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Bartonella Endocarditis-Associated Glomerulonephritis: A Mimicker of Autoimmunity and Vasculitis

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Introduction: *Bartonella spp.* are highly fastidious gram-negative facultative intracellular bacteria which can cause a culture-negative infective endocarditis (IE) with unique clinicopathologic features.

Methods: In this study, we assembled 20 cases of glomerulonephritis (GN) due to *Bartonella* IE from 3 institutions and compared them with 49 cases of culture-positive IEGN and 30 cases of non-endocarditis infection-related GN (IRGN).

Results: IEGN was seen in approximately 0.15% to 0.4% of native renal biopsies, with *Bartonella* causing 8% to 21% of IEGN. Patients with *Bartonella* IEGN had preexisting cardiac valve alterations (75%); antineutrophil cytoplasmic autoantibody (ANCA) positivity (67%); hypocomplementemia (75%); antinuclear antibody positivity (53%); cryoglobulinemia (45%); and hematologic manifestations, including B-symptoms (79%), splenomegaly (59%), thrombocytopenia (83%), and pancytopenia (44%). In 75% of the cases, *Bartonella* endocarditis was not diagnosed until after kidney biopsy. Pathologically, *Bartonella* IEGN presented as a focally crescentic GN, which was C3 codominant (80%) with strong IgM (65%) and/or C1q (55%), or pauci-immune (10%), with predominantly mesangial deposits and limited exudative features. At a median follow-up time of 15 months, progression to end-stage kidney disease (ESKD) for all-comers with IEGN was associated with higher creatinine levels at diagnosis, presence of nephrotic syndrome, female sex, and C1q staining intensity. Although delayed diagnosis of infection and immunosuppressive therapy for presumed autoimmune disease before kidney biopsy were more common in *Bartonella* IEGN than in culture-positive IEGN, neither were associated with ESKD.

Conclusion: IEGNs share laboratory and biopsy features with autoimmunity, which may obfuscate identification of underlying bacterial infection.

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Bartonella spp. are fastidious, facultative intracellular gram-negative bacteria first recognized as causes of endocarditis in 1993.[1-4] *Bartonella* is estimated to cause 28% of culture-negative endocarditis in the USA.[5] Of the many members of genus *Bartonella* recognized as human pathogens, the two species most prominently associated with culture-negative endocarditis are *B. henselae*, associated with previous valvulopathy and cat contact; and *B. quintana*, the agent of trench fever and associated with poor sanitation, homelessness, and body louse infestation.[1] In the USA, approximately 22,000 people per year develop cat scratch disease, and 28% of domesticated cats are chronically infected with *B. henselae* without clinical symptoms.[6] The cat flea (*Ctenocephalides felis*) is the primary vector for transmission of *B. henselae* between cats, and human inoculation by *B. henselae*–contaminated flea feces usually occurs from cat scratches.[7]

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Bartonella IE-associated GN was first described in 2004 by Bookman *et al*.[8,9] and in multiple subsequent case reports and small series. The most recent series by Kitamura *et al*. described 4 cases with an extensive review and pooled analysis of 89 previously published cases of *Bartonella* IEGN (including 54 case reports and series and 18 abstracts) and compared them with 51 cases of culture-positive (culture+) IEGN from Ohio State University.[10] Among patients with IE, those with *Bartonella* are significantly more likely to develop a GN, compared with IE because of other organisms.[11] In this multi-institutional study, we sought to delineate clinical and pathologic features, and outcomes of glomerulonephritides associated with various infections, particularly focusing on the unique findings in *Bartonella* IEGN compared with culture-positive IEGN and non–endocarditis IRGN, especially those seen in skin and soft tissue infections.

METHODS

Renal pathology biopsy databases from the Oregon Health and Science University (OHSU), Cedars-Sinai Medical Center, and Cleveland Clinic were searched for previously unpublished cases with a diagnosis, comment, or known follow-up suggesting blood culture-positive or culture-negative IE between 2015 and 2023. Culture-negative versus culture-positive designations were used to reflect diagnostic information commonly available at the time of nephrology consultation and kidney biopsy. However, because all culture-negative IEGN cases in this cohort were found to be *Bartonella*, the results could instead be considered as *Bartonella* IEGN versus non-*Bartonella* IEGN. All patients with IEGN and renal biopsies were included from OHSU and Cedars Sinai. Only *Bartonella*-associated IEGN cases were included from Cleveland Clinic. A cohort of patients with non-IE IRGN was obtained from Oregon Health and Science University for comparison. Non-IE IRGN was associated with skin and soft tissue infections with or without osteomyelitis in 16 of 30, pneumonia in 3, infected hardware in 2, spontaneous bacterial peritonitis in 2, dental infection in 1, and an unknown site of infection in 6.

Biopsies were cut at multiple levels and stained with Jones methenamine silver, periodic acid-Schiff, hematoxylin and eosin, and Masson's trichrome. For immunofluorescence (IF), frozen tissue was stained with antibodies against IgG, IgA, IgM, C3, C1q, fibrin/fibrinogen, κ, λ, and albumin. The dominant and/or codominant immunoreactants were noted; these and any other listed as "strong" staining were required to have a staining intensity of 2+ (on a scale of 0–4+) or greater. In this study, cases with < 2+ staining intensity for the brightest immunoreactants were considered in the pauci-immune spectrum. Clinical history was obtained through discussions with nephrologists and review of medical records.

Descriptive statistics were summarized as median and range for continuous variables, which were compared between groups using Mann-Whitney U-tests, whereas categorical variables were compared between groups using Fisher exact test using GraphPad Prism 8 (San Diego, CA). Regression analysis for the overall cohort was performed using the available outcome data ($n = 47$, 68% of the overall cohort and 95% of *the Bartonella* cohort). Survival analyses with Cox proportional hazard models and multivariate analyses were performed using Stata 13 (College Station, TX).

