Original Article

Pulmonary manifestations of Q fever: analysis of 38 patients

Diana J. Kelm[1], Darin B. White[2], Hind J. Fadel[3], Jay H. Ryu[1], Fabien Maldonado[4], Misbah Baqir[1]

[1]Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, [2]Department of Radiology, [3]Department of Internal Medicine, Division of Infectious Diseases, Mayo Clinic Rochester, Minnesota, USA; [4]Department of Internal Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University, Nashville, Tennessee, USA

Contributions: (I) Conception and design: DJ Kelm, F Maldonado, M Baqir; (II) Administrative support: None; (III) Provision of study materials or patients: DJ Kelm, DB White; (IV) Collection and assembly of data: DJ Kelm, DB White; (V) Data analysis and interpretation: DJ Kelm, DB White, JH Ryu, M Baqir; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Diana J. Kelm, MD. Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Clinic Rochester, 200 First Street SW, Rochester, MN 55905, USA. Email: Kelm.Diana@mayo.edu.

Background: Lung involvement in both acute and chronic Q fever is not well described with only a few reported cases of pseudotumor or pulmonary fibrosis in chronic Q fever. The aim of this study was to better understand the pulmonary manifestations of Q fever.

Methods: We conducted a retrospective cohort study of patients with diagnosis of Q fever at Mayo Clinic Rochester. A total of 69 patients were initially identified between 2001 and 2014. Thirty-eight patients were included in this study as 3 were pediatric patients, 20 did not meet serologic criteria for Q fever, and 8 did not have imaging available at time of initial diagnosis. Descriptive analysis was conducted using JMP software.

Results: The median age was 57 years [interquartile range (IQR) 43, 62], 84% from the Midwest, and 13% worked in an occupation involving animals. The most common presentation was fevers (61%). Respiratory symptoms, such as cough, were noted in only 4 patients (11%). Twelve patients (29%) had abnormal imaging studies attributed to Q fever. Three patients (25%) with acute Q fever had findings of consolidation, lymphadenopathy, pleural effusions, and nonspecific pulmonary nodules. Radiographic findings of chronic Q fever were seen in 9 patients (75%) and included consolidation, ground-glass opacities, pleural effusions, lymphadenopathy, pulmonary edema, and lung pseudotumor.

Conclusions: Our results demonstrate that pulmonary manifestations are uncommon in Q fever but include cough and consolidation for acute Q fever and radiographic findings of pulmonary edema with pleural effusions, consolidation, and pseudotumor in those with chronic Q fever.

Keywords: Acute Q fever; chronic Q fever; pulmonary manifestations; thoracic radiology

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Introduction

Q fever is caused by *Coxiella burnetii*, which can result in both acute and chronic manifestations. Lung involvement is rare, but is more often seen in acute Q fever (1-3). Symptoms can last from 10–90 days (4) and are more common in adults and in men (5). A study from Spain found that 65% of those with acute Q fever had respiratory symptoms (2). Pneumonia in these cases often present as non-productive cough, and fever (4). These patients have extrapulmonary manifestations as well including severe headache, myalgias, and arthralgias. Some patients can even present in acute respiratory distress. One study found nonspecific radiographic findings with similar appearance to those associated with pneumonia caused by viruses, *mycoplasma pneumoniae*, *or chlamydia pneumoniae*, or presenting as multiple rounded opacities (4). There have been a few reported cases of pseudotumor of the lung (6-8) and pulmonary fibrosis in chronic Q fever (9). Various studies

have looked specifically at the radiographic findings with differing results, but these studies were done over 15 years ago (2,10,11).

Because of the nonspecific symptoms and various clinical presentations, there is often a delay in the diagnosis of Q fever, which may result in increased patient morbidity and mortality. The pulmonary manifestations of Q fever, specifically respiratory symptomology and thoracic radiographic findings, remain unclear especially in more recent years. The aim of this retrospective study is to provide a more updated review of the pulmonary presentation of Q fever, both acute and chronic.

Methods

We conducted a retrospective cohort study of patients with a diagnosis of Q fever between July 1, 2001 and December 31, 2014 at Mayo Clinic Rochester. This study was approved by the Mayo Institutional Review Board (#14-008728).

Diagnosis

We used a computer-assisted database search of clinical notes for a diagnosis of Q fever using the following terms 'Q fever' or '*Coxiella burnetii*'. A total of 69 patients were identified during this time period. Inclusion criteria included age ≥18 years, thoracic imaging around the time of diagnosis, and a confirmed diagnosis of either acute or chronic Q fever as based on the following: clinical diagnosis as per history and documentation AND *C. burnetii* phase I or II antigen titer >1:16 IgG (in serum), or positive *C. burnetii* polymerase chain reaction (in serum or tissue), or positive culture. Acute Q fever was suggested by a high IgG phase II titer and chronic Q fever by a high IgG phase I titer.

