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# Chronic Q fever associated with systemic sclerosis

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## Abstract

**Background:** After the Q fever outbreak in the Netherlands between 2007 and 2010, more than 300 patients with chronic Q fever have been identified. Some patients were also diagnosed with systemic sclerosis, a rare immune-mediated disease. We aimed to increase awareness of concomitant chronic Q fever infection and systemic sclerosis and to give insight into the course of systemic sclerosis during persistent Q fever infection.

**Materials and methods:** Chronic Q fever patients were identified after the Dutch Q fever outbreak in 2007–2010. Systemic sclerosis was diagnosed by a scleroderma expert and patients fulfilled the 2013 Classification Criteria for Systemic Sclerosis.

**Results:** Four cases presented with chronic Q fever, persistent *Coxiella burnetii* infection, shortly preceded or followed by the diagnosis of limited cutaneous systemic sclerosis. The three male patients of 60 years or older developed a relatively mild systemic sclerosis, which did not require immunosuppressive therapy during adequate treatment of the chronic Q fever infection. The 58-year-old female patient used immunosuppressives for her newly diagnosed systemic sclerosis at the time she likely developed a chronic Q fever infection.

**Conclusions:** In this case series, chronic Q fever preceding systemic sclerosis was associated with a mild course of systemic sclerosis without the necessity of immunosuppressive drugs, while chronic Q fever development due to immunocompromised state was associated with a more deteriorating course of systemic sclerosis.

## KEYWORDS

chronic Q fever, *Coxiella burnetii*, persistent focalized Q fever infection, systemic sclerosis

## 1 | INTRODUCTION

Chronic Q fever is a persistent infection with the intracellular bacterium *Coxiella burnetii*, which affects individuals with pre-existing heart valve abnormalities, aneurysms, aortic prostheses, a compromised immune system or pregnancy.<sup>1</sup> After the major Q fever outbreak in the Netherlands (2007–2011), chronic Q fever patients presented with diverse

clinical symptoms and complications. The infection is severe, life-threatening and can be associated with immunological phenomena and autoimmune diseases.<sup>2,3</sup>

Systemic sclerosis (SSc) is a complex immune disorder with an unknown pathogenesis. It has three distinctive hallmarks: inflammation, vasculopathy and extensive fibrosis. Clinically, these hallmarks are expressed as progressive fibrosis of skin and internal organs, digital ulcers, pulmonary

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arterial hypertension, interstitial lung disease and renal disease. Infectious agents have long been implicated in the pathology of SSc, and different views exist on how they contribute to the development of SSc.<sup>4</sup> One of those is the discovery of the interferon signature in patients with SSc, which implies that innate immunity is imperative in the disease process.<sup>5</sup> While chronic viral infections have been postulated to be involved in the development of SSc, this link is not firmly established for bacterial infections.<sup>6</sup> Until now, SSc has not been associated with Q fever.

We report four cases of chronic Q fever coinciding with SSc, although presentation and diagnostic course varied greatly. By reporting these four cases, we aim to raise awareness for the concomitant occurrence of chronic Q fever and systemic sclerosis.

## 2 | METHODS

Patients were identified after the Dutch Q fever outbreak in 2007-2010. Chronic Q fever was diagnosed in patients with a positive PCR for *C burnetii* in blood or tissue, or IgG phase I titres measured by immunofluorescence assay (IFA) of  $\geq 1:1024$  and a definite endocarditis according to the modified Duke criteria or proven large vessel or prosthesis

infection. Patients with IgG phase I titres of  $\geq 1:1024$  and immunosuppressive drug use were classified as "probable".<sup>7</sup> SSc was diagnosed by a scleroderma expert and patients fulfilled the 2013 Classification Criteria for Systemic Sclerosis. All patients or their legal representatives provided written informed consent for publication. Patients characteristics are described in Table 1.

