



Case report

Doxycycline desensitization in chronic Q fever—A critical tool for the clinician



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ARTICLE INFO

Keywords:

Q fever
Coxiella burnetii
 Doxycycline
 Desensitization
 Moxifloxacin
 Clarithromycin

ABSTRACT

We present the case of a 45 year old woman with acute Q fever pneumonia who progressed to the chronic phase of the disease despite azithromycin therapy. A trial of doxycycline was halted because of severe allergy and she was put on clarithromycin and later moxifloxacin. Failure of both drugs required desensitization to doxycycline with escalating doses. After two-year treatment with doxycycline-hydroxychloroquine combination, complete recovery was declared. Our case highlights the option of doxycycline desensitization when an acute allergic reaction poses an obstacle to optimal treatment.

Introduction

Q fever is a zoonotic infection caused by *Coxiella burnetii*. Q fever may present as an acute illness with fever, pneumonia and hepatitis being the most common manifestations. After the acute illness or an asymptomatic primary infection, patients may develop a chronic focal infection that can be life threatening and require prolonged combination of antimicrobials for cure. While the treatment of acute Q fever is based on doxycycline alone, treatment of chronic Q fever is comprised of a prolonged (at least 18 months) combination of doxycycline and hydroxychloroquine. Alternatives to this regimen have rarely been tested systematically. Furthermore, inability to use doxycycline in Q fever, as in cases of allergy or pregnancy poses a major challenge to the clinician. Herein we present a case of chronic Q fever that required desensitization to doxycycline due to treatment failure with an alternative regimen.

Case presentation

A 45 year old woman presented to her primary care physician in August 2014 because of one week of fever up to 40 °C, nonproductive cough, night sweats, and vomiting. The patient was living in the Krayot area in northern Israel, known to be endemic for Q fever [1]. She was working as a nurse in a geriatric hospital and denied direct contact with farm animals. Her physical examination and chest X-ray were

unremarkable. Her blood count showed no leukocytosis, and platelets were in normal range. The C-reactive protein was slightly elevated and the liver enzymes were normal.

She received empiric treatment for suspected pneumonia with azithromycin for five days. However, after completing this course she continued to suffer from low grade fever, cough, general malaise and night sweats, and she was referred to an infectious diseases specialist for further work up. Serology for Q fever was sent out to the Israeli Center for Rickettsial Diseases and the values were consistent with acute *C. burnetii* infection: Phase I- IgM positive, Phase I- IgG negative, Phase II- IgM positive, Phase II- IgG positive (titer of 1:800) (Table 1). Transthoracic echocardiography showed minimal pericardial effusion and mitral valve prolapse but no regurgitation or valvular vegetations.

Treatment with doxycycline was initiated. The patient did not recall previous exposure to doxycycline. However, the first tablet caused intense itching all over her body and the second tablet caused a sensation of suffocation. She did not seek medical help but stopped taking the drug. Treatment was therefore switched to clarithromycin for 10 days, and in light of persistent cough and malaise, treatment was followed by a course of moxifloxacin for another 15 days. Nevertheless, she continued to be symptomatic with low grade fever, persistent cough, night sweats and weight loss. Due to lack of improvement, the patient was hospitalized in December 2014. Again, physical examination was unremarkable. Chest CT demonstrated soft infiltrates in the RUL. Serology for Q fever at that time showed an increase of phase I- IgG to 1600,

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<https://doi.org/10.1016/j.idcr.2018.01.006>

Received 17 December 2017; Received in revised form 17 January 2018; Accepted 17 January 2018

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Table 1
Chronological order of serology results and antimicrobial treatment.

Date	Serology				Treatment
	Phase I, IgM	Phase I, IgG	Phase II, IgM	Phase II, IgG	
19/8/2014					Azithromycin, 5 days
31/08/2014	positive	negative	Positive	1:800	
29/8/2014					Doxycycline started but discontinued after one day d/t allergic reaction
02/10/2014					Clarithromycin, 10 days
20/10/2014	positive	1:400	Positive	1:3200	
20/11/2014					Moxifloxacin, 15 days
09/12/2014	negative	1:100	Negative	1:6400	
21/12/2014					TMP/SMX and Hydroxychloroquine started
28/12/2014					DESENSITIZATION: continued treatment with Doxycycline, TMP/SMX and Hydroxychloroquine
15/1/2015	borderline	1:1600	Positive	Higher than 1:6400	
15/2/2015	negative	1:400	Negative	1:3200	
16/3/2015	negative	1:400	borderline	1:1600	
23/6/2015	negative	negative	Negative	1:400	
30/9/2015	negative	borderline	Negative	borderline	
January 2017					Finished treatment

phase I- IgM was positive; Phase II IgG was > 6400. A transesophageal echocardiography (TEE) did not show vegetations.

