Case Series of Q Fever Infection Over a Fifteen-year Period: Our Experience at Sultan Qaboos University Hospital, Oman

Kowthar S. Hassan[1]*, Batool Al Lawati[2] and Turkiya Al-Siyabi[3]

[1]Department of Medicine, Infectious Diseases Unit, Sultan Qaboos University Hospital, Muscat, Oman

[2]Department of Medicine, Rheumatology Unit, Sultan Qaboos University Hospital, Muscat, Oman

[3]Department of Microbiology and Immunology, Sultan Qaboos University Hospital, Muscat, Oman

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*Corresponding author: kowhassan@gmail.com

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Abstract

Objectives: Q fever is a worldwide zoonosis, yet, its prevalence might be underestimated in part due to the difficulties in establishing the diagnosis. Here we present a number of cases we saw over a fifteen-year period (1/1/2009-30/11/2023) at Sultan Qaboos University Hospital that we treated for Q fever infection based mainly on their clinical features and the available laboratory tests highlighting the challenges in establishing the diagnosis.

Methods: Relevant patient information was obtained from the electronic hospital records under ethical approval MREC # 3139.

Results: We treated seventeen patients from a total of 1481 patients tested. Median age was of 38 years with a male to female ratio of 1.4:1. Fever was the commonest feature and six patients had weight loss. Hepato-biliary, respiratory, neurological and musculoskeletal symptoms occurred in ten, six, five and four patients respectively. Three patients also developed rashes during their illness. Two patients had definite and one had probable infective endocarditis and two patients had pericardial effusion.

Conclusion: Q fever should be considered in the differential diagnosis of a wide range of clinical presentations. However, as it can be clinically challenging and serological test interpretation can be difficult in areas of endemicity and with limited diagnostic tests, combination of compatible clinical illness and appropriate diagnostic tests are necessary for the correct diagnosis.

Keywords: Q Fever; *Coxiella Burnetti*; Oman; Serology; Infective Endocarditis; Hepatitis; SLE; Rheumatoid Arthritis.

Introduction

Q fever is a worldwide zoonosis caused by the obligate intracellular Gram negative cocobacillus *Coxiella burnetti* and named so as a query because the etiology was not identified. The main reservoir in the environment is farm animals and the main route of transmission is through contact with infected animals and drinking unpasteurized dairy products.[1] Hard ticks are also thought to have a role in transmission albeit not major.[2] The disease may manifest in acute or chronic forms but establishing the diagnosis is often a challenging task. The prevalence of Q fever in Oman is not known. Over a 15 year-period (1/1/2009- 30/11/ 2023) at Sultan Qaboos University Hospital (SQUH) we saw a number of patients that we considered Q fever as a possible diagnosis and treated them as such. This was based primarily on their clinical presentations and supported by the available laboratory investigations (qualitative and quantitative serology and nucleic acid amplification test NAAT). Here we like to share our experience shedding some light on the difficulty in reaching the diagnosis.

Case 1. A 27-year-old man referred from Salalah for splenomegaly and bicytopenia developed jaundice and jerky movements during his admission and referred to the infectious diseases team (ID) for possible infectious etiology. Q fever serology was positive for IgG antibodies to phase I antigen (anti IgG I) and his echocardiogram (ECHO) showed thickening of mitral and aortic valve leaflets but no clear mass. He was commenced on doxycycline and hydroxychloroquine (HCQ). One month later he was asymptomatic with improved blood parameters. He was referred back to Sala for completion of treatment [Tables 1 and 2].

Table 1: characteristics of seventeen patients treated for Q fever. SOB; shortness of breath, LOC: loss of consciousness, WBC: white blood cell count, CRP: C-reactive protein, ESR; erythrocyte sedimentation rate. sero; serology, qlt; qualitative, qnt; quantitative. NK: not known.