RESULTS

Clinical Presentation

IEGN was seen in approximately 0.15% to 0.4% of native renal biopsies, and *Bartonella* represented 8% to 21% of IEGN. Patients with *Bartonella* IEGN ($n = 20$; Table 1, Figure 1) were predominantly male (80%) and presented with a median age of 58 (range: 12–79) years. B-symptoms, including fatigue, weight loss, fever, and night sweats, were significantly more common in *Bartonella* IEGN (79%) than in culture+ IEGN (41%, $P = 0.01$) or IRGN (3%, $P < 0.01$). Splenomegaly was significantly more common in *Bartonella* (59%) than in the culture+ IEGN group (18%, $P = 0.02$). One patient had *Bartonella*-associated lymphadenopathy (confirmed with polymerase chain reaction on lymph node biopsy), approximately 2 years before the diagnosis of endocarditis. The rates of underlying hepatitis C viral infection (54% vs. 5%, $P < 0.01$) and intravenous (i.v.) or injection drug use(62% vs. 0%, $P<0.01$) were significantly higher in the culture+ IEGN group than *Bartonella* IEGN group.

All patients with *Bartonella* IEGN had acute kidney injury or progressive renal insufficiency (median Cr: 4.2 mg/dl), with a previously normal creatinine level in at least 12 (60%). All had proteinuria (median: 1.28 g/g, 13% in the nephrotic range) and hematuria. Cytopenias (in 100%), particularly thrombocytopenia (83% vs. 33%, $P < 0.01$) and pancytopenia (44% vs. 3%, $P < 0.01$), were common and significantly enriched in patients with *Bartonella* compared with those with culture+ IEGN. Hematologic abnormalities prompted bone marrow biopsy before kidney biopsy in 7 patients with *Bartonella* IEGN (35%). These were negative in all but 1 patient in whom an atypical CD8+ T-cell infiltrate suspicious for large granular T-cell lymphoma was identified. Subsequent T-cell clonality studies were

Table 1. Presenting clinical and laboratory features of *Bartonella* IEGN, culture+ IEGN, and non-IE IRGN

Variable	*Bartonella* IEGN ($n = 20$)	Culture+ IEGN ($n = 49$)	*Bartonella* vs. culture+ IEGN	Non-IE IRGN ($n = 30$)	*Bartonella* IEGN vs. non-IE IRGN
Median age, yrs	58 (range: 12–79)	47 (range: 25–80)	$P = 0.07$	58 (range: 31–85)	$P = 0.62$
Male, %	80% (16/20)	65% (32/49)	$P = 0.26$	63% (19/30)	$P = 0.35$
Diabetes, %	10% (2/20)	16% (8/49)	$P = 0.71$	33% (10/30)	$P = 0.09$
HTN, %	65% (13/20)	45% (21/47)	$P = 0.18$	81% (17/21)	$P = 0.31$
B-symptoms, %	79% (15/19)	41% (15/37)	$P = 0.01$	3% (1/29)	$P < 0.01$
Rash, %	25% (5/20)	8% (4/49)	$P = 0.11$	10% (3/30)	$P = 0.24$
Splenomegaly, %	59% (10/17)	18% (4/22)	$P = 0.02$	NA	NA
Hx IVDU, %	0% (0/20)	62% (28/45)	$P < 0.01$	13% (4/30)	$P = 0.14$
Hx HCV, %	5% (1/20)	54% (19/35)	$P < 0.01$	15% (3/20)	$P = 0.61$
Hx cirrhosis, %	0% (0/20)	2% (1/49)	$P > 0.99$	20% (6/30)	$P = 0.07$
Laboratory results					
Median creatinine at presentation (mg/dl)	4.2 (range: 2.2–8.9)	3.6 (range: 1.7–14.3)	$P = 0.77$	3.6 (range: 0.6–5)	$P = 0.31$
Median proteinuria, % nephrotic range	1.28 (0.76–4.3), 13% (2/16)	3 (range: 0.4–15), 47% (9/19)	$P = 0.04$, $P = 0.04$	2.4 (range: 1.8–7.6), 27% (3/11)	$P < 0.01$, $P = 0.37$
Hematuria, %	100% (19/19)	88% (30/34)	$P = 0.28$	95% (18/19)	$P > 0.99$
Cytopenias: Any, %	100% (18/18)	93% (37/40)	$P = 0.55$	NA	NA
Thrombocytopenia, %	83% (15/18)	33% (13/40)	$P < 0.01$	NA	NA
Pancytopenia, %	44% (8/18)	3% (1/40)	$P < 0.01$	NA	NA
Anemia only, %	11% (2/18)	60% (24/40)	$P < 0.01$	NA	NA
ANCA positive, %	67% (14/20)	33% (7/28)	$P < 0.01$	4% (1/26)	$P < 0.01$
ANA and/or related autoantibody positive, %	53% (10/19)	22% (5/23)	$P = 0.05$	4% (1/26)	$P < 0.01$
Hypocomplementemia: any, low C3, C4, both , %	75% (15/20), 65% (13/20), 35%(7/20), 25% (5/20)	56% (18/32), 56% (18/32), 35% (11/32), 35% (11/32)	$P = 0.24$, 0.57, > 0.99, 0.55	25% (4/16), 25% (4/16), 6% (1/16), 6% (1/16)	$P < 0.01$, 0.02, 0.05, 0.20
Cryoglobulin positive, %	45% (9/20)	8% (4/49)	$P < 0.01$	NA	NA
Initially suspected autoimmune disease and/or tx with steroids, %	55% (11/20)	10% (5/49)	$P < 0.01$	7% (2/30)	$P < 0.01$

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; HCV, hepatitis C virus infection; HTN, hypertension; Hx, history; IEGN, infective endocarditis–associated glomerulonephritis; IRGN, infection–related GN; IVDU, i.v. drug use; NA, not available; tx, treated.
Statistically significant results are shown with *P values* < 0.05.

