Austin Journal of Nephrology and Hypertension

Open Access

Austin Publishing Group

Case Report

Nephrotic Syndrome Secondary to Q Fever Endocarditis: A 30-Month Follow-up

Domingos AT[1]*, Vidinha J[1], Gomes A[3] and Neves PL[1,2]

[1]Division of Nephrology - Centro Hospitalar e Universitario do Algarve-Faro, Portugal

[2]University of Algarve - Department of Biomedical Sciences and Medicine -Faro, Portugal

[3]Division of Infectious Diseases - Centro Hospitalar e Universitario do Algarve -Faro, Portugal

***Corresponding author:** Domingos AT, Division of Nephrology, Centro Hospitalar e Universitario do Algarve-Faro, Portugal

Received: August 13, 2020; **Accepted:** October 12, 2020; **Published:** October 19, 2020

Abstract

Background: Q fever, a zoonosis caused by *Coxiella burnetti*, may present as an acute infection (a self-limiting febrile syndrome, pneumonia, hepatitis) or as a chronic infection (typically endocarditis). There is minimal literature on renal involvement in cases of acute Q fever, but glomerulonephritis (GN) is a recognized complication of endocarditis due to chronic Q fever.

Case Presentation: We present a 30-month follow-up of an elderly man, a rural resident and diabetic with a prosthetic valve, who presented with Nephrotic Syndrome (NS), plasmatic Creatinine [pCr] of 3.3 mg/dL (unknown baseline), Proteinuria (Pu) of 8 g/day, decreased C4 and positive Anti-Phospholipid Antibodies (APL). Transthoracic echocardiogram suggested valve vegetation and antibody screening presented positive results for *C. burnetti*. Renal Biopsy (RB) wasn't possible and Membranoproliferative GN was assumed. He was medicated with doxycycline and hydroxychloroquine. At 30 months of follow-up the patient presented two relapsing episodes of anasarca, with a maximum Pu of 11.9 g/day. He attained NS remission at 11 months, with C4 normalization and APL negativity. He currently presents pCr of 1.5 mg/dL, Pu of 0.3 g/day and has maintained reduction of anti-*C.burnetti* antibodies.

Conclusion: The epidemiological context, valve prosthesis and diabetic status were key factors to the diagnosis of NS secondary to Q fever endocarditis. Characteristically, secondary renal involvement responds to therapy directed at the underlying disease. The impossibility of RB hindered decision-making, since empirical immunosuppression could initially be considered. This could have had potentially serious side effects, particularly infectious. Residual proteinuria may result from residual sclerosis.

Keywords: Q fever; Glomerulonephritis; Endocarditis

Introduction

Q fever is a zoonosis caused by *Coxiella burnetti*, an obligate intracellular and Gram-negative bacterium [1-5]. The main reservoirs of *C. burnetti* are ticks, birds and mammals; however, infection in humans derives mainly from contact with domestic mammals such as cattle, sheep, goats, dogs and cats [1,2,4,5]. Its elimination is mainly through urine, feces, milk and products released during deliveries of contaminated animals [1,2]. It presents a sporulation-like process, allowing long survival in the external environment, as well as high infectivity [1,2]. Transmission is mainly through direct skin penetration and inhalation of aerosols or dust containing agent spores, even far away from the contaminated area, since wind can drag spores up to 30 km [1,2,4]. Other ways of contamination are described, such as consumption of food from infected animals and human-to-human transmission (for example, through infected aerosols and blood transfusion) [1,2].

The clinical presentation may vary from asymptomatic (50% of cases) to acute infection (particularly self-limited febrile syndrome, pneumonia or hepatitis), or chronic infection when lasting more than 6 months (presenting mainly as endocarditis). The presence of valvular prosthesis is the most important risk factor for progression to endocarditis after primary infection by *C. burnetti* [1,2,4]. There is minimal literature on renal involvement in cases of acute Q fever, with the first reports appearing in the 1990s [7,8]. GN is a recognized complication of endocarditis due to chronic Q fever. Other, more unusual manifestations include meningitis, meningoencephalitis, peripheral sensory neuropathy or Guillain-Barré syndrome [1,9]. Q fever fatigue syndrome is a prevalent sequela after an acute infection [21].

There are direct and indirect diagnostic techniques. Indirect techniques include detection of antibodies by Indirect Fluorescent Antibody (IFA) tests, namely antibodies anti-phase I (associated with persistent infection) and anti-phase II (predominant during primary infection) [1,2,4]. Recent infection is suggested by phase II IgG titers of 200 or greater and/or IgM of 50 or greater. Chronic infection is indicated by elevated phase I IgG titer (800 or greater) [1,4]. Residual IgG antibody titers may be detectable for years after initial infection and even for the duration of the patient's life [1].