The patient was then referred again to an ID specialist who consulted with the Immunology/Allergy Unit of our hospital. Because of previous treatment failures with alternative regimens, doxycycline desensitization was proposed. In the meantime treatment with TMP/SMX and hydroxychloroquine was commenced. She was hospitalized at our institution for doxycycline desensitization which she underwent without complications. The desensitization was performed according to a previously published protocol based on IV doxycycline administered as slow IV pushes in escalating concentrations until after 4 h the oral dose of 100 mg is given (Table 2) [2]. After successful desensitization, doxycycline was added to the regimen of hydroxychloroquine and TMP/SMX.

With this regimen there was a fast improvement in her condition. She stopped coughing and her temperature went back to normal. Follow-up serology in February 2015 (after 1.5 months of treatment) showed a decline in phase I- IgG from 1600 to 400, phase II IgG declined from > 6400 to 3200, phase I and II IgM became negative. Under prolonged treatment with a combination of TMP/SMX, hydroxychloroquine and doxycycline, phase I IgG decline continued until it was completely undetectable after 6 months of treatment (June 2015). Phase II IgG decreased to 400. The patient felt well except for slight occasional nausea, probably as a side effect of the antimicrobial treatment. The combined treatment was continued until January 2017.

Table 2
Doxycycline desensitization protocol.

Dosage (in mg)	Time (in minutes)
0.001	0
0.002	15
0.005	30
0.01	45
0.02	60
0.05	75
0.1	90
0.2	105
0.5	120
1	135
2	150
5	165
10	180
25	195
55	210
100 oral	240

Discussion

We present a case of a patient with acute Q fever pneumonia who progressed to the chronic phase of the disease. Treatment regimens without doxycycline failed to cure the patient, therefore doxycycline desensitization was performed. In our opinion the patient can clearly be diagnosed as having developed chronic Q fever in light of the persistence of symptoms, the serological tests and the signs of pneumonia on chest CT, which can be regarded as the probable local focus. However, based on current recommendations, adding a PCR blood test, and/or FDG-PET/CT could have enhanced the diagnostic accuracy.

As *Coxiella burnetii* is a strictly intracellular pathogen conventional antimicrobial susceptibility testing is not feasible and assessing the *in-vitro* activity of different drugs is challenging as clinical trials comparing their efficacy for treatment of Q fever are complicated by two aspects: firstly, the self-limited course of acute Q fever in the majority of patients and second because of the need for prolonged therapy and follow up for the chronic localized disease. *In-vitro*, clarithromycin and moxifloxacin that were used as alternatives in our case have been proved to be effective [3,4]. However, only few clinical trials assessed their clinical efficacy: Gikas et al. retrospectively assessed 113 patients with acute Q fever who received treatment before the availability of serology results: time to defervescence was significantly shorter in patients treated with macrolides than in patients who received beta-lactams (with clarithromycin performing best of the given macrolides). Time to defervescence, however, was still longer than in patients treated with doxycycline [5]. Another retrospective study from Croatia included 77 patients with acute Q fever receiving doxycycline, clarithromycin or moxifloxacin. In this study, mean time to defervescence was 2.4 days for those receiving doxycycline, 1.9 days for those receiving clarithromycin, and 2.2 days for those receiving moxifloxacin, suggesting non-inferiority of these two alternative antibiotics [6]. In both studies however there was no long term follow up regarding progression to chronic disease.

The superiority of hydroxychloroquine/doxycycline combination treatment in chronic Q fever is probably due to the fact that hydroxychloroquine renders doxycycline bactericidal to *Coxiella burnetii* by raising the pH in the pseudolysosomal vacuole [7]. No trials have evaluated treatment regimens for persistent localized infection that do not contain doxycycline.

Desensitization should be considered for patients with an immediate type drug reaction for whom there are no available alternative treatments. There are two previous case reports of successful desensitization to doxycycline for the treatment of Q fever and Ehrlichiosis [2,8]. Data from the French Pharmacovigilance Database (FPD) suggest that

hypersensitivity reactions to tetracyclines, especially to doxycycline, are generally rare events [9]. Allergic reaction to doxycycline is a clinical diagnosis as no skin test is available today. Our patient developed pruritus and shortness of breath upon treatment with doxycycline, signs that are typical of immediate type allergic reactions, without other exposures to new drugs. The process of desensitization alters the immune response to the specific drug and results in temporary tolerance, which means that the patient can take an uninterrupted course of the medication safely. Our patient was considered an appropriate candidate for desensitization due to her type of drug reaction and the failure of alternative treatments.

In summary, our case report points out the clinical importance to consider the option of desensitization if acute allergic reactions pose an obstacle to indispensable antimicrobial treatment as it undoubtedly is the case for the treatment of chronic localized Q fever with doxycycline containing regimens.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report.

Disclosure

The authors declare that they have no competing interests.

Acknowledgements

Not applicable.

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