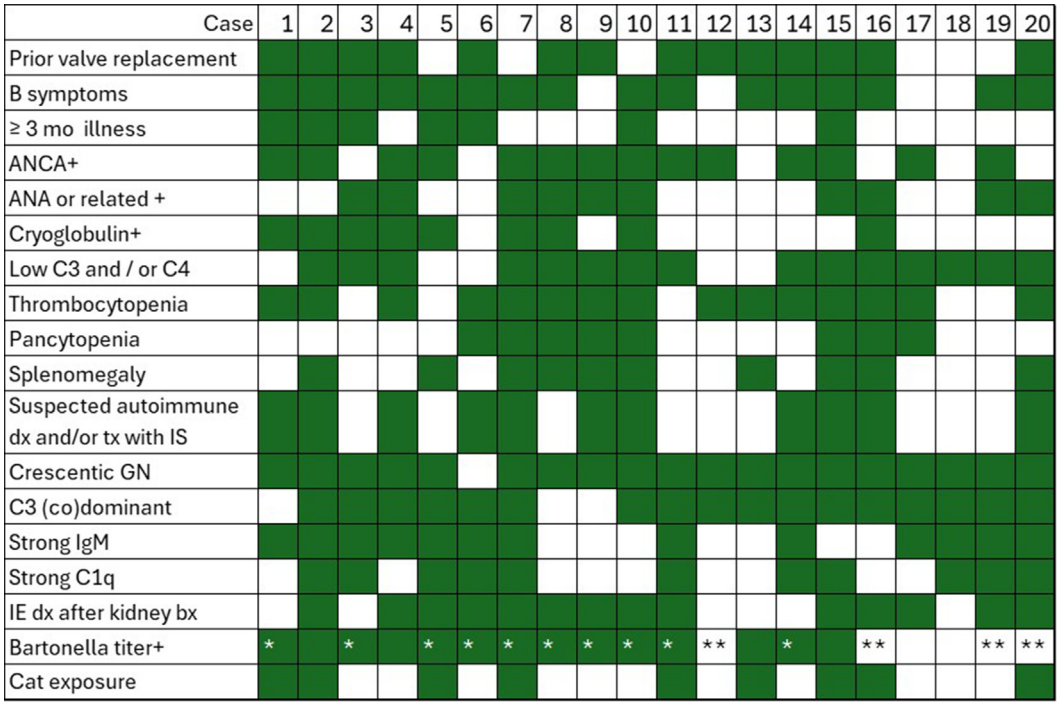

Figure 1. Details of patients with *Bartonella*-endocarditis associated glomerulonephritis. Green shading indicates variable is present in the patient. * indicates polymerase chain reaction positive in blood and/or valve tissue. ** indicates positive microbial cell-free DNA sequencing (Karius). *Bartonella* test details were not available for patients 17 and 18.

negative, and the findings were attributed in retrospect to *Bartonella* infection.

Fourteen patients (67%) with *Bartonella* IEGN had a positive ANCA, particularly directed to proteinase 3 (PR3, 11 patients, 55%), which was accompanied by a cANCA in 6 (30%); one anti–PR3 positive patient was dual anti-myeloperoxidase (MPO) positive, and the second had equivocal anti-MPO reactivity. One patient tested positive for MPO and pANCA positive. Two patients had only cANCA or pANCA (1 each) with negative MPO and PR3 studies results. Before presenting with *Bartonella* endocarditis, none of the patients had an established autoimmune disease; however, 53% had positive autoimmune serology during the workup. These included a positive antinuclear antibody (8, 40%), anti-double stranded DNA (2, 10%), ribonucleoprotein antibody (1, 5%) and combinations of anti-cardiolipin and β2 glycoprotein-1 Ig (2, 10%), anti-Ro/SSA and anti-La/SSB (1), anti-chromatin and anti-SCL-70 (topoisomerase 1) antibodies (1), rheumatoid factor and poly-specific Coombs (1).

Rates of malignancy and paraproteinemia were not significantly different between the 2 IEGN groups. Previous malignancies were present in 3 patients with culture+ IEGN (6%) and consisted of polycythemia vera, carcinoid, and colon and lung cancer. Two patients (10%) with *Bartonella* IEGN had a previous history of malignancy, consisting of non-Hodgkin's lymphoma and cutaneous squamous cell carcinoma. Monoclonal gammopathy of undetermined significance (MGUS) was present in 1 patient with culture+ IEGN (2%) and 1 patient with *Bartonella* IEGN (5%). Two additional patients with *Bartonella* IEGN had serum protein electrophoresis (SPEP) suggestive of a monoclonal protein; in 1 case, immunofixation was negative with a normal k/l ratio. In the second patient, there was a possible band in IgG kappa that was too small to quantify with a normal k/l ratio. Bone marrow biopsies in all 3 patients with *Bartonella* IEGN and MGUS, or possible MGUS were negative for lymphoproliferative disorders. If patients with MGUS and indeterminate SPEP results were considered together, 15% of patients with *Bartonella* IEGN had serum protein electrophoresis alteration raising the possibility of a monoclonal protein, which showed a trend toward enrichment ($P = 0.07$) compared with culture+ IEGN.

Pathology

Light microscopy revealed that 90% of *Bartonella* IEGN cases displayed crescents (vs. 65% of culture+ IEGN, $P = 0.04$; and 53% of IRGN, $P = 0.01$) (Table 2, Figure 2). These were generally focal (median: 16%, range: 1%–65%), with only 1 case having more than 50% crescents. A variable mesangial proliferative pattern was present in 7 (35%), and rates of endocapillary hypercellularity (60%) and exudative features (35%) were similar to those of culture+ IEGN and significantly less than those of IRGN (93%, $P = 0.01$, and 87%, $P < 0.01$, respectively). None of the patients had a background of diabetic nephropathy, which was again more comparable to culture+ IEGN (12%) than IRGN (30%, $P = 0.01$). A relatively similar proportion of cases in all 3 cohorts had accompanying acute tubulointerstitial inflammation (50%–85%), including neutrophils (30%–33%) and eosinophils (27%–33%). Tubular atrophy and interstitial fibrosis were significantly lower in patients with culture+ IEGN (median: 10% vs. 23% in *Bartonella* GN, $P < 0.01$), which may partly reflect the trend of younger age in this cohort (median age: 47 years in culture+ IEGN versus 58 years in both *Bartonella* and IRGN, $P = 0.07$), time to diagnosis, or other factors.