Data collection

Chart review was completed assessing demographics, co-morbidities, exposure history, risk factors for Q fever, symptoms and radiographic findings at time of diagnosis. A board certified chest radiologist (DW) reviewed all imaging of the chest including chest radiographs, computerized tomography (CT) chest, and positron emission tomography (PET) scan at time of diagnosis of Q fever. Based on clinical history, study investigators (DJ Kelm, DB White, M Baqir) determined if imaging could be correlated to Q fever. In cases that were not clear, a consensus was reached amongst the study investigators.

Statistical analysis

Descriptive analysis was conducted using JMP (version 10.0) software. Median and interquartile range (IQR) for continuous variables and frequency and percentage for categorical variables were used to summarize the data. To compare differences between acute versus chronic Q fever, a chi-square test was performed. P valued ≤0.05 were considered statistically significant.

Results

A total of 69 patients were initially identified between 2001 and 2014. Thirty-one patients were excluded: 3 pediatric patients, 20 patients did not meet serologic criteria for Q fever and 8 patients did not have imaging available from the time of initial diagnosis. We analyzed the remaining 38 patients.

Demographics

Table 1 describes the baseline characteristics of this study cohort. The median age was 57 years (IQR 43, 62) with 82% males. Thirty-two patients (84%) were from the Midwest. Nineteen cases (50%) had a diagnosis of acute Q fever. Four (21%) of those progressed to chronic Q fever.

History and clinical presentation

In this cohort, 4 (11%) were immunocompromised and 10 (28%) had a prosthetic heart valve. Those with a prosthetic heart valve were more likely to develop chronic Q fever (P=0.005). Most had nonspecific symptoms such as fevers (61%), chills (18%), and night sweats (21%). Acute respiratory symptoms were noted in 4 patients (11%), which consisted predominantly of cough, one of which also had hemoptysis. Respiratory symptoms were more commonly seen in acute Q fever (P=0.004). One patient with chronic Q fever presented with a lower extremity rash that was biopsied which was consistent with leukocytoclastic vasculitis.

Five patients (13%) had an occupation in which they had significant animal exposure, such as veterinary medicine, livestock farming and zoo keeper. Four (11%) were in close proximity or were involved with animal birthing. Another 5 patients (13%) had significant animal exposure to sheep, cattle, and/or goats. Sixteen patients (42%) lived on a farm, lived near a farm or farming facility, or had recently been on

Table 1 Baseline characteristics of the study cohort

Baseline characteristics	Combined	Acute Q fever, n=19	Chronic Q fever, n=19
Demographics			
Age, median (IQR)	57 [43–62]	58 [45–66]	53 [41–60]
Male, n (%)	31 [82]	16 [84]	15 [79]
Caucasian, n (%)	33 [87]	16 [84]	17 [89]
Patient residence, n (%)			
Midwest	32 [84]	16 [84]	16 [84]
Outside of US	1 [3]	1 [5]	0 [0]
Co-Morbidities, n (%)			
Diabetes mellitus	3 [8]	2 [11]	1 [5]
Congestive heart failure	2 [5]	0 [0]	2 [11]
Lung disease	7 [18]	4 [21]	3 [16]
Risk factors, n (%)			
Occupation*	5 [13]	1 [5]	4 [21]
Animal exposure±	8 [21]	0 [0]	8 [42]
Location§	16 [42]	2 [11]	14 [74]
Immunosuppressed	4 [11]	2 [11]	2 [11]
Prosthetic valve	10 [26]	1 [5]	9 [47]
Clinical history, n (%)			
Respiratory symptoms (cough, dyspnea)	4 [11]	3 [16]	1 [5]
Vascular involvement	14 [37]	3 [16]	11 [58]

*, occupation—veterinary medicine, meat processing, livestock farming and animal research; ±, animal—cattle, sheep, goats; §, location—either live on a farm or live near a farm or farming facility. IOR, interquartile range.

a farm; the majority of these patients had chronic Q fever. In total, 26 patients (68%) had potential exposure to animal reservoir of Q fever.

Radiographic findings

In this cohort, chest radiographs were obtained around the time of diagnosis in 30 patients (79%), 16 acute and 14 chronic Q fever. A CT chest was obtained in 22 patients (58%)—9 in acute and 13 in chronic. There were 9 total PET scans obtained (24%), 4 in acute and 3 in chronic.