Symptoms are more frequently reported in men than women, with similar exposure to the bacteria, excluding the possibility of a tendency related to a higher male exposition to farm work; instead, a less effective immunological response seems to be related [1,2,5,6] and even sex hormones have been suggested to play a role [1,4,22]. Particularly in pregnant women, infection reactivation, as well as pre-

Citation: Domingos AT, Vidinha J, Gomes A and Neves PL. Nephrotic Syndrome Secondary to Q Fever Endocarditis: A 30-Month Follow-up. Austin J Nephrol Hypertens. 2020; 7(1): 1088.

term delivery, low birth weight and pregnancy loss may occur, the latter recurrent in chronic disease [4,22].

Treatment usually includes doxycycline and hydroxychloroquine for at least 18 months (nonprosthetic infections) to 24 months (prosthetic infections) [1,4,10]. If untreated, the disease carries a poor prognosis [10].

We present a 30-month follow-up of an elderly man, resident in Portugal, diabetic with a prosthetic valve, who presented with NS, which later turned out to be secondary to Q fever endocarditis. The diagnostic and therapeutic options are described, especially given the rarity of the presentation and the impossibility of performing Renal Biopsy (RB). Early detection and treatment are essential.

In 2017, a report by the European Centre for Disease Prevention and Control ranked Portugal as the country with the fourth-highest number of confirmed cases [3].

Case Presentation

M.J.F. is an 81-year-old white rural male with a personal history of arterial hypertension, type II diabetes mellitus, benign prostate hyperplasia, heart failure (not stratified) and valvuloplasty with aortic biological prosthesis. His usual medication included gliclazide, diltiazem, spironolactone, furosemide, tamsulosin and finasteride.

Table 1: Summary of laboratory analysis.

Blood analysis	Result	Reference value
Hemoglobin (g/dL)	11.4	11.5-15.5
MCV	84	83-101
MCH	28.4	27-32
Hematocrit (%)	34%	35-45
Leukocytes (x10^9/L)	3.7	4-10
Platelets (x10^9/L)	99.000	150-400
pCr (mg/dL)	3.3 (unknown baseline value)	0.6-1.1
BUN (mg/dL)	48	9.8-20.1
BNP (pg/mL)	1473	0-100
Albumin (g/dL)	2.3	3.4-4.8
C4 (g/L)	0.085	0.160-0.380
CRP (mg/L)	<3	<5
APL antibodies	Positive	
Ionogram	Normal	
Hepatic function		
Arterial blood gas		
Urinalysis	**Result**	
Hematuria	5+	
Pu	4+	
Leukocyturia	+	
Nitrites	-	
Glycosuria	2+	
24-hour urine collection	8000 mg of proteins	

APL: Antiphospholipid; BNP: Brain Natriuretic Peptide; BUN: Blood Urea Nitrogen; CRP: C-Reactive Protein; pCr: plasmatic Creatinine; Pu: proteinuria.

The patient was admitted with a 3-week history of aggravated tiredness, edema and pain of the right hand and wrist, lower limb edema and macroscopic hematuria. Just before admission, he was prescribed levofloxacin due to suspected Urinary Tract Infection (UTI). There was no other nephrotoxic consumption.

Table 1 summarizes relevant blood work results.

Chest x-ray showed cardiomegaly, interstitial reinforcement in both lungs and blunting of the left costophrenic angle. An upper right limb venous ultrasound Doppler excluded thrombosis and showed edema and densification of skin, subcutaneous tissue and all muscle groups. Renal ultrasound revealed normal dimensions and contours, good corticomedullary differentiation and several cortical cysts, plus normal bladder and slightly enlarged prostate. Transthoracic echocardiogram revealed probable valve vegetation.

Infectious study was extended, including serology for Brucellosis and Q fever. These came back positive for *C. burnetti* and phase I and II antibody screening confirmed the suspicion (Table 2). In addition, *Klebsiella pneumoniae* ESBL was isolated in urine culture with the remaining cultures negative. It was resolved with directed antibiotherapy.

During hospitalization, the patient required platelet and blood transfusion. Complementary study revealed an iron deficiency but also a chronic disease component (associated with chronic infection).

Overall, he evolved favorably from anasarca with intravenous diuretic (9 kg loss) and antiproteinuric drugs and started treatment with doxycycline and hydroxychloroquine. Membranoproliferative GN was assumed, since RB was contraindicated due to the presence of large renal cysts, bilaterally.

At discharge date, he had a pCr of 1.8 mg/dL with resolution of anasarca and initial symptomatology. Ambulatory treatment with doxycycline, hydroxychloroquine and usual agents for NS was maintained.