By IF, C3 was the dominant or codominant immune reactant in all 3 cohorts for 80%–86% of cases. *Bartonella* IEGN was distinguished by the presence of strong IgM staining (65%, $P < 0.01$) and/or strong C1q staining (55%, $P < 0.01$). Strong IgA staining was primarily a feature of IRGN (57%), rather than *Bartonella*, (5%, $P < 0.01$) or culture+ IEGN (16%). IgG was strong in a minority of cases (7%–15%) across all 3 groups. A similar percentage of cases in all 3 groups (7–14%) had limited or pauci-immune complex staining.

The glomerular distribution of complement and immune complexes by IF staining in patients with *Bartonella* IEGN was more likely to be limited to the mesangium than in patients with IRGN (60% vs. 30%, $P = 0.04$). Electron microscopy revealed mesangial (100%) and subendothelial (47%) immune deposits; however, subepithelial and intramembranous deposits were significantly less common in *Bartonella* IEGN (not seen in any case) than in culture+ IEGN (53%, $P < 0.01$) and IRGN (36%, $P < 0.01$).

Culture+ IEGN and IRGN

Clinicopathologic features of culture+ IEGN are summarized in Tables 1, 2, and 3 and were not the primary focus of this investigation. Most culture+ IEGN were due to *Staphylococcus aureus* infection (76%). Organism information was not collected for the IRGN cohort; however, 53% of these were due to skin and soft tissue infections. Compared with non-endocarditis IRGN, patients with culture+ IEGN were more likely to have a history of i.v. drug use ($P < 0.001$), hepatitis C virus ($P = 0.005$), B-symptoms ($P < 0.001$), and trend toward a positive ANCA ($P = 0.052$), and less likely to have hypertension ($P = 0.007$). Histologically, biopsies in culture+ IEGN shared similarities with *Bartonella* IEGN in that they were less likely to have

Table 2. Pathological features of *Bartonella* IEGN, culture+ IEGN, and non-IE IRGN

Variable	*Bartonella* IEGN ($n = 20$)	Culture+ IEGN ($n = 49$)	*Bartonella* vs. Culture+ IEGN	Non-IE IRGN ($n = 30$)	*Bartonella* IEGN vs. non-IE IRGN
Light microscopy					
Crescents: % with any, median	90% (18/20),16% (range: 1–65)	65% (32/49), 6% (range: 2–75)	$P = 0.04$, $P = 0.25$	53% (16/30), 5% (range: 4–27)	$P = 0.01$, $P < 0.01$
Endocapillary hypercellularity	60% (12)	63% (31)	$P = 0.79$	93% (28)	$P = 0.01$
Exudative GN	35% (7)	31% (15)	$P = 0.78$	87% (26)	$P<0.01$
Diabetic GS	0% (0)	12% (6)	$P = 0.17$	30% (9)	$P = 0.01$
AIN	65% (13)	84% (41)	$P = 0.11$	50% (15)	$P = 0.39$
With neutrophils	30% (6)	31% (15)	$P > 0.99$	33% (10)	$P > 0.99$
With eosinophils	30% (6)	27% (13)	$P = 0.77$	33% (10)	$P > 0.99$
Median %global GS	9% (range: 0–57)	4% (range: 0–70)	$P = 0.17$	15% (range: 0–69)	$P = 0.11$
Median %IFTA	23% (range: 0–60)	10% (range: 0–60)	$P < 0.01$	28% (range: 5–80)	$P = 0.15$
Vascular disease	as: 1, ah: 0.25	as: 1, ah: 0.75	$P = 0.30$, 0.03	as: 1 ah: 0.25	$P = 0.85$, 0.04
Immunofluorescence					
C3 (co)dominant	80% (16)	82% (40)	$P > 0.99$	86% (24/28)	$P = 0.70$
Strong IgG	15% (3)	8% (4)	$P = 0.41$	7% (2)	$P = 0.38$
Strong IgA	5% (1)	16% (8)	$P = 0.27$	57% (17)	$P < 0.01$
Strong IgM	65% (13)	22% (11)	$P<0.01$	0% (0)	$P < 0.01$
Strong C1q	55% (11)	20% (10)	$P<0.01$	3% (1)	$P < 0.01$
Pauci-immune	10% (2)	14% (7)	$P = 0.71$	7% (2)	$P > 0.99$
Mes & PCW, mes only	40% (8), 60% (12)	57% (28), 39% (19)	$P = 0.29$, 0.12	70% (21), 30% (9)	$P = 0.04$, 0.04
Extraglomerular deposits	0% (0)	6% (3)	$P = 0.55$	0% (0)	$P = 0.26$
Electron microscopy					
Mes/subendo/subepi/ intramembranous	100% (19/19), 47% (9), 0% (0), 0% (0),	94% (45/48), 52% (25) 53% (26), 33% (16)	$P = 0.55$, 0.79, <0.01, < 0.01	93% (26/28), 54% (15), 36% (10), 14% (4)	$P = 0.51$, 0.77, < 0.01, 0.14

AIN, acute interstitial nephritis; GN, glomerulonephritis; GS, glomerulosclerosis; IEGN, infective endocarditis–associated glomerulonephritis; IRGN, infection–related GN; IFTA, tubular atrophy and interstitial fibrosis; Mes, mesangial; PCW, peripheral capillary wall.
For IRGN, an additional 11 cases (37%) had IgA as the strongest immunoglobulin staining; however, at an intensity below 2+ (scale 0–4+).
Twenty-two percent of patients with culture+ IEGN had moderate or severe arteriolar hyalinosis compared with none of the patients with moderate or severe hyalinosis with *Bartonella* IEGN.
Statistically significant results are shown with P values < 0.05.