G/Age	year Presentation	Presentation	Area	Animal Contact	WBC	LFT	CRP/ESR	Method of diagnosis
M/27	2009	bicytopenia, splenomegaly, jaundice, no fever	Salalah	NK	4.7	ALP: 340 Bilirubin: 19	178/112	sero qlt
M/59	2011	3–4-week of fever, dry cough, syncope, headaches, reduced appetite.	Denmark, Muscat	dog	10.4	ALT/AST: 2-3 x normal	122/65	sero qlt, qnt
M/35	2011	5 days of fever, chill, sweating, then 5 d fever 40, bilateral knee pain, jaundice, Splenomegaly, Achilles pain, mouth ulcers one month before.	Muscat	no	4	ALT/AST: x 2 normal	124/69	sero qlt
F/41	2011	2-3 weeks of fever, SOB, cough of, chest pain, palps, memory impairment, joint swelling and pain, . Flu A	Al Shaqiya	NK	23.9	ALT/AST: x 2 normal	98/48	sero qlt
M/38	2013	1-month unwell, dizzy, dark urine, jaundice, bloody stools, 3-days of lower abdominal pain, oligouria, hepatitis, 10 kg weight loss in 1 month	Al Sharqiya	NK	15.7	AST: x 3 normal, bilirubin: 240	87/34	sero qlt
F/48	2013	1 month fv chills, ten latent TB 9 month, rcr 2015 with new murmur	Muscat	no	7.9	normal	73/95	sero qlt
F/13	2013	11 days of fever, cough, anorexia, night sweats	Al Batina	NK	3.3	ATL/AST: 1.5 x normal	54/41	sero qlt
M/36	2014	4 weeks of fever, profuse sweating, 7 kg weight loss, arthralgia10 d after returning from Tailand	Al Batina	goats	7.8	normal	75/67	sero qlt
M'37	2014	3 months of intermittent fever. TTE showed possible vegetation on mitral valve.	Al Sharqiya	yes	9.8	ALT/AST: marginal increase	50	sero qlt

F/38	2015	1 month of ever with generalised pain, rigors, sweating after returning from India.	Al Batinah	NK	3.2	ALT/AST: 3 x normal	2/33	sero qlt,
M/46	2016	3 months FUO, polyarthritis, anaemia, lymphopenia, thrombocytopenia, purpuric rash	Al Dhahira	yes	6.4	normal	336/93	sero qlt
F/52	2016	fever, hepatitis	Al Dhahira	NK	3.2	ALT/AST: normal, bilirubin: 320	14/39	sero qlt,
F/38	2018	infective endocarditis	Al Sharqiya	NK	29.2	normal	83/5	sero qlt, qnt
M/28	2020	8 days of fever/chills, headaches, jaundice.	Muscat	yes	6.3	ALT: 10 x normal, bilirubin: 79	61/NK	sero qlt, , PCR
M/38	2021	2 months of fever sweating, 6 kg weight loss.	Al Dakhiliya	NK	5.3	normal	13/NK	sero qlt, qnt, PCR
M/38	2021	1 week of left sided weakness, headache, nausea, 1 day dizziness, slurred speech, LOC.	Al Dakhiliya	Live stock	2.6	ALT/AST: 2-3 x normal	104/NK	sero qlt, qnt
F/57	2022	lesion on mitral valve	Al Batina	no	11.6	ALT/AST: normal, bilirubin: 56	9/NK	sero qlt, qnt + PCR

Table 2: Sequential serology results of patients treated for Q fever with interpretation. Quantitative serology is mentioned when available. Note that IgA was not measured in all tests, IgG II in case 1 was not reported and repeat testing was not done at standard intervals. D; day, Eqv; equivocal. Interpretation of the serology Cleary illustrates the difficulty in making the diagnosis and distinguishing acute from chronic form in the absence of quantitative serology.

