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Review Article

Autoimmunity and B-cell dyscrasia in acute and chronic Q fever: A review of the literature

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ABSTRACT

Q fever infection can lead to chronic Q fever, a potentially lethal disease occurring in 1–5% of patients infected with *Coxiella burnetii*, characterized by the persistence of this intracellular bacterium. It usually presents as endocarditis, infected vascular aneurysms, or infected vascular prostheses. This systematic review of the literature discusses the various autoimmune syndromes and B-cell dyscrasias in acute and chronic Q fever patients, that may interfere with or impede recognition and diagnosis of Q fever. Reportedly, high concentrations of anti-cardiolipin antibodies may be found in acute Q fever patients, while specifically cardiac muscle antibodies have been reported during chronic Q fever. Systemic lupus erythematosus and antiphospholipid syndrome are the most frequently reported autoimmune syndromes, followed by neuromuscular disorders and vasculitis. B-cell dyscrasia, mostly cryoglobulinaemia, is predominantly described in chronic Q fever patients with endocarditis. We conclude that immunological (*epi*)phenomena are not rare during Q fever and may obscure the infectious etiology of the disease.

1. Introduction

Q fever is a zoonosis caused by the intracellular bacterium *Coxiella burnetii* [1]. Upon inhalation of the bacterium, approximately 40% of patients develop symptomatic disease, referred to as acute Q fever, while 60% remain asymptomatic. Acute Q fever usually presents as a flu-like illness with fever, headache, and occasionally pneumonia or hepatitis [1]. Of those who get infected with *C. burnetii*, including those who undergo an asymptomatic infection, around 1–5% will develop chronic Q fever, a disease with high mortality that is characterized by the persistence of *C. burnetii*. Chronic Q fever usually manifests as endocarditis or infection of pre-existing aneurysms or vascular prostheses [2].

Recently, we were confronted with a patient with a chronic Q fever infection who simultaneously presented with various autoimmune syndromes, a Monoclonal Gammopathy of Unknown significance (MGUS) and cryoglobulinaemia. During follow-up, anti-*C. burnetii* IgG phase I antibodies declined dramatically even though the patients' clinical condition worsened. Further research however showed high anti-*C. burnetii* IgG phase I antibodies in the cryoprecipitate. This surprising finding, that could have erroneously led to the assumption that the infection was treated successfully, and the observation that various chronic Q fever patients in our hospital had one or more positive immunological laboratory tests, motivated us to perform a literature study. We aim to inform clinicians of the clinical relevance of these concomitant immunological phenomena through a review of literature on such epiphenomena in relation to both chronic and acute Q fever.

Abbreviations: aCL, anti-cardiolipin antibodies; ASMA, anti-smooth muscle antibodie; CMA, cardiac muscle antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; ANA, anti-nuclear antibodies; anti-GBM, anti-glomerular basement membrane antibodies; GPLU, IgG Phospholipid Units; PCA, parietal cell antibodies; MGUS, monoclonal gammopathy of unknown significance

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2. Methods

2.1. Search strategy and study selection

Articles were identified through a systematic search in the scientific database Medline on the subjects autoimmunity and Q fever. Studies dating back to 1960 were traced up to October 2016. The following terms were used: “Q fever” and (“autoimmun*” or “autoantibodies” or “cryoglobulinaemia” or “vasculitis” or “SLE” or MESH [Monoclonal Gammopathy of Unknown Significance] or “gammaopathy”). The reference lists of the included studies were checked for studies that were not found with the search strategy. Studies in English and French were included in the search. Only human studies were considered for inclusion. Records were screened for full text availability and assessed for eligibility. Only full-text articles were included. Eligibility criteria included the presence of an acute of chronic Q fever infection and the presence of autoimmune phenomena. Reports that did not or only remotely addressed Q fever issues, such as Q fever vaccine effects, were excluded. Reports describing inflammatory conditions of non-autoimmune etiology were excluded, except for B-cell dyscrasias. Study eligibility was assessed by one author (AFMJ) and in case of uncertainty, a second author (MvD) was consulted. Detailed search strategy is described in Supplementary Table 1.

2.2. Data extraction and items

A data extraction form was designed to collect data from the reports. For the articles in qualitative review, the following items were recorded i.e. research question, detailed methods (number of participants, inclusion and exclusion criteria, Q fever diagnosis criteria, determinants, primary outcome measure, statistical analysis) and results (outcome, follow-up time). For case series and case reports in the case analysis (or quantitative analysis), extracted data for every patient comprised Q fever status, gender, age at diagnosis and symptoms of autoimmune phenomena. Anti-*C. burnetii* titers, PCR positivity and all immunological parameters were extracted from the manuscript. The final diagnosis with regard to autoimmune phenomena was described and the course of the autoimmune phenomena and follow-up time was included. Q fever diagnosis was revised by the authors and the criteria of the Dutch consensus guideline [3] were applied if there was a discrepancy between the definition of acute or chronic Q fever in the report and the Dutch consensus guidelines.