The main radiographic findings seen on chest radiographs or CT chest were consolidation (unilateral < bilateral), ground-glass opacities (unilateral > bilateral), pleural effusions (unilateral < bilateral), lymphadenopathy (hilar < mediastinal), pulmonary edema, and nonspecific pulmonary nodules. All those with consolidation were non-segmental.

Of these, 12 patients (32%) had imaging that was thought to be attributable to Q fever—3 (25%) with acute Q fever and 9 (75%) with chronic Q fever (*Table 2*). The right upper lobe mass-like consolidation (*Figure 1*), seen in a patient with chronic Q fever, was biopsied via CT-guidance with the pathology significant for lymphoplasmacytic infiltration in the background of fibrosis. No patients in this study were found to have findings of pulmonary fibrosis attributable to Q fever.

The findings noted on PET scan in those with chronic Q fever included fluorodeoxyglucose (FDG) avidity along a vascular graft and increased FDG accumulation in the soft tissue thickening along the ascending aorta, contiguous medial right upper lobe consolidation, and manubrial

erosion (*Figure 1*). For acute Q fever, there was one patient with FDG avid thoracic and abdominal lymphadenopathy that was biopsy negative for malignancy and consistent with a granulomatous process (without findings of a fibrin ring or "doughnut" granuloma seen in Q fever) with hepatic and bone lesions presumed to be secondary to melanoma metastases.

Table 2 Radiographic imaging compatible with Q fever

Radiographic Imaging	Acute Q fever (n=3)	Chronic Q fever (n=9)
Consolidation, n (%)		
Unilateral	0	2 [22]
Bilateral	1 [33]	3 [33]
Ground glass opacity, n (%)		
Unilateral	1 [33]	2 [22]
Bilateral	0	2 [22]
Lymphadenopathy, n (%)		
Hilar/Mediastinal	2 [67]	5 [56]
Pleural effusion, n (%)		
Unilateral	1 [33]	1 [11]
Bilateral	1 [33]	5 [56]
Bronchial wall thickening, n (%)	2 [67]	2 [22]
Pulmonary edema, n (%)	0	5 [56]
Pulmonary nodules, n (%)	3 [100]	3 [33]
Lung mass, n (%)	0	1 [11]
Vascular complications, n (%)	0	3 [33]

Treatment and outcomes

The management of Q fever depended on whether it was acute or chronic, but often included either doxycycline alone or a combination of doxycycline and hydroxychloroquine. In those with chronic Q fever, surgical intervention was required in 8 cases (21%); the type of intervention depended on the specific involvement of Q fever: 2 aortic root replacements/repair; 2 aortic valve replacements; 3 spinal debridements. Those with imaging findings consistent with chronic Q fever were more likely to have underwent surgical intervention (P=0.0006).

In this cohort, there were 3 deaths (8%); one of which was attributed to chronic Q fever with endocarditis, mycotic aneurysm and vertebral infection. The cause of death in the other 2 cases is unknown, but both had chronic Q fever (one with aortitis and graft infection and the other with endocarditis).

Discussion

Our study found that pulmonary manifestations were uncommon in Q fever but included cough in acute Q fever and imaging findings of vascular complications, pulmonary edema with pleural effusions, and consolidation were more likely to be seen in chronic Q fever.

The demographics noted in our study cohort are similar to prior studies. Specifically, we had a male predominance as seen in France with a male/female ratio of 2.45 for acute Q fever (12). Men are more likely to be engaged in occupations associated with risk for development of Q fever. Additionally,

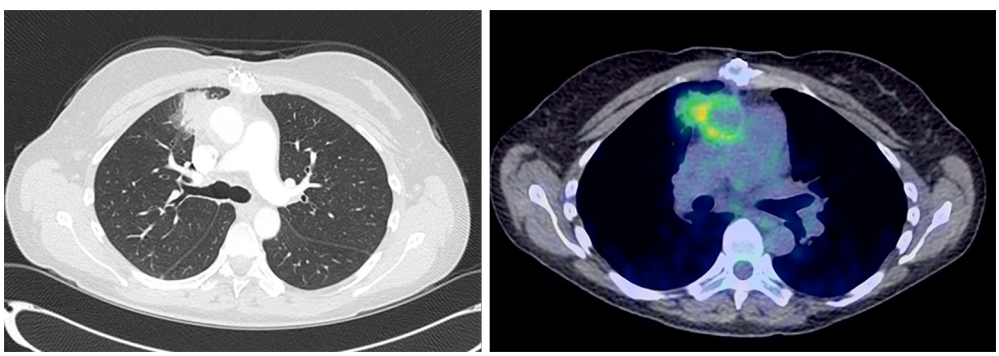

Figure 1 Chronic Q fever lung pseudotumor. One patient with chronic Q fever was noted to have a right upper lobe mass-like consolidation, which exhibited lymphoplasmacytic infiltration in the background of fibrosis on CT-guided needle biopsy. Subsequent, PET scan showed increased FDG accumulation in the soft tissue thickening along the ascending aorta and contiguous medial right upper lobe consolidation and manubrial erosion.