## 3 | RESULTS

### 3.1 | Patient 1

This 62-year-old man was diagnosed with chronic Q fever in November 2009 after several months of malaise with bouts of fever. He had recently been diagnosed with an aortic aneurysm, which was treated with an endovascular aneurysm repair (EVAR). His anti-*C burnetii* phase I IgG antibodies were 1:4096, indicative of a chronic Q fever infection. Pus removed around the EVAR during another operative procedure was PCR-positive for *C burnetii*. He was started on doxycycline 200 mg and hydroxychloroquine 600 mg. In the same month, the patient was referred to a dermatologist because of red purpuric lesions on his toes. A skin biopsy unveiled superficial and deep perivascular chronic dermatitis with signs of a vasculopathy, a lymphocytic infiltrate and a thickened vascular

**TABLE 1** Patient characteristics

	Patient 1	Patient 2	Patient 3	Patient 4
Gender	Man	Man	Man	Woman
Age	62 years	68 years	63 years	58 years
Deceased	Yes	No	No	Yes
Q fever-related characteristics				
Q fever status	Proven	Proven	Proven	Probable
Diagnosis	11 2009	09 2016	11 2016	09 2009 (already positive serology in 2007)
IgG phase I at diagnosis	1:4096	1:8192	1:1024	1:8192
Focus of infection	Vascular	Vascular	Vascular	Unknown
Prosthesis	EVAR	None	EVAR	None
Complications	–	EVAR for aneurysm expansion	Abscesses	–
PCR	Tissue positive	Blood negative	Blood negative	Blood negative
Treatment duration	24 months	Ongoing > 24 months	Ongoing > 23 months	26 months
Scleroderma-related characteristics				
Diagnosis	09 2010	01 2012	04 2017	03 2007
Symptoms at first visit	Raynaud's phenomenon, red purpuric lesions, facial telangiectasia, nailfold lesions	Raynaud's phenomenon, nailfold lesions	Raynaud's phenomenon, puffy fingers, nailfold lesions	Raynaud's phenomenon, sclerodactyly, interstitial lung disease
mRSS at first visit	9	0	0	2
Autoantibodies	ANA, ACA	ANA, ACA, pANCA	ANA, anti-Scl-70	ANA, ENA, anti-SSA

wall. A rheumatologist diagnosed him with limited cutaneous systemic sclerosis (LcSSc), which was based on positive antinuclear antibodies (ANA), positive anticentromere antibodies (ACA), skin sclerosis, Raynaud's phenomenon, facial telangiectasia and nailfold capillaroscopic changes consistent with an active scleroderma pattern. The modified Rodnan skin score (mRSS), which is used to monitor the extensiveness of skin involvement, was nine at his first visit. There were no signs of organ involvement. Therapy was not started due to the relatively mild complaints. During follow-up visits, the patient presented with digital ulcers and sclerodactyly. In November 2011, anti-*C burnetii* phase I antibody titres had sufficiently decreased to 1:128 and the treatment for chronic Q fever was stopped. The LcSSc remained uneventful.

### 3.2 | Patient 2

This 68-year-old man was referred to the outpatient clinic of the Rheumatology department on suspicion of systemic sclerosis by his general physician in January 2012. His medical history revealed arterial and venous insufficiency with venous thrombosis and pulmonary emboli in 2011. Since 4 years, he experienced Raynaud's phenomenon and recently started to feel the skin of his fingers thicken. The mRSS was 0 at that time. Nailfold capillaroscopy, however, demonstrated an early scleroderma pattern with dilated loops, irregular structure and micro-haemorrhages. His laboratory parameters revealed positive ANA and anticentromere antibodies. He was diagnosed with early LcSSc, and nifedipine 2 dd 40mg was prescribed for his Raynaud's phenomenon. Gradually, sclerodactyly developed and his mRSS increased to 2 in 2014. There were no signs of pitting scars, digital ulcers or internal organ involvement. Meanwhile in 2013, an aortic aneurysm was discovered and follow-up visits were performed yearly. An FDG PET/CT scan performed in September 2016 showed an aneurysm with surrounding infected soft tissue. Upon this finding, anti-*C burnetii* phase I IgG antibodies were determined and a highly increased titre of 1:8192 was detected, and PCR for *C burnetii* on blood was negative. Chronic Q fever was diagnosed, and he was started with doxycycline and hydroxychloroquine therapy. In July 2017, his mRSS was 3, based on skin thickening of the fingers and lower arm. Due to a sudden expansion of his aneurysm, an EVAR was performed. He is currently still being treated and monitored for his chronic Q fever infection and LcSSc, respectively.

