocarditis. With proper diagnosis and early treatment, a patient may be able to recover renal function and experience a better clinical outcome.

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## CONFLICT OF INTEREST

Authors have no potential conflicts of interest to disclose.

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