Case 1	**Possible acute infection**				
	D0	**D18**	**D96**		
IgM II	+	+	-		
IgA I	-	-	-		
IgG I	+	+	+		
Case 2	**Acute infection**				
	D0	**D35**	**D105**	**Yr3**	**Yr6**
IgM II	+	+	+	-	-
IgG II	+	+	+	+	eqv
IgA I	+	+	+	-	-
IgG I	+	+	-	+	+
Biomnis	**D35**	**D60**			
IgM II	+	+			
IgM I	Weak +	Weak +			
IgG II	512	256			
IgG I	< 64	< 64			
Case 3	**Possible acute infection**				
	D0	**D110**			
IgM II	+	+			
IgG II	+	+			
IgA I	-	_-			
IgG I	-	-			
Case 4	**Possible acute infection**				
	D0	**D80**			
IgM II	+	+			
IgG II	+				
IgA I	Weak +				
IgG I	-	-			
Case 5	**possible past infection**				
	D0	**D10**			
IgM II	eqv	eqv			
IgG II	eqv	-			
IgA I	+	+			
IgG I	+	+			
Case 6	**Possible acute infection**				
	D0	**D32**			
IgM II	+	eqv			
IgG II	+	+			
IgA I	-	-			
IgG I	-	-			
Case 7	**Possible acute infection**				
	D0	**D30**	**D85**	**Y2**	
IgM II	-	+	weak +	-	
IgG II	-	+	+	+	
IgA I	-	-	-	-	
IgG I	-	-	-	+	
Case 8	**Possible acute of non-specific reaction**				
	D0	**D35**			
IgM II	+	-			
IgG II	eqv	eqv			
IgA I	-	-			
IgG I	-	-			

Case 9	**Possible past infection**							
	D0	**D15**	**D45**					
IgM II	-	-	-					
IgG II	-	eqv	-					
IgA I	-	-	-					
IgG I	+	+	+					
Case 10	**Possible chronic infection**							
	D0	**D35**	**D270**	**D360**	**D430**	**D450**	**Yr3**	**Yr4**
IgM II	-	-	-	-	-	-	-	-
IgG II	+	+	+	+	-	+	+	+
IgA I	+	+	+	+	+	+	+	+
IgG I	+	eqv	+	eqv	+	+	eqv	+
Case 11								
	D0	**D80**						
IgM II	eqv	-						
IgG II	+	+						
IgA I	-	-						
IgG I	+	+						
Case 12	**Possible chronic infection**							
	D0	**D350**	**D480**					
IgM II	-	-	-					
IgG II	eqv	+	+					
IgA I	-	+	+					
IgG I	-	+	+					
Case 13	**Chronic infection**							
	D0	**D210**	**D450**					
IgM II	-	-						
IgG II	+	2048	1024					
IgA I	+	+	+					
IgG I	+	1024	256					
Case 14	**Possible acute infection**							
	D0	**D50**						
IgM II	+	+						
IgG II	-	+						
IgA I	-	-						
IgG I	-	-						
Case 15	**Resolving infection**							
	D0	**D150**	**D330**	**D630**				
IgM II	+	-	+	-				
IgG II	+	-	+	+				
IgA I	-	-	+	+				
IgG I	-	+	+	+				
	D0 Lyon France	**D180 Lyon France**	**D480 Mayo USA**					
IgM II	-	-	< 1:16					
IgG II	2048	2048	1: 128					
IgA I	-	-	< 1: 16					
IgG I	1024	1024	1: 256					
Case 16	**Chronic infection**							
	D0	**D24**	**D130**	**D340**	**D490**	**D730**		
IgM II	+	+	+	+	-	-		
IgG II	-	+	+	+	+	+		
IgA I	-	-	-	+	+	eqv		
IgG I	-	-	+	+	+	+		
Case 17	**Chronic infection**							
	D130	**D340**	**D490**	**D580**				
IgM II	+	-	< 1:16	<1:16				
IgG II	2048	256	1:128	1:64				

IgA I	+	-	< 1: 16	<1:16
Ig GI	1024	256	1:128	1:256
Case17	D0	D8	D150	
IgM II	+	eqv	-	
IgG II	+	+	+	
IgA I	+	+	+	
IgG I	+	+	+	
	D14			
IgM II	-			
IgG II	>2048			
IgM I	-			
IgG I	>2048			