### 3.3 | Patient 3

In 2016, a 63-year-old man received an EVAR for his recently identified aneurysm of the abdominal aorta and distal common iliac artery. Although he had an unremarkable medical history before surgery, he experienced night sweats and lost 15% of his initial weight after surgery. Anti-*C burnetii* phase I IgG titre was found to be 1:1024,

and an infected EVAR with abscesses was visualized on an FDG PET/CT scan. PCR on blood and drained pus from a perianal abscess remained negative for *C burnetii*. He was started on doxycycline and hydroxychloroquine. Because the abscesses around the iliac artery were closely related to the rectosigmoid junction and cultured different intestinal bacteria, a fistula was suspected. In a routine screening, autoantibodies were determined and revealed positive ANA and anti-topoisomerase I antibodies (anti-Scl-70). The patient appeared to have a new onset of Raynaud's phenomenon and mild puffy fingers. Nailfold capillaroscopy showed aspecific changes consisting of a normal capillary density, micro-haemorrhages and broadening of the apexes. Giant capillaries were not present. Based on these clinical data, the patient was diagnosed with early SSc and is currently being monitored in the outpatient clinic.

### 3.4 | Patient 4

This 58-year-old woman presented with increasing complaints of discoloured fingers and toes at the outpatient clinic of the Rheumatology department in 2007. Upon physical investigation, radial folds around the mouth were discovered. She evidently suffered from swollen fingers with sclerodactyly and thickened cuticles accounting for a mRSS of 2. Laboratory investigation showed a sedimentation rate of 24 mm/h and the presence of ANA. She was diagnosed with LcSSc based on sclerodactyly, Raynaud's phenomenon, ANA positivity, an early scleroderma pattern on nailfold capillaroscopy and interstitial lung diseases. She was shortly prescribed methotrexate (20mg weekly), but this was stopped due to disease progression under therapy. Prednisone 10mg daily was started, although this also failed to result in remission of the disease. In 2008, her mouth orifice was further limited, and she presented with a polyarthritis of both knees, metacarpal phalanx (MCP) I, and PIP III and IV. Methotrexate 20mg weekly was again started in September 2008 without any improvement. Therefore, 120mg intramuscular methylprednisolone injections every 6 weeks were initiated.

Meanwhile, in 2008, she was admitted with a presumed acute Q fever infection based on positive anti-*C burnetii* IgG, for which she was prescribed doxycycline 100mg twice daily for 2 weeks. In January 2009, IgG phase I titres were again tested and turned out to be 1:8192. Retrospectively, IgG phase I titres from serum in 2007 were already 1:4096. She was diagnosed with probable chronic Q fever,<sup>7</sup> based on high serology titres and the immune suppressants she had used around 2007. A focus for the infection could not be identified.

With regard to the LcSSc, her condition gradually deteriorated, borderline pulmonary hypertension was diagnosed, and methotrexate was prescribed in addition to prednisone, despite the chronic infection. The serologic titres slowly declined fourfold with doxycycline and hydroxychloroquine,

which were stopped after 2 years of treatment in 2011, when anti-*C burnetii* IgG phase I was 1:2048.

## 4 | DISCUSSION

The present study describes four chronic Q fever patients with concomitant LcSSc, differing in presentation and diagnostic process. In all four cases, the Q fever infection coincided with the beginning or worsening of SSc symptoms, although the disease entities were not diagnosed simultaneously. The Q fever outbreak in the Netherlands,<sup>8</sup> which started in 2007 and ended in 2010, offered a well-defined time frame in which Q fever was most likely contracted, as before and after the outbreak, incidence levels were neglectably low. Most patients, however, already had Raynaud's phenomenon for a longer period of time, indicating that they likely had an increased susceptibility for SSc, the onset of which was possibly triggered by the chronic Q fever infection. The three male patients developed a relatively mild disease, which did not require immunosuppressive therapy. Furthermore, with adequate treatment of the chronic Q fever infection, the SSc remained present.

