Iron–Doxycycline Interaction Leading to Obvious Treatment Failure in Chronic Q Fever: A Case Report

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Chronic Q fever, caused by *Coxiella burnetii*, is a persistent infection that primarily affects individuals with underlying valvular or vascular abnormalities. The standard treatment regimen consists of prolonged dual therapy with doxycycline and hydroxychloroquine, typically administered for a minimum of 18 months [1]. This combination targets both the intracellular pathogen and the acidic vacuolar environment in which it resides. A key indicator of therapeutic response is the progressive decline in phase I IgG antibody titers, which is generally observed within the first few months of treatment [2].

However, in rare instances, antibody titers may remain persistently elevated despite prolonged therapy, raising concerns about treatment failure, resistance, or host-related factors. The following case highlights an unusual drug interaction that interfered with treatment efficacy, ultimately preventing complete clinical resolution.

PATIENT DESCRIPTION

A 73-year-old man with a medical history of type 2 diabetes mellitus, hyperlipidemia, hypertension, and chronic bronchitis developed a thoracic aortic aneurysm. He underwent thoracic endovascular aortic repair (TEVAR) using a Gore stent graft in November 2022 due to progressive aneurysmal dilation. Two months post-procedure, he developed community-acquired pneumonia, which was treated empirically with cephalosporin and azithromycin, resulting in temporary clinical improvement.

Several weeks later, he began experiencing recurrent chest pain radiating from the back to the anterior chest wall, similar in character to the pain he experienced prior to the aneurysm repair. He also reported unintentional weight loss totaling 9 kg over 6 months. He denied fever, chills, or night sweats. These symptoms prompted a 10-day hospitalization for further evaluation. On discharge, laboratory testing revealed an elevated C-reactive protein (CRP) level of 4.4 mg/dl (upper limit 0.5 mg/dl). Despite an extensive diagnostic workup during his hospitalization, no definitive etiology was identified.

A magnetic resonance imaging (MRI) of the thoracic aorta and ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) revealed periprosthetic edema and increased uptake around the vascular graft, raising suspicion for graft infection. His family physician then submitted serologic testing for *Coxiella burnetii.* Results returned one week later and showed phase II immunoglobulin M (IgM) negative, phase II immunoglobulin G (IgG) > 1:3200, phase I IgM negative, and phase I IgG > 1:3200. These findings were consistent with chronic Q fever most probably on the endovascular graft. Epidemiologic investigation identified a sheepfold within 700 meters of his home. Dual therapy with doxycycline 100 mg twice daily and hydroxychloroquine 200 mg thrice daily was started. Follow-up CRP levels measured 3 months later had normalized and remained within the reference range throughout the remainder of treatment.

Although the patient reported adherence to the prescribed regimen, follow-up serologies over 12 months showed no significant de-

cline in antibody titers [Table 1], with phase I IgG persistently elevated at 1:12,800. During a one-year period, he did not complain of fever, chills, or night sweats, but he had chest and backaches. A repeat ^{18}F-FDG PET/CT conducted 13 months after treatment commencement showed non-homogenous uptake of the isotope on the left side of the aortic patch. Due to the lack of serological response after 18 months of treatment, the case was discussed with a clinical pharmacologist. A detailed medication review revealed that among multiple other drugs that the patient had been taking, an oral iron supplement was the most likely to interfere with doxycycline absorption. The iron supplement was discontinued. Repeat serologic testing 3 months later demonstrated a marked decline in phase I IgG titers to 1:800, and 5 months further to borderline (approximately 1:100), consistent with restored doxycycline activity and treatment response.

COMMENT

This case highlights a clinically significant and underappreciated drug–nutrient interaction that may compromise the treatment of chronic Q fever: the interference of oral iron supplementation with doxycycline absorption. Despite adherence to the recommended doxycycline–hydroxychloroquine regimen, the patient still had symptoms of chest pain, and his phase I IgG titers remained markedly elevated after one year of treatment, raising concern for therapeutic failure. Only after the identification and discontinuation of concomitant oral iron did a serological response occur, demonstrating a rapid and marked decline in antibody titers.

The interaction between iron and tetracycline-class antibiotics, including doxycycline, is well-established pharmacologically but often overlooked in routine clinical practice. Divalent and trivalent cations, such as those found in iron supplements, can chelate tetracyclines within the gastrointestinal tract, forming insoluble complexes that markedly reduce the antibiotic's bioavailability. This phenomenon was first described in detail by Neuvonen [3] in 1970, in which concomitant administration of ferrous sulfate was shown to significantly impair tetracycline absorption in human subjects [3].