as based on mouse models, the gender difference could be related to hormones in which estradiol may play a protective role (13). Exposure has been linked to parturient cats and rabbits, sheep and cattle, and ingestion of contaminated milk products (14,15). It is more likely that inhalation of infected aerosolized particles results in transmission due to its hypothesized sporulation process (16). In our cohort, 10 patients were directly in contact with animals either by their job or for other reasons. Many either lived on a farm or lived close to a farm. Even without known direct contact, transmission is thought to occur through the wind as a prior study has found only 25% of those that developed Q fever to have direct animal exposure (17), which is similar to our study cohort as 32% did not have any known exposure history to suggest Q fever.

Acute and chronic Q fever has various clinical presentations. Acute Q fever is often asymptomatic (18); if there are symptoms, it is often a self-limited febrile illness with headaches. Lung involvement is often nonspecific and similar in appearance to those associated with atypical pneumonia (2,18-20). The most common clinical presentation in our study was fever with only a few cases of cough. Chronic Q fever is defined as duration of infection for more than 6 months; it occurs in approximately 1–5% of those infected with *C. burnetii* (4). Pregnant females, immunocompromised hosts, and those with underlying valvular or vascular disease are at an increased risk for development of chronic Q fever. Our study also found that prosthetic valve resulted in a statistically significant risk for development of chronic versus acute Q fever. Presentation at this stage most commonly includes endocarditis, infection of aneurysms or vascular grafts and osteomyelitis (4). In our cohort, vascular complications included aortic pseudoaneurysm, graft infection, endocarditis, osteomyelitis, encephalitis, and prosthetic knee infection. Lung involvement in chronic Q fever is rare. In our study, there was one case of pulmonary pseudotumor contiguous with abnormal periaortic soft tissue in the setting of infected pseudoaneurysm. Prior case reports noted pseudotumor of the lung in acute Q fever (6,7,9) and more recently this has been described in chronic Q fever (8). Additionally, chronic pulmonary fibrosis has also been reported (9,21) though not seen in our study.

Prior studies evaluating the radiographic findings of Q fever found 75% had lung consolidation (lower lobe predominance) (2) and that the most common abnormalities were unilateral, single-segmental opacities, often in the upper lobes (10). Lobar opacities were less common. The findings of acute Q fever pneumonia on CT chest has been found to be multi-lobar airspace consolidation with a nodular pattern with surrounding halo of ground-glass opacification and necrotizing pneumonia less common (11). Pleural effusions and mild lymph node enlargement were also noted (11). In our study, findings of acute Q fever included consolidation, ground-glass opacity, pleural effusions, nonspecific pulmonary nodules, and reactive lymphadenopathy. Those with chronic Q fever were more likely to have imaging findings related to edema, pleural effusions, or cardiovascular complications. The imaging findings of Q fever are nonspecific; however chest radiography and CT may demonstrate important findings in symptomatic patients especially with respiratory symptomatology. Chest CT or CT angiography is particularly helpful in patients with suspected cardiovascular complications in the setting of chronic Q fever. The role of PET scan remains unclear but may have utility in those patients with chronic Q fever and a known cardiac valve or vascular surgical history.

The limitations of this study relate to the small sample size and inherent flaws of a retrospective study including selection bias. The strengths include the long time frame reviewed and the inclusion of various thoracic radiology modalities. The results of this study provides the pulmonologist a better understanding of the underlying respiratory symptoms and radiographic findings to be considered in the diagnosis of both acute and chronic Q fever and especially in those cases in which the diagnosis remains unclear. To better understand these uncommon pulmonary findings of Q fever would require future research involving multiple institutions across the world due to the various geographic locations of this zoonotic infection and include a long time frame of review due to its rarity.

In conclusion, pulmonary symptomatology and chest imaging findings such as consolidation, lymphadenopathy, or lung mass seen with Q fever is uncommon, but can occur in chronic Q fever and should be considered in the appropriate clinical context.

Acknowledgements

None.

Footnote

Conflicts of Interest: This work was presented as a poster at CHEST 2015 in Montreal on October 28th, 2015.

Ethical Statement: This study was approved by the Mayo Institutional Review Board (#14-008728).

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