The prevalence of systemic sclerosis in the Netherlands is 8.9 per 100 000 adults.<sup>9</sup> After the Q fever outbreak in the Netherlands, the prevalence of systemic sclerosis among proven and probable chronic Q fever patients is 4 in 322 individuals (*unpublished data from Q fever database*). Extrapolating these numbers (1242:100 000), this indicates a possible association between chronic Q fever and systemic sclerosis. Although this is a highly selected group of individuals, bias based on population characteristics is unlikely. Supportive of this notion is that systemic sclerosis is usually more prevalent among women, while chronic Q fever is not, and systemic sclerosis is generally diagnosed earlier (median of 50 years),<sup>9</sup> compared to chronic Q fever (median of 71 years).<sup>10</sup> Silica exposure is a known environmental risk factor for the development of systemic sclerosis, and studies indicate that the percentage of previous environmental risk factor exposure is especially high in men with systemic sclerosis.<sup>11</sup>

It is documented that chronic Q fever infection can trigger autoimmune diseases and other immunological syndromes.<sup>2,3</sup> In favour of this is the typically older age of onset and the male gender of the cases, both features that are more commonly seen in chronic Q fever than SSc.<sup>1</sup> Furthermore, an increasing body of evidence suggests that infectious agents can trigger SSc, for example, antibodies to cytomegalovirus, parvovirus B19, hepatitis B, Toxoplasma and *Helicobacter pylori* are more common in SSc patients than in matched control groups.<sup>12-15</sup> The mechanisms for this have yet to be elucidated, but among others, molecular mimicry seems conceivable, as retroviral proteins show similarity to

topoisomerase antigen.<sup>16</sup> Molecular mimicry has not yet been examined for *C burnetii*. Generally, loss of self-tolerance underlies autoimmune diseases and may be provoked by excessive inflammation. The possible mechanism for autoantibody production remains elusive in many infectious diseases that predispose to autoimmune syndromes. With regard to Q fever, intriguingly, *C burnetii* infection and SSc both share the activation of the interferon type I pathway in dendritic cells.<sup>17,18</sup> Not excluding other theories, *C burnetii* might also facilitate the progression of early systemic sclerosis, possibly through the induction of CXCL10 and CXCL11. These chemokines are abundantly produced by immune cells of chronic Q fever patients<sup>19</sup> and are biomarkers for disease progression of early SSc.<sup>20,21</sup> Interesting in this notion is that CXCL10, induced by TNF $\alpha$ , interferons and fibroblasts, is anti-angiogenic and promotes vascular smooth muscle cell proliferation.<sup>22</sup>

This study shows that chronic Q fever can coincide with systemic sclerosis, but a causal interaction cannot be deduced from this case series. Larger prospective studies among chronic Q fever patients would be needed to prove any causal relationship, but these are highly unlikely due to the rarity of this disease.

Evidently differing from the other cases, case 4 suffered from LcSSc with interstitial lung disease that required immunosuppressive therapy. Here, effective treatment of the infection did not noticeably improve the course of the SSc. Whether Q fever or SSc precedes the other is unclear, but both scenarios seem plausible. It is known that rheumatoid arthritis patients have an increased risk for the development of chronic Q fever, while anti-tumour necrosis factor (TNF) therapy was found not to be an independent risk factor.<sup>23</sup>

This case series describes the coincidence of chronic Q fever and systemic sclerosis, but the role of chronic Q fever infection in the pathogenesis or disease progression of systemic sclerosis remains to be elucidated. The three male patients diagnosed after 60 years of age showed mild SSc in the absence of immunosuppressive therapy, while the female patient presented with a more aggressive course of SSc, possibly due to a non-Q fever-related aetiology. By describing these four cases, we would like to raise awareness for concomitant chronic Q fever and systemic sclerosis and their clinical course.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## AUTHOR CONTRIBUTIONS

AJ and RR performed the study; AJ wrote the paper; CB, MV and MD contributed to the conception of the work and interpreted the findings; CB and MV included the patients; and RR, CB, MV and MD critically revised the manuscript.

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