Case 2. A 59-year-old man presented with a one-week history of fever up to 39º C associated with dry cough, reduced appetite and headache after returning from a five week visit to Denmark. He received Tazocin for *Achromobacter* bacteremia. His Q fever serology was positive for anti IgG I and IgG II. One week after starting doxycycline he was still febrile and his anti-citrullinated peptide (ACPA) and rheumatoid factor (RF) were positive but totally asymptomatic after 3 weeks with normal ACPA and RF. See tables 1 & 2. 92

Case 3. A 35-year-old man presented with a two-week history fever (40ºC) with chill/rigors, dry eyes, jaundice and splenomegaly. His Q fever serology was positive for phase II (IgM and Ig) and phase I (IgA and IgG) as were RF and ACPA. He was started on doxycycline two weeks after which he defervesced with a decrease in his inflammatory markers. However, his eye dryness persisted and he developed pain in right Achilles tendon and heel. After 1.5 months he was asymptomatic with normalization of his RF and ACPA. See tables 1 & 2.

Case 4. A 41-year-old woman presented with a two-to-three-week history of fever, dyspnoea, cough, chest pain, hand small joint arthritis and later a rash. She required intubation for acute respiratory distress syndrome (ARDS) due to influenza A infection. CT brain (done for poor memory) suggested vasculitis for which she was started on prednisolone 40mg. Her ECHO showed pericardial effusion and Q fever serology was positive for IgG II. She was started on doxycycline with HCQ. After three months of doxycycline alone (HCQ stopped due to intolerance) she was asymptomatic. Three months after stopping doxycycline and with tapering of steroids, her arthritis recurred and was diagnosed as seronegative RA and fibromyalgia. See tables 1 & 2.

Case 5. A 38-year-old man presented with one month of being unwell, jaundice, 10 kg weight loss, lower abdominal pain and per-rectal bleeding and had hepatic and renal impairment with hypotension. He had used an unknown herbal medication after developing jaundice. Tests for Leptospira, dengue and Crimean Congo haemorrhagic fever (CCHF) were all negative as were his blood cultures and tests for haemophagocytic lymphohistiocytosis (HLH). Doxycycline was started based on his equivocal IgM II positive IgG I and as a good antibiotic choice for many infections but he expired four days later. See tables 1 & 2.

Case 6. A 48-year-old woman presented with a one-month history of fever with chill and rigors, weight loss (2kg), dysuria and flank pain. Her CT abdomen, however, showed sacroiliitis. She also had a one-year history of knee pain labeled as osteoarthritis (OA). Based on her Q fever serology results (positive for phase II IgM and IgG) she was started on doxycycline and HCQ but continued only on doxycycline due to intolerance to HCQ. Five weeks later she was completely asymptomatic with normalization of her inflammatory markers. See tables 1 & 2.

Case 7. A 13-year-old girl presented with a ten-day history of fever, night sweats, cough and body aches. Her CT abdomen showed mesenteric lymphadenopathy and sacroiliitis. Her tests for TB were negative and Q fever serology was suggestive of acute Q fever. Six weeks after doxycycline, she was afebrile with resolution of her lymphadenopathy. This patient, however, had a recurrence of her knee pains along with mouth ulcers and was diagnosed as Behcet's disease and later found to be heterozygous for MC4R gene which is linked to obesity. See tables 1 & 2.

Case 8. A 36-year-old man presented with eight weeks of fever (40ºC) with chills and profuse night sweating, decreased appetite and 7 kg weight loss. Q fever IgM II was positive and he was started on doxycycline. Two weeks later, he was afebrile but developed new pains in knee and ankle, despite dropping inflammatory markers. At the end of six weeks, he was afebrile and asymptomatic. See tables 1 & 2.

Case 9. A 37-year-old man presented with twelve days of fever reaching 40ºC peaking at night and afternoon associated with headache and one month of intermittent right iliac fossa pain associated with reduced appetite but no weight loss. His ECHO showed a suspicious mass and had Q fever serology positive for IgG I. He was commenced on doxycycline and HCQ and planned for transesophageal ECHO (TEE), however, he defaulted. See tables 1 & 2.