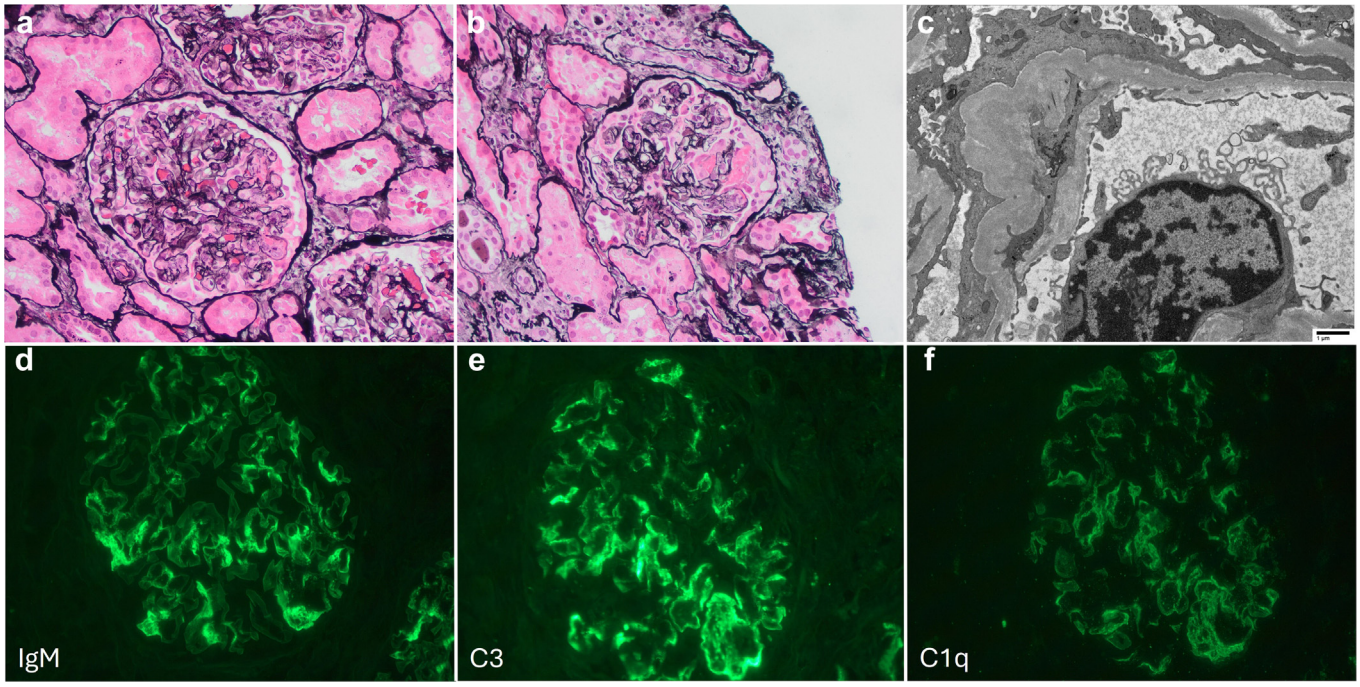

Figure 2. Pathologic features of B*artonella* IEGN, with (a and b) segmental endocapillary hypercellularity, necrosis, and small crescent formation (Jones silver stain 200×), (c) mesangial immune deposits (transmission electron microscopy, 2900x), and granular mesangial with segmental capillary wall staining for (d) IgM, (e) C3, and (f) C1q. IEGN, infective endocarditis–associated glomerulonephritis.

Table 3. Endocarditis or infection details and follow-up

Variable	*Bartonella* IEGN ($n = 20$)	Culture+ IEGN ($n = 49$)	*Bartonella* vs. culture+ IEGN
% preexisting cardiac valve replacement or alteration	75% (15/20): AVR: 9, bicuspid or stenotic AV: 3, Tetralogy of Fallot: 3, LVAD: 1	18% (9/49): AVR: 4, tricuspid: 2, previous endocarditis: 2, MVR: 1	$P < 0.01$
Organism	*Bartonella spp.*: 100% (20/20)	*Staphylococcus aureus*: 76% (29/38), *Streptococcus spp.*: 16% (6/38), *Enterococcus spp.*: 8% (3/38), *Neisseria spp.*: 3% (1/38), *Pseudomonas aeruginosa*: 3% (1/38), *Escherichia coli*: 3% (1/38)	NA
Valve involved:			
Tricuspid	5% (1/20)	64% (23/36)	$P < 0.01$
Pulmonic	15% (3/20)	0% (0)	$P = 0.04$
Mitral	15% (3/20)	19% (7/36)	$P > 0.99$
Aortic	75% (15/20)	25% (9/36)	$P < 0.01$
Method of organism identification	Culture: 0, serology: 77% (14/18), PCR-based only: 22% (4/18)	Culture: 100% (39/39)	NA
Infection diagnosed after kidney biopsy	75% (15/20)	0% (0/49)	$P < 0.01$
Short term dialysis required	56% (10/18)	57% (16/38)	$P > 0.99$
ESKD or death at follow-up	26% (5/19)	18% (5/28)	$P = 0.50$

AV, aortic valve; AVR, aortic valve replacement; ESKD, end-stage kidney disease; LVAD, left ventricular assist device; MVR, mitral valve replacement; PCR, polymerase chain reaction.
For both *Bartonella* and culture+ IEGN, 3 patients had 2 valves.
For culture+ IEGN, polymicrobials were found in 3 patients.
One patient had gram-positive cocci with no species identified.
Statistically significant results are shown with P values < 0.05.

endocapillary hypercellularity ($P = 0.003$), exudative features ($P < 0.001$), or strong IgA staining ($P < 0.001$) and were more likely to have strong IgM ($P = 0.005$) and/or C1q ($P = 0.044$) staining than IRGN.

Notable case features not included in these summaries were the concurrent histological presence of concurrent necrotizing arteritis in 1 patient with a history of i.v. drug use (ANCA studies not available), membranous nephropathy in 1 patient with hepatitis C virus (PLA2R staining not available), and tubulointerstitial immune deposits in 2 patients, both of whom had a history of i.v. drug use.

