

## Association of Q fever with Autoimmune Hepatitis

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### Abstract

Human infection by *Coxiella burnetii*, a zoonosis, is associated with the development of autoantibodies, though the clinical significance of these is unclear. We describe two patients with high-titer Q fever antibodies associated with autoimmune hepatitis (AIH) as demonstrated on biopsy and supported by autoantibody results. For one, the chronology of serologic results uniquely demonstrates the development of autoantibodies after Q fever antibodies were detected, providing supportive evidence that *Coxiella burnetii* infection may have been a trigger for autoimmune hepatitis.

**Keywords:** *Coxiella burnetii*; Q Fever; Hepatitis, Autoimmune

**Abbreviations:** Autoimmune hepatitis (AIH); Anti-nuclear antibody (ANA); Anti-neutrophil cytoplasmic antibody (ANCA); Anti-smooth muscle antibody (ASMA)

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### Introduction

Type 1 AIH is characterized by immune dysregulation, wherein autoreactive T-cells injure hepatocytes. One pathogenetic hypothesis of autoimmune disease is that self-tolerance is broken down after exposure to a triggering exogenous antigen which induces cross-reactivity to self-antigens through molecular mimicry. Another hypothesis is that a pro-inflammatory milieu in particular organs can overcome immune tolerance. Infection by various pathogens can potentially trigger autoimmunity through either or both mechanisms. *Coxiella burnetii* is one pathogen that is often associated with autoimmune antibodies, though uncommonly with clinically relevant autoimmune disease.

### Case I

A 31 year-old Hispanic male farm-hand with a history of alcohol use worked with a calving operation. The herd was reported to be infected by *Coxiella burnetii*, and the patient had direct contact with stillborn calves in the weeks before onset of his illness. He developed intermittent epigastric and bilateral lower abdominal pain, anorexia and nausea with vomiting over 2 months accompanied by a 25-pound weight loss. He denied any fever, chills or night sweats. Liver tests at presentation and subsequent evaluations are shown in **(Table 1)**, demonstrating a marked rise in total and direct bilirubin and markedly elevated transaminases during the early course of his illness. Hepatitis A, B, C and E serologies, *Leptospira* and *Brucella* serologies and blood polymerase chain reaction for Epstein Barr Virus

and cytomegalovirus were negative. Serum ceruloplasmin and alpha-1 antitrypsin levels were normal. Endoscopic retrograde cholangiopancreatography was unremarkable. Serial results of autoantibody tests are shown in **Table 1**, demonstrating negative studies initially. Q fever Phase II IgG showed a 4-fold rise during the first month of evaluation (**Table 1**). He was diagnosed with Q fever, and doxycycline and levofloxacin were begun. After more than 2 weeks of this therapy, liver enzymes worsened. Antinuclear antibody (ANA) was now low-positive, anti-smooth muscle antibody (ASMA) was highly positive and antineutrophil cytoplasmic antibody (ANCA) was positive. Liver biopsy showed severe acute and chronic inflammation with abundant plasma cells and moderate fibrosis with focal bridging (**Figures 1 and 2**). No fibrin ring granulomas were identified. Based on laboratory results, history and biopsy results, he was diagnosed with probable AIH based on the revised International Autoimmune Hepatitis Group scoring system (1). Budesonide and azathioprine were initiated in addition to continuation of levofloxacin and doxycycline with marked improvement of transaminase levels. A flare in transaminases when the patient

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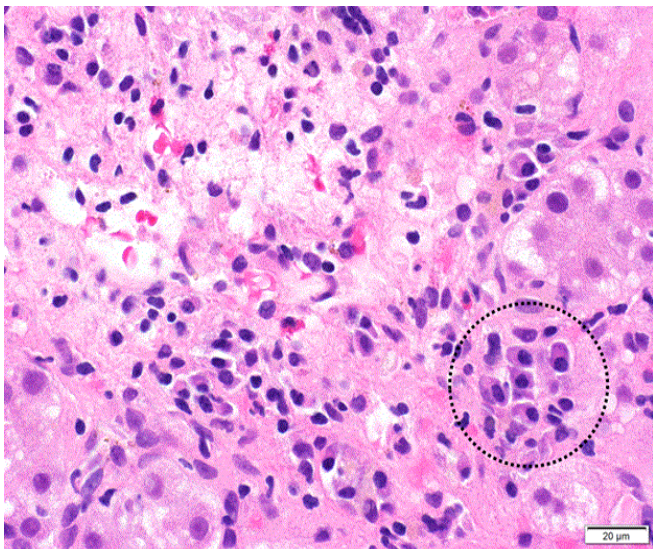
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