Case 10. A 38-year-old woman, a known case of SLE with good adherence to medication presented with a one-month history of high fever starting one week after returning from India associated with sweating and rigors. She also had body aches, swelling on the dorsum of hand, sore throat and cough productive of whitish sputum. CT chest showed pericardial effusion. She was parainfluenza 3 positive and her Q fever serology showed positive IgG I and II. She was commenced on doxycycline and HCQ planned for one year. Her fever resolved as did her pericardial effusion with treatment for Q fever. See tables 1 & 2.

Case 11. A 46-year-old man presented with a one-month history of fever with rigors and sweating, polyarthritis (shoulders, small joints of hands, knees, elbows) and morning stiffness. His Q fever serology was positive for IgG I and II. Two weeks after commencing doxycycline his joint pain improved by 80% and his fever resolved. However, two weeks later he again had fever, arthralgia and developed non-pruritic purpuric rash although his CRP dropped from 147 to 1. His RF and ACPA were negative, and he was considered as possible seronegative rheumatoid arthritis/adult onset Still's disease (AOSD). Currently he is still followed up by rheumatology. See tables 1 & 2.

Case 12. A 52-year-old woman presented with jaundice and transaminitis followed by fever and neutropenia. Her bone marrow biopsy showed histiocytes and intracellular organisms with inclusion bodies. Infectious aetiology was suggestive of Q fever by serology but PCR was negative. Two weeks after commencing doxycycline, she defervesced with improvement in her bilirubin but had slight increase in transaminases and developed a new maculopapular rash. She was treated with doxycycline for four months and followed up by hepatologists for autoimmune hepatitis. See tables 1 & 2.

Case 13. A 38-year-old woman presented with a two-month history of fever (39º C), seven kg weight loss and cough productive of yellow sputum. She had been treated at her regional hospital with courses of antibiotics without improvement. She also gave a month-long history of pain and swelling of lower back. Her past medical history included systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APL) for which she was on mycophenolate (MMF), and HCQ. A transthoracic ECHO (TTE) showed a highly mobile mass on the anterior leaflet of the mitral valve. Four sets of blood cultures were negative. See image 1 & 2. Q fever serology was positive for IgG I and II and she was commenced on doxycycline with increase in the dose of HCQ to three times per day. Repeat ECHOs in 2019 and 2021 showed resolution of the vegetation. See tables 1 & 2.

Case 14. A 28-year-old man presented with one week history of fever (39ºC) with shivering, nausea, jaundice, dysuria, decreased appetite and dark urine. His bilirubin was up to 79 µmol/L. He had swum in a *falaj* (irrigation water aqueducts) in the week prior to his illness. Leptospira serology was negative but Q fever serology was positive for IgM II and IgG II. He was started on doxycycline two weeks after which he defervesced with improvement in the liver function test (LFT). See tables 1 & 2.

Case 15. A 38-year-old man presented with two months of fever (39.5ºC) with profuse sweating, reduced appetite and weight loss of 6 kg. Q fever PCR from blood was positive and he was commenced on doxycycline but developed knee and elbow pains and stiffness after two weeks of treatment. He also had memory problems that had started in 2006 and had been seen by a psychiatrist in 2013. He has completed 18 months of treatment with much improvement in his anxiety but his impaired memory persisted until last seen last month. See tables 1 & 2

Case 16. A 38-year-old man presented with nine days history of fever (39.5ºC), severe headache and seven days of left side weakness, slurred speech, facial twitching and dizziness. He also had multiple syncopal attacks during those nine days. His CT brain showed a 3 cm calcified lesion in the right occipital region likely to represent a benign lesion and not explaining his symptoms. His serology was positive for phase II IgM. The patient received 18 months of HCQ and doxycycline with resolution of his headaches and other neurological symptoms. See tables 1 & 2.