Endocarditis Details and *Bartonella* Testing

In most cases (75%), *Bartonella* endocarditis was diagnosed after renal biopsy, whereas nearly all ($P < 0.01$) patients with culture+ IEGN had a confirmed or suspected diagnosis of endocarditis before renal biopsy. Indeed 7 patients with *Bartonella* endocarditis (35%) had ≥ 3 months of unexplained symptoms before diagnosis often prompting detailed rheumatologic evaluation, including 2 patients with 2 years of symptoms and 3 patients with ≥ 6 months of symptoms. Preexisting cardiac valve replacement or alteration was significantly more common in *Bartonella* GN (75%) than in culture+ IEGN (18%, $P < 0.01$) and often consisted of aortic valve replacement in 9 patients (45%) or bicuspid or stenotic aortic valve (15%) (Table 3). *Bartonella* IE usually involved the aortic valve (75%), whereas tricuspid IE was more common in the culture+ IEGN group (64%, $P < 0.01$). *Bartonella* exposure was identified in 9 patients (45%) and consisted of cat contact.

Identification of *Bartonella* infection was facilitated by positive IgG antibody titers against *B. henselae* in 14 of 18 patients with available information (77%), 1 of whom had high-titer antibodies (> 1:1024) against *B. quintana*. Of the 12 patients with detailed titer information available, 11 (92%) had a high-titer (>1:1024) antibody to *B. henselae* and 1 had a lower-titer antibody (1:256; positive ≥ 1:256). *B. henselae* IgM titers were available for 3 patients and ranged from 1:64 to 1:128 (positive ≥ 1:16). The 16S polymerase chain reaction was positive for *Bartonella spp.* in 10 of the 10 patients whose blood and/or resected valve tissues were tested. In 4 patients (22%), serologic testing for *Bartonella* was negative, and infection was identified through blood microbial cell-free DNA sequencing (Karius) (Figure 1 and Supplementary Table S1).

Treatment

Given the high rate of positivity for ANCA and/or autoimmune serologies, B-symptoms, and variable smoldering to accelerated disease tempo, 11 patients (55%) were suspected of having autoimmune disease and/or vasculitis before kidney biopsy, 9 (45%) of whom received immunosuppression (corticosteroids in 9, oral cyclophosphamide in 2, and hydroxychloroquine in 1). The exposure to prebiopsy immunosuppression ranged from a few days during hospitalization for suspected vasculitis or other GN to weeks or months of immunosuppression, including for:

suspected lupus (for 3 weeks before biopsy), suspected giant cell arteritis (1 month before biopsy), autoimmune hemolytic anemia (2 months before biopsy), "membranoproliferative glomerulonephritis" on outside biopsy of unclear etiology (5 months before repeat biopsy and *Bartonella* diagnosis), and vague inflammatory disorder with leukocytoclastic vasculitis (intermittently for a year) (Supplementary Table S1). In 1 patient with Tetralogy of Fallot repair and suspected new lupus, fever did not develop until administration of cyclophosphamide; incomplete transthoracic echo did not visualize vegetation; *Bartonella* serologies performed after biopsy were negative; however, a DNA-based assay (Karius) identified *Bartonella* infection. Immunosuppression was stopped after correct diagnosis in all adult patients; 1 pediatric patient with no delay in the diagnosis of Bartonella IEGN was administered steroids with antibiotics after biopsy because of the degree of the crescents.

At the time of biopsy, more than half of the patients with either *Bartonella* IEGN or culture+ IEGN required short-term dialysis (56% and 57%, respectively), ranging from 2 to 14 weeks. All patients with IE were treated with antibiotics. For those with *Bartonella* endocarditis, doxycycline (used in 95% of the cases) was the most common agent, often used in combination with rifampicin (63%) and/or ceftriaxone (58%), with treatment periods lasting weeks to months. Approximately 68% of patients with *Bartonella* IEGN underwent surgical valve repair compared with 36% of patients with culture+ IEGN ($P = 0.04$).

Outcomes

At a median follow-up time of 15 (range: 0.5–102) months, 10 of 47 patients with available data, including 26% of patients with *Bartonella* IEGN and 18% with culture+ IEGN progressed to ESKD, 2 of whom subsequently died. On univariate analysis for all-comers with IEGN, progression to ESKD was associated with female sex (hazard ratio [HR]: 7.22, $P = 0.018$, 95% confidence interval [CI]:1.40–37.29), higher creatinine at diagnosis (HR: 1.47, $P = 0.002$, 95% CI: 1.15–1.89), presence of nephrotic syndrome (HR: 6.29, $P = 0.029$, 95% CI: 1.20–32.84), and intensity of C1q staining (HR: 2.08, $P = 0.024$, 95% CI: 1.10–3.95), but not with any other tested clinical or pathologic variable, including *Bartonella* versus culture+ IEGN or receipt of immunosuppression (Figure 3 and Supplementary Figure S1). On multivariable analysis, both female sex (adjusted HR: 6.177, $P = 0.031$, 95% CI: 1.18–32.37), and higher creatinine at diagnosis (adjusted HR: 1.49, $P = 0.004$, 95% CI: 1.13–1.96) remained statistically significant.