The patient maintains follow-up in Nephrology, Cardiology, Infectious Diseases and Ophthalmology (due to treatment with hydroxychloroquine).

At 30 months of follow-up he presented three hospitalizations, one due to drug-induced photosensitivity (doxycycline) plus UTI due to *K. pneumoniae*, and the other two episodes related to relapsing anasarca, with a maximum Pu of 11.9 g/day. NS remission was attained after 11 months, with C4 normalization and APL negativity. After 15 months it was necessary to discontinue antibiotic treatment due to gastrointestinal intolerance. He currently presents pCr of 1.5 mg/dL, Pu of 0.3 g/day and maintained reduction of IgG phase I (6400) and II (1600) antibodies.

Discussion

Q fever often has a nonspecific presentation and multiorgan attainment. The epidemiological context, the presence of valve

Table 2: *C. burnetti* antibody screening.

	IgG titers	IgM titers
Phase I	25600	100
Phase II	6400	<50

prosthesis and diabetic status are key factors in this case. Data describe about a 40% incidence of endocarditis after *C. burnetti* infection in patients with valvulopathy [1,9]. Male sex is also considered a risk factor [1]. In untreated chronic Q fever, mortality rates of up to 60% are reported [10].

Infection-associated GN includes post-infectious GN (PIGN, after infection resolution) and GN associated with an ongoing infection. Endocarditis-associated GN is considered an infection-associated GN [17]. PIGN was previously called "post-streptococcal glomerulonephritis" since most cases appeared after streptococcal infections, classically in children and residents of developing countries [13-17]. In the modern era, developed countries are affected differently, with a higher prevalence among adult males-particularly elderly and immunocompromised-with several comorbidities, including alcoholism, diabetes, malignancy and diffuse vascular disease; in this set, staphylococcal infections are now as common as streptococcal infections [15,16]. Almost half of the cases in developed countries are associated with infections of Gram-negative bacilli [14].

Diagnosis of infection-associated GN in the elderly is particularly challenging, as their presentation may be atypical or unspecific, without fever or leukocytosis, or manifested as decompensated comorbidities, such as aggravated fatigue, decompensated heart failure and, in diabetic patients, uncontrolled glycemia [15,17]. Nephrotic syndrome and rapidly progressive GN are rare [11,17].

There is minimal literature on renal involvement in cases of acute Q fever, with the first reports appearing in the 1990s [7,8]. Some case reports reviewed by Ana Fernandes and colleagues [7] describe several patterns in this context, such as proliferative Glomerulonephritis (GN), tubulointerstitial nephritis and acute tubular necrosis. GN is a recognized complication of endocarditis due to chronic Q fever. It usually presents with microscopic hematuria, acute kidney injury and, histologically, an immune complex GN [2,7,11]. Endocarditis-associated GN, now recognized as an immune-mediated glomerular injury (instead of exclusively an embolization phenomenon due to the vegetations), histologically presents mainly as a crescentic GN or diffuse, focal or mild mesangial proliferative GN. Tubular injury and interstitial inflammation are also patent [17,18]. Nephrotic Syndrome (NS) is a less common manifestation [11]. Reductions in C3 and C4 complement are common [11]. Other findings may include positive ANCAs, rheumatoid factor, anti-GBM autoantibodies, lupus anticoagulant or Anti-Phospholipid (APL) antibodies [7,11,12]. The latter may be associated with acute Q fever endocarditis and/or the development of persistent infection [7,12].

PIGN outcomes reported in the elderly reveal residual chronic kidney disease in more than 50% of patients, with a death rate around 25% [15]. Some prognostic factors of end-stage renal disease include patient age, serum creatinine at presentation, the degree of residual Pu after acute phase, the need for hemodialysis and, histologically, the presence of underlying diabetic glomerulosclerosis, interstitial fibrosis, tubular atrophy and the number of crescents [15]. In endocarditis-associated GN, similar mortality and persistent renal disease rates are described, since infection resolution does not guarantee favorable outcomes [19]. Moreover, Q fever endocarditis itself can lead to a mortality of approximately 20% [20], but adequate antibiotic treatment reduces this mortality to <5% [10].

Conclusion

This association between chronic infection due to *C. burnetti* and renal manifestations is plausible given the renal remission after directed treatment for the underlying infection and after excluding other possible causes. The impossibility of performing RB hindered decision-making, since empirical immunosuppression could initially be considered. Given the follow-up, this could have had potentially serious side effects, particularly infectious, in a very elderly patient. Our patient presented with chronic infection as well as with complications classically associated with prosthetic valves. Furthermore, its presentation as NS and with positive APL antibodies is relatively uncommon.