Case 17. A 57-year-old woman presented with a one-month history of intermittent fever (38.5ºC), palpitations sweating and undocumented weight loss in addition to two days of dyspnoea. Her past medical history included Grave's disease, atrial fibrillation but she had defaulted three years ago stopping all her medication. Upon presentation, she had thyrotoxicosis and was positive for parainfluenza 1. Her fever and palpitations resolved upon commencement of carbimazole, however, her, Q fever PCR and serology (sent initially for fever) were positive. Her ECHO showed mitral valve vegetation and she was commenced on doxycycline and HCQ planned for a minimum of 18 months for infective endocarditis (IE). Unfortunately, she defaulted again five months after the presentation. See tables 1 & 2

Discussion

Q fever a world-wide zoonosis, was first reported in 1935 as an outbreak of febrile illness with flu-like symptoms in abattoir workers in Queensland Australia and named so as a query because the etiology was not identified.[3]

Prevalence of Q fever in the human population in Oman is unknown. In 2003 Scrimgeour reported a seroprevalence positivity in human population (n = 102) in Oman presenting to SQUH for various diseases (DM, IHD) to be 9.8%. Seropositivity from healthy 52 randomly selected goats reached up to 52%.[4]

In our neighboring country Kingdome of Saudi Arabia (KSA), human screening was similar to Oman at 8% while animal seropositivity was much lower at 30.7%.[5,6] Q fever has a large reservoir in nature including livestock, pet animals, birds and even marine mammals.[7, 8.] Routes of transmission include contact with infected animals, consumption of raw dairy products, hard tick bites, blood transfusion, vertical from mother to fetus and possibly sexual contact.[1,9]

Over a fifteen-year period (1/1/ 2009-30/11/2023) we identified seventeen patients that we had initiated treatment for Q fever based on their presentation and the tests results. The median age was 38 years (min: 13-max: 59) and men to women ratio was 1.43: 1 similar to previously reported elsewhere of 2.5:1.[10] Patients were from the various governorates in Oman including Muscat, Al Batina, Al Sharqiya, Al Dakhiliya, Al Dhahira and Dofar (4, 4, 4, 2, 2 and 1 respectively). Occupational history was obtained from twelve patients, one of which was a camel jockey and was missed from the rest. Q fever seropositivity has been reported in camels and this could have been the source of the infection in him.[11,12] History of animal contact or raw dairy consumption was positive in six patients, negative in three and missed in eight patients. Case 2 had a dog coughing but whether that was relevant was not explored by us.

The infection may manifest in acute or chronic forms. The acute form usually occurs 2-5 weeks post exposure and ranges from asymptomatic infections (60%), self-limited flu-like illness to severe disease of pneumonia or hepatitis.[13] Atypical acute presentations include perimyocarditis, neurological or hematological involvement and aseptic meningitis.[14] Chronic disease occurs in < 5% and develops months or years later (1). Manifestations include endovascular infections in the form of infective endocarditis and infections of vascular prosthetic devices, granulomatous hepatitis, osteomyelitis and interstitial pulmonary fibrosis.[15,16,17] Infective endocarditis has also been reported in acute Q fever.[18]

Fever was the commonest clinical feature (88%), reaching 40ºC in some patients and was associated with sweating and chills/rigors. Hepatitis presenting as transaminitis was seen in ten patients (58.8%), while four patients had high bilirubin (19, 56, 240, 320) and clinically evident jaundice summing up to twelve patients (70.6%) similar to that reported previously of 61.8%.[19] Weight loss occurred in six patients (35.3%). Splenomegaly is reported to occur in 5% of acute Q fever in agreement with the 6% of cases in our cohort.[20, 21] Six patients (35.3%) had respiratory symptoms in the form of sore throat, dyspnoea, cough and chest pain. Three of them had co-infections with influenza A, parainfluenza 3 and parainfluenza 1 (case 4, 10 and 17 respectively). Ten patients had normal chest imaging, one had pulmonary oedema, one had nodules, three had minimal pleural effusion and one had consolidation summing up the pulmonary involvement to 11.76% much lower than previously reported of 45.8%.[19] Some of the respiratory symptoms might be attributed to their coinfection with other pathogens. Neurological symptoms occurred in five patients (29.4%) in the form of severe headache, poor memory, focal neurological signs, involuntary movements, and seizures much lower than the 40.9% previously reported in acute Q fever.[22] Case 3 presented five years after initial presentation with a stroke at the age of 41 years. Q fever has been reported to cause stroke and this might have been a relapse of Q fever but, we were not aware of his presentation to explore that possibility.[23] Case 16 presented with severe headache with a normal CSF