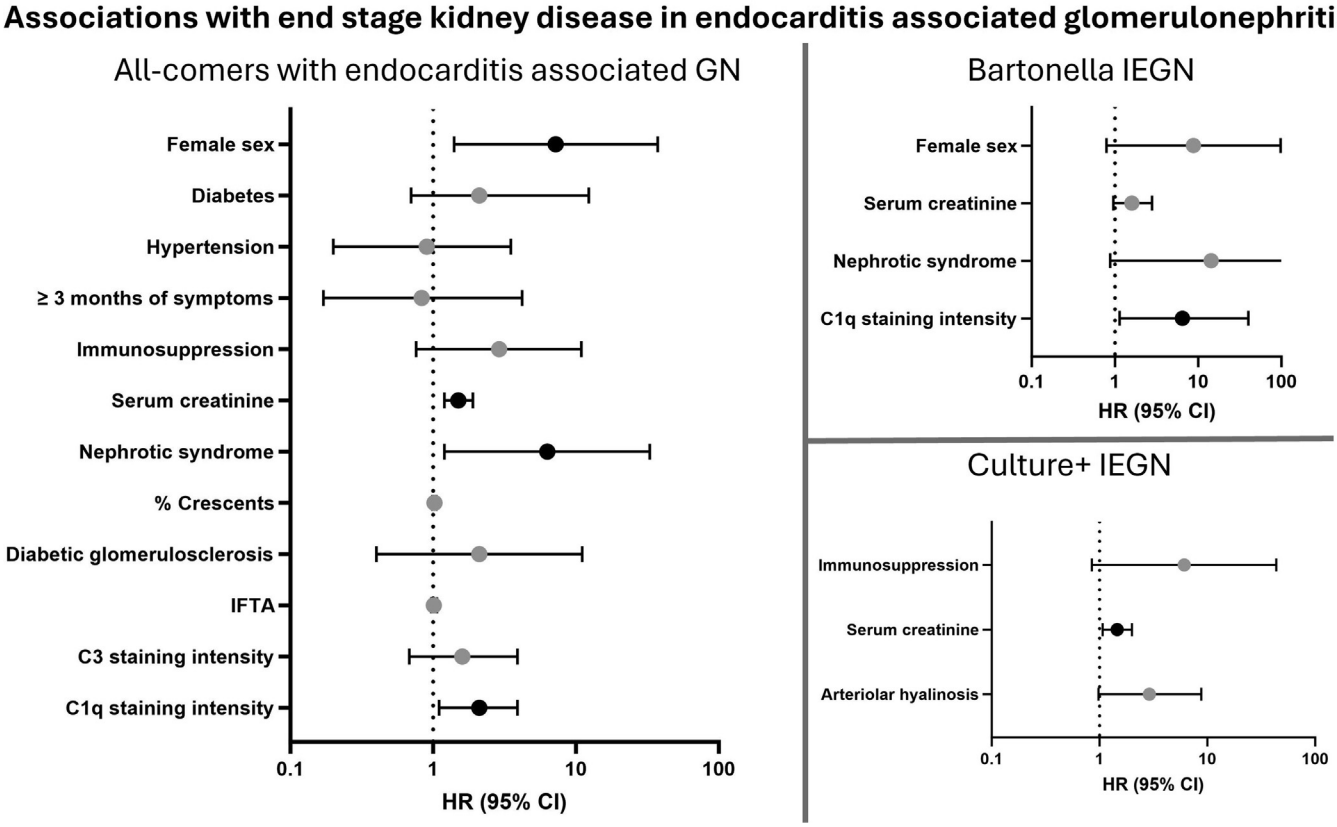

Figure 3. Forest plot of variables associated with outcome of ESKD in all-comers with IEGN, *Bartonella* IEGN, and culture+ IEGN. ESKD, end stage kidney disease; IEGN, infective endocarditis–associated glomerulonephritis.

Among the tested variables, no statistically significant differences were found between males and females, including age, comorbid conditions, time to diagnosis, creatinine level at diagnosis, other laboratory findings, or treatment.

In the *Bartonella* cohort, 5 of 19 patients (26%) with available follow-up data progressed to ESKD. Of the tested variables, only the intensity of C1q deposition (HR: 6.48, P=0.045, 95% CI: 1.04–40.2) was associated with progression to ESKD (median C1q intensity 2.5+ in progressors vs. 1.5+ in those not progressing to ESKD, $P = 0.01$); variables significant in the overall cohort had a trend for significance in this smaller cohort, including female sex ($P = 0.077$), creatinine at diagnosis ($P = 0.071$), and nephrotic syndrome ($P = 0.061$). In patients with culture+ IEGN, only creatinine at diagnosis (HR: 1.46, $P = 0.017$, 95% CI: 1.07–2.0) was significantly associated with progression to ESKD, with trends for significance with the degree of arteriolar hyalinosis (P=0.054) and receipt of immunosuppression ($P = 0.072$) (Figure 3).

DISCUSSION

In this kidney biopsy-based cohort, 75% of *Bartonella* endocarditis cases were diagnosed after kidney biopsy, highlighting the importance of interdisciplinary communication among pathology, nephrology, and infectious diseases in patients with unusual C3, IgM, or C1q dominant or lupus-like focally crescentic GNs and a constellation of newly positive serologies or cytopenias. Our study adds to the literature on the treatment, recovery timing, and outcomes of *Bartonella* and culture+ IEGN. Specifically, we demonstrated the prevalence of cardiac valve alterations (75%), ANCA positivity (67%), hypocomplementemia (75%), antinuclear antibody positivity (53%), and cryoglobulinemia (45%) in patients with *Bartonella* IEGN compared with those with culture+ IEGN or non-endocarditis IRGN. Pathologically, *Bartonella* IEGN presents as a focally crescentic GN, which is C3 (co)-dominant (80%) with strong IgM (65%) and/or strong C1q (55%) with mesangial-predominant deposits but fewer exudative features than IRGN. Approximately 10% of cases may be pauci-immune, leading to further confusion regarding ANCA-associated vasculitis. Even in cases with modest IF staining, the degree of crescentic activity was occasionally disproportionate relative to the number of immune complexes observed by IF and electron microscopy. Overall, the clinical and pathologic findings of patients with *Bartonella* IEGN presented here are highly concordant with those described in the robust pooled analysis by Kitamura and colleagues.[10] We identified a significant enrichment of hematologic symptoms, including B-symptoms (79%), splenomegaly (59%), thrombocytopenia (83%), and/or pancytopenia (44%), in patients with *Bartonella* compared with culture+ IRGN.

On follow-up in their pooled analysis, Kitamura and colleagues[10] found that of 45 of 89 patients with *Bartonella* IEGN were treated with immunosuppressants, similar to 55% in our cohort. They found a significant difference in timing to kidney biopsy between *Bartonella* IEGN (3 months) compared with culture+ IRGN (1 month)[10]; delay in diagnosis is reflected in our cohort, in which 35% of *Bartonella* IEGN had ≥ 3 months of unexplained symptoms before diagnosis. Our study provides additional details on the complex scenarios leading to diagnostic confusion with an autoimmune disease (initially suspected in 55% of cases) and reveals that the potential delay in diagnosis and/or receipt of immunosuppression was not statistically associated with ESKD.