2.3. Quality assessment

Quality of case control and cross-sectional studies was assessed with the Newcastle-Ottawa Scale for assessing non-randomized studies [4]. The quality of case series was assessed with the checklist ‘quality appraisal of case series studies using a modified Delphi technique’ [5]. Case reports were not quality assessed as they generally have a low level of evidence.

2.4. Review

The presence of immunological manifestations in various chronic Q fever patients treated at our hospital prompted us to conduct an analysis of case reports and a review of cross sectional studies of immunological and autoimmune phenomena in acute and chronic Q fever patients. In the qualitative analysis, 1610 acute Q fever patients and 372 chronic Q fever patients (mostly endocarditis) were included in total. In the case analysis, we identified 37 studies reporting on 33 acute Q fever patients and 8 chronic Q fever patients with immunological phenomena (Fig. 1). The quality of the included papers was generally low to moderate according to the NOS scores (see Table 1), due to the fact that most articles did not include a control group.

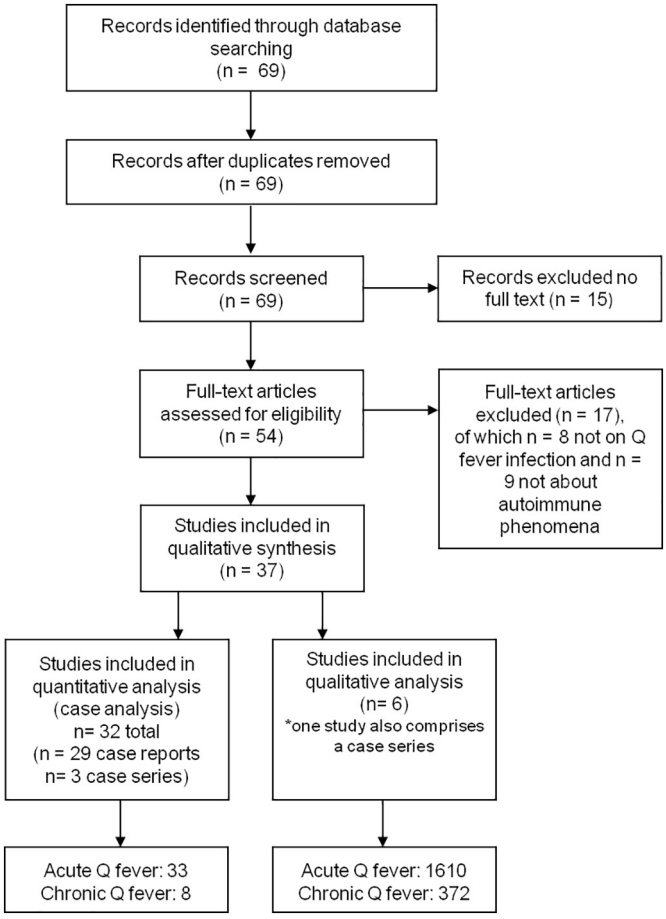

Fig. 1. Search flow diagram, indicating the search flow with 32 reports included in the quantitative analysis (case analysis) and 6 studies that were suitable for the qualitative analysis.

2.4.1. Autoimmunity

Autoimmunity, defined as an immune response of T- and B-cells directed against self-antigens, is recognized as a disease state, i.e. autoimmune syndrome, if the immune response results in tissue injury. To prevent autoimmunity, several mechanisms are adopted either centrally, e.g. in the thymus or bone marrow, or peripherally, where self-reactive lymphocytes await deletion (death) or anergy, an unresponsive state. Failure of these mechanisms gives self-reactive lymphocytes the opportunity to survive and become activated. Certain conditions are necessary to develop autoimmunity. It is assumed that the HLA type and other genetic traits predispose to autoimmunity following an environmental trigger, such as an infection [6]. Various mechanisms of infection-related autoimmunity induction have been proposed, of which molecular mimicry is the most accepted [7, 8]. For example, membrane proteins of *Chlamydia* species show similarity to myosin present in the myocardium and it has been shown that *Chlamydia*-derived peptides can induce autoimmune myocarditis in mice [9]. Another, non-excluding, theory is that of epitope spreading, characterized by the start of a response to a primary specific self-epitope, which, via immune activation and cell damage, leads to diversification of recognition of self-epitopes. This mechanism of autoimmunity was first described using a mouse model of experimental autoimmune encephalitis, which starts with the self-reactive response to one myelin basic protein epitope, but progresses to multiple other myelin basic protein epitopes as the disease advances [10]. A third theory, called bystander activation, is related to this concept and based on excessive local production of inflammatory mediators and the presence of bacterial superantigens, that by the polyclonal activation of T-cells also