excluding meningitis and the CT brain showed a 3 cm calcified lesion unlikely to cause his symptoms. He was asymptomatic after completing 18 months of treatment. A repeat CT scan is planned in due course.

Five patients (29.4%) presented with musculoskeletal symptoms in the form of sacroiliitis and asymmetric small joints of hands arthralgia (cases 6, 7, 4 respectively), much higher than previously reported at 2%.[24] Three patients developed new pains in knees, ankles, and Achilles tendon during or just after completion of treatment (cases 8, 15 and 3) that could be due to the killing of the bacteria and liberation of its LPS in a manner similar to Gram negative bacterial killing. LPS is indeed a virulence factor for *Coxiella* being different in the different stages of the virulent phase I.[25] Three patients (17.6%) developed maculopapular or purpuric rashes (cases 4, 11, 12) in agreement with skin rashes described in 5-21%.[26] It is not clear, however, whether this was part of the Q fever or drug reactions. Two patients had haematological involvement in the form of bicytopenia and neutropenia and one patient had lymphadenopathy.

Two patients had infective endocarditis. Case 13, a case of SLE, had a mass attached to the mitral valve with negative blood cultures. It was not clear whether this was Libman-Sacks (LS) or culture negative IE. There was no evidence of active SLE disease, neither clinically nor serological. In addition, the LS vegetations which occur in 11% of patients with SLE are usually small or medium sized vegetations on either or both sides of the valve leaflet, whereas the vegetation in IE are large irregular masses and extend to the cord.[27] Her Q fever serology was positive with high titers and she was commenced on treatment of IE with doxycycline and HCQ for 2.5 years. A follow up ECHO should complete resolution of the vegetation with treatment. Case 17 had defaulted before from previous Graves, and atrial fibrillation (AF) treatment and defaulted from treatment of Q fever IE after five months into treatment. Upon contacting her to attend our clinic we learnt she had expired. Case 1 was also treated as probable IE although the ECHO showed increased valvular leaflet thickening rather than vegetation. Transesophageal ECHO (TEE) was not done and the patient was referred back to his local hospital without any further follow up with us. Case 4 had pericardial effusion that was eventually believed to be due to Q fever and not SLE flare as the complements were normal and the patient did not respond to steroids. She responded to doxycycline only as she was intolerant to HCQ.

White cell count (WCC) was increased in four patients who also had *Achomobacter*, influenza A, parainfluenza 3 and parainfluenza 1 (cases 2, 4, 10 and 17). In the remaining cases WCC was normal in agreement with other reports.[28] CRP was significantly raised in 13 patients ranging from 50-336. ESR was raised in all that were tested but we could not continue monitoring its levels due to withdrawal of its use at our institution.