This multi-institutional cohort included 4 cases (22%) of *Bartonella* IEGN in which molecular techniques were required for diagnosis, because conventional serologic testing was negative. The 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis[12] added newer nucleic acid–based microbiologic techniques for blood culture negative endocarditis as a major criterion, specifically: "positive polymerase chain reaction or other nucleic acid–based techniques for *Coxiella burnetii*, *Bartonella spp*., or *Tropheryma whipplei* from blood." Before this addition, in one study of 106 patients with *Bartonella* endocarditis, Eduoard *et al*. demonstrated that whereas all tested by Western blot were positive for *Bartonella*, indirect IF assay was negative (in 9%) or positive only at low titer (IgG 1:100–1:800, in 37%) in a substantial minority of patients, and more strongly positive (≥ 1:800) in only 58% of cases, with a serum RT-polymerase chain reaction sensitivity of 36%.[1] Approximately 2% to 20% of persons experiencing homelessness have antibodies to *B. quintana*.[13] Thus, low-level positives and false negatives are challenges in the serologic assessment of *Bartonella spp*. infection when assessing for active endocarditis and/or the etiology of a GN.

Mechanistically, intracellular *Bartonella spp*. survive and avoid the immune system by producing biofilms, inducing angiogenesis, avoiding neutrophil phagocytosis (assisted by *Bartonella* adhesin A in *B. henselae*), resisting fusion and thus, degradation by lysosomes, and increasing production of the anti-inflammatory interleukin (IL)-10.[14] As an antipyretic, IL-10 may contribute to delay in diagnosis by inhibiting fever production[15] in earlier stages of infection. IL-10

decreases platelet production,[16] potentially accounting for the increase in thrombocytopenia in patients with *Bartonella* IEGN. Patients with cat scratch disease have increased levels of IL-6,[17] a cytokine associated with B-cell lymphomas and B-symptoms,[18] which may contribute to the high incidence of B-symptoms seen in *Bartonella* but not in culture+ IEGN or IRGN.

Bartonella causes 0% to 15.6% of IE in Europe, and along with *C. burnetii*, is among the most common causes of culture-negative endocarditis.[1,5] *Bartonella* and *Coxiella* are both intracellular bacteria, which can evoke a similar cytokine response including IL-6 and IL-10,[19] and mimic a systemic vasculitis.[20] A recent series of 7 patients with *C. burnetii* (Q-fever) associated GN showed substantial similarities with *Bartonella* IEGN, specifically, a male predominance, longer duration of kidney disease before diagnosis (> 6 months in 4/7), splenomegaly (4/7), pancytopenia (2/7), positive PR3 ANCA (3/7), cryoglobulinemia (in all), endocarditis or aortic arch infection (4/7) and preexisting cardiac valve abnormality, replacement, and/or aortic dissection (in all). Biopsies from patients with Q-fever show a mesangial proliferative to membranoproliferative pattern of glomerular injury with endocapillary hypercellularity, focal crescents, and frequent IgM and C3 staining.[21] Neither *Bartonella* nor *Coxiella* DNA has been found in affected tissue biopsies from patients with associated vasculitis.[20] Thus, *Bartonella*- and *Coxiella*-associated GN can have substantial overlap in clinical and pathologic features, and it is prudent to test for both agents serologically and/or molecularly in the setting of high clinical concern or with the described biopsy findings.

We identify C1q intensity as associated with ESKD in patients with *Bartonella* IEGN. Mesangial C1q deposition has been associated with a worse prognosis in IgA nephropathy,[22,23] and persistent C1q positivity in repeat biopsies from patients with lupus nephritis may be associated with a worse outcome.[24] Both the alternative and classical complement pathways are involved in host response to *Bartonella*,[7] and in this case, differences in C1q intensity may reflect host complement system differences, duration or severity of infection among others.

Weaknesses of this study include the low number of patients progressing to ESKD, limiting the strength of the conclusions on the association with outcomes. However, our outcome analysis revealing creatinine at diagnosis as a variable associated with progression to ESKD was concordant with the study by Boils *et al.*,[25] previously the largest case series of IEGN ($n = 49$) composed largely of culture-positive endocarditis (90%) due to staphylococcal (53%) or streptococcal (23%) infections with 8% having *Bartonella* IEGN. Unexpectedly, we identified female sex as associated with progression to ESKD in the overall IEGN cohort. This is discordant with trends for worse prognosis in males reported for lupus nephritis,[26] membranous nephropathy, and focal segmental glomerulosclerosis,[27] but not for IgA nephropathy or ANCA GN,[27,28] and is likely multifactorial and requires further study. In addition, for patients with culture+ IEGN versus IRGN, we examined differences by location of infection, but not by organism type or other factors. With this caveat, certain features were significantly more common in IEGN—strong IgM and C1q staining, with less IgA deposition or exudative features and a trend toward ANCA positivity—compared with non-endocarditis IRGN. In a review of published cases of ANCA-positive endocarditis, 18% to 43% of patients with endocarditis developed a positive ANCA, which subsequently became negative in 69%.[29] It has been suggested that ANCA may develop in patients with endocarditis because of molecular mimicry and/ or infection-induced neutrophil activation, degranulation, and NETosis, or production of net-like traps composed of chromatin and bactericidal proteins from neutrophil granules and cytoplasm which have been associated with ANCA development.[29-31]

In conclusion, IRGNs are heterogeneous. Different pathological patterns and clinical presentations of IRGN reflect how the kidney, and glomerular inflammation and injury in particular, offer a window into the immune responses to different inciting microbes. Because gram-negative intracellular bacteria produce a subacute to chronic systemic infection, *Bartonella spp*. elicit a different host response than the robust and acute immune activation typically triggered by gram-positive extracellular bacteria such as *S aureus*. Likely at least in part reflecting these differences, we showed that the clinicopathological features of *Bartonella* IEGN significantly differ from those of predominantly *S. aureus*–related culture-positive IEGN and non-endocarditis IRGN, although certain clinicopathological features are more common in IE than in other IRGNs, regardless of organism. Our findings corroborate the hallmark features of *Bartonella* IEGN and underscore the need for further studies on the diverse glomerular manifestations of host responses to infection and secondary autoimmunity.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Forest plot of tested variables associated with end stage kidney disease in all-comers with endocarditis associated glomerulonephritis.

Table S1. Details of patients with Bartonella-endocarditis associated glomerulonephritis.

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