It can be speculated that since doxycycline was administered twice daily, while iron was given only once daily there was still partial activity of doxycycline.

Table 1. Iron–doxycycline interaction in chronic Q fever

Date	Q fever phase I IgG antibody titers	CRP mg/dl (n < 0.5)	Remarks
Nov. 2022			TEVAR aortic graft
Jan. 2023			Community acquired pneumonia
May 2023			Hospitalization for weight loss and chest pain, no fever or chills
May 2023	≥ 3200	4.4	Phase II IgG ≥ 3200, IgM-neg
June 2023	≥ 6400	2.7	MRI + ^{18}F-FDG PET/CT: peri-graft edema and increased uptake
July 2023			Started doxycycline and hydroxychloroquine
Nov. 2023	12,800	0.5	Back and chest pain, no fever or chills or night sweats
Feb. 2024	12,800		Back and chest pain, ESR 46 mm/hour
June 2024	12,800	0.5	
July 2024			^{18}F-FDG PET/CT: high uptake on the left side of the TEVAR patch
Sept. 2024	3200		
Dec. 2024	3200		
Feb. 2025			Iron supplement stopped
May 2025	800		Q fever treatment continued
Oct. 2025	100		

^{18}F-FDG PET/CT = ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IgG = immunoglobulin G, IgM = immunoglobulin M, MRI = magnetic resonance imaging, TEVAR = thoracic endovascular aortic repair

While clinicians are generally advised to space tetracycline and iron administration by several hours, real-world adherence to this recommendation may be inconsistent, particularly in older adults taking complex medication regimens. In this case, even though the patients did not take iron simultaneously with doxycycline, its efficacy was impaired throughout the treatment course. This timing ultimately rendered the doxycycline ineffective for much of the therapy duration, explaining the lack of serologic and clinical improvement.

The implications of this interaction are particularly important in the treatment of chronic Q fever, where bacteriostatic antibiotic efficacy depends on prolonged, uninterrupted exposure to intracellular concentrations sufficient to suppress *C. burnetii*. Treatment failure, as suggested by persistently elevated phase I IgG titers, can lead to prolonged infection, increased risk of relapse, and endovascular complications.

This case underscores the importance of comprehensive medication reconciliation and patient education in the management of complex infections. Clinicians should maintain a high index of suspicion for pharmacokinetic interactions in cases of apparent treatment failure and consider consultation with a clinical pharmacologist when appropriate.

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Capsule

Inhibition of 15-hydroxy prostaglandin dehydrogenase promotes cartilage regeneration

Osteoarthritis is a common debilitating disease that is difficult to treat effectively. **Singla** et al. found that treatment with a small-molecule inhibitor of the enzyme 15-hydroxy prostaglandin dehydrogenase (15-PGDH) could decrease pain and promote regeneration of cartilage in aged or young mice after injury. The inhibitor also decreased inflammation and promoted regeneration in explants from human patients with osteoarthritis. Characterization of cellular changes indicated that alterations in gene expression in existing chondrocytes, rather than activation of stem or progenitor cells, were responsible for the regenerative effects.

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Capsule

In vivo site-specific engineering to reprogram T cells

Engineered T cells, reprogrammed to express chimeric antigen receptors (CAR) or T cell receptors (TCR), have transformed cancer treatment and are being explored as therapeutics for autoimmune and infectious diseases. In vivo generation of CAR T cells could overcome these barriers, but current methods rely either on transient expression with limited durability or on random integration of DNA payloads that lack specificity. **Nyberg** and colleagues demonstrated that stable and cell-specific transgene expression can be achieved through in vivo site-specific integration of large DNA payloads. They developed a two-vector system to deliver CRISPR–Cas9 ribonucleoproteins and a DNA donor template, using enveloped delivery vehicles and adeno-associated viruses, respectively. The authors optimized both vectors for T cell-specific delivery and gene-targeting efficiency. By integrating a CAR transgene into a T cell-specific locus, they generate therapeutic levels of CAR T cells in vivo in humanized mouse models of B cell aplasia, and hematological and solid malignancies. These findings offer a pathway to more efficient, precise and widely accessible T cell therapies.

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