Diagnosis of Q fever is based on serology as culturing the organism is hazardous requiring level 3 protection which is not available at all laboratories. Indirect fluorescent antibodies (IFA) is the gold standard serological test which can provide antibody titers. During natural human infection, antibodies produced react in a time sequence to phase II and I antigens. In acute infection, they react to phase II antigens and in chronic infection, they react to a mixture of phase I and II antigens. Immunoglobulin M (IgM) and IgG anti phase II antibodies are detected 2 to 3 weeks after infection. Detection of IgG I at titers of $\geq$ 1:800 by microimmunofluorescence assay indicates chronic Q fever.[20] At our institution, testing for Q fever is done using a commercial qualitative ELISA test (Institut Virion/Serion Gmbh, Germany). This can be useful as an initial screening test, however, it cannot be used solely to diagnose Q fever infection, particularly chronic infection. As the current diagnostic criteria require titers determination, diagnosing Q fever infection using a qualitative assay is a challenge, particularly in endemic areas. The presence of rheumatoid factors (RF) in patients' samples can also cross react with Q fever IgM assay, resulting in false positive results. In our cohort, two patients (case 2 & 3) had positive RF and ACPA at presentation that turned negative after treatment of Q fever indicating that Q fever infection can cause false positive RF and ACPA. Cross reactivity of Q fever serology has been described as well with other infections including *Legionella* and *Bartonella* depending on the test used which can further add to the diagnostic confusion, but this can be resolved with titers determination.[20] Nucleic acid detection tests (NAATs) like PCR can be used to diagnose acute Q fever infection in the first two weeks after infection where it is more sensitive than serology but rapidly and significantly drops thereafter. However, NAATs can also be used to diagnose chronic Q fever infection using tissues such as valves in IE.[29]

Treatment of Q fever depends on its presentation. Treatment of complex chronic form includes doxycycline 100 mg twice per day and HCQ 200 mg three times per day for 12-18 months. We noted, however, in case 4 and 6 that doxycycline was given alone due to intolerance to HCQ. Although alternative agents like quinolones can be used, we were not aware of the lack of compliance with the HCQ until near the end of the treatment, hence the two patients continued on doxycycline alone and responded, an observation that merits further investigation.

Over the 15 years period, our testing for Q fever was not based on the presence of history of animal contact/raw dairy consumption as Q fever has been reported in cases that did not recall any such histories.[31,32] This is because transmission of infection also occurs through inhalation of spores by passersby an area where previously infected animals shed their placenta during birth giving up to >30 km away.[33] Spores are resistant to common environmental conditions such as heat, drying and some common disinfectants. They can survive up to 120 days. In addition, Q fever is the most infectious bacteria with only one bacterium being sufficient to cause the illness.[34] The total number of patients we tested was 1481, only seventeen of whom were treated for Q fever. On the one hand, we showed the need to consider Q fever in the differential diagnosis in many cases but on the other hand, this significant difference between the number of patients tested and those treated shows the huge cost involved in diagnosing one case. Moreover, qualitative positive serology is not enough to establish a diagnosis especially in endemic areas.

We noted that in more than one case, Q fever was a co-infection with another illness and it could have been easily missed in the case 17 presenting with thyrotoxicosis as her initial symptoms could have been easily attributed to thyrotoxicosis. Whether this is a pure coincidence or reflects the underestimated prevalence of Q fever needs to be further investigated. Despite repeating the qualitative serology multiple times, we still had doubts in establishing the diagnoses in some cases which were at a later date given other diagnoses like Behcet's, seronegative RA and autoimmune hepatitis. In addition, diagnosis of case 5 remains a puzzle as his investigations were not suggestive of HLH, all blood cultures were negative, ANA was negative, and lupus anticoagulant was negative. Unfortunately, post-mortem examination is not practiced in our region based on religious doctrine. At our institute, we started sending some samples for immunofluorescence assay (IFA) abroad few years ago, after getting initial positive qualitative ELISA results, depending on physician requests. PCR is also currently available at a local reference laboratory, which has improved our diagnostic capabilities.

Our small study clearly illustrates that Q fever should be considered in a wide range of clinical presentations but that is can be also be over tested with unnecessary costs. Adopting diagnostic algorithms for Q fever infection (both clinical and laboratory based), might further improve Q-fever infection diagnostic challenge.

The unavailability of the appropriate laboratory tests at all times when needed was a major limitation in this small cohort. Other limitations included the lack of continuity of care of the patients due to their transfer to other hospitals or default.

Conclusion

Q fever should be considered as a potential differential in many clinical presentations. Most appropriate laboratory tests for diagnosis should be discussed with the medical microbiologists and the results should be interpreted along with the patients' clinical context

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