In this case, although doxycycline and hydroxychloroquine therapy has been discontinued, the patient maintains a favorable renal and infectious response. Residual proteinuria may result from residual sclerosis.

References

1. Eldin C, Melenotte C, Mediannikov O, Ghigo E, Million M, Edouard S, et al. From Q Fever to Coxiella burnetii Infection: a Paradigm Change. Clinical Microbiology Reviews. 2017; 30: 115-190.
2. Santos S, Bacellar F, Franca A. Febre Q: revisao de conceitos. Rev Soc Port de Med Inter. 2007; 14: 90-99.
3. European Centre for Disease Prevention and Control. Surveillance report: Q Fever, Annual epidemiological report for 2017. Stockholm. 2019.
4. Hartzell J, Wood-morris R, Martinez L, Trotta R. Q Fever: Epidemiology, Diagnosis, and Treatment. Mayo Clin Proc. 2008; 83: 574-579.
5. Maurin M, Raoult D. Q Fever. Clin Microbiol Rev. 1999; 12: 518-553.
6. Tissot Dupont H, Raoult D, Brouqui P, Janbon F, Peyramond D, Weiller PJ, et al. Epidemiologic features and clinical presentation of acute Q Fever in hospitalized patients: 323 French cases. Am J Med. 1992; 93: 427-434.
7. Fernandes AR, Gouveia F, Viegas M, Coelho S, Soares E, Luis N, et al. Acute kidney injury due to Q Fever. Port J Nephrol Hypert. 2016; 30: 303-307.
8. Korman T, Spelman D, Perry G, Dowling J. Acute Glomerulonephritis Associated with Acute Q Fever: Case Report and Review of the Renal Complications of Coxiella burnetii Infection. Clin Infect Dis. 1998; 26: 359-364.
9. Rustscheff S. Q Fever as a cause of pure sensory polyneuropathy-the six-year itch: a follow-up of an indigenous Swedish case. Scand J Infect Dis. 2005; 37:949-950.
10. Kampschreur L, Wegdam-Blans M, Wever P, Renders N, Delsing C, Sprong T, et al. Chronic Q Fever Diagnosis-Consensus Guideline versus Expert Opinion. Emerging Infectious Diseases. CDC. 2015; 21.
11. Stein A, Raoult D. Q Fever endocarditis. Eur Heart J. 1995; 16: 19-23.
12. Million M, Walter G, Bardin N, Camoin L, Giorgi R, Bongrand P, et al. Immunoglobulin G anticardiolipin antibodies and progression to Q Fever endocarditis. Clin Infect Dis. 2013; 57: 57-64.
13. Nasr S, Fidler M, Valeri A, Cornell L, Sethi S, Zoller A, et al. Postinfectious Glomerulonephritis in the Elderly. JASN. 2011; 22: 187-195.
14. Kanjanabuch T, Kittikowit W, Eiam-Ong S. An update on acute postinfectiousglomerulonephritis worldwide. Nat Rev Nephrol. 2009; 5: 259-269.
15. Stratta P, Musetti C, Barreca A, Mazzucco G. New trends of an old disease: the acute post infectious glomerulonephritis at the beginning of the new millennium. J Nephrol. 2014; 27: 229-239.

16. Nasr S, Radhakrishnan J, D'Agati V. Bacterial infection-related glomerulonephritisin adults. Kidney Int. 2013; 83: 792-803.

17. Satoskar A, Parikh S, Nadasdy T. Epidemiology, pathogenesis, treatment and outcomes of infection associated glomerulonephritis. Nat Rev Nephrol. 2020; 16: 32-50.

18. Satoskar A, Suleiman S, Ayoub I, Hemminger J, Parikh S, Brodsky SV, et al. Staphylococcus Infection-Associated GN - Spectrum of IgA Staining and Prevalence of ANCA in a Single-Center Cohort.Clin J Am Soc Nephrol. 2017; 12: 39-49.

19. Boils CL, Nasr SH, Walker PD, Couser WG, Larsen CP. Update on endocarditis-associated glomerulonephritis. Kidney Int. 2015; 87: 1241-1249.

20. Million M, Thuny F, Richet H, Raoult D. Long-term outcome of Q fever endocarditis: a 26-year personal survey.Lancet Infect Dis. 2010; 10: 527-535.

21. Keijmel S, Delsing C, Sprong T, Bleijenberg G, Meer J, Knoop H, et al. The Qure study: Q fever fatigue syndrome – response to treatment; a randomized placebo-controlled trial.BMC Infect Dis. 2013; 13: 157.

22. Raoult D, Marrie T, Mege J. Natural history and pathophysiology of Q fever. Lancet Infect Dis. 2005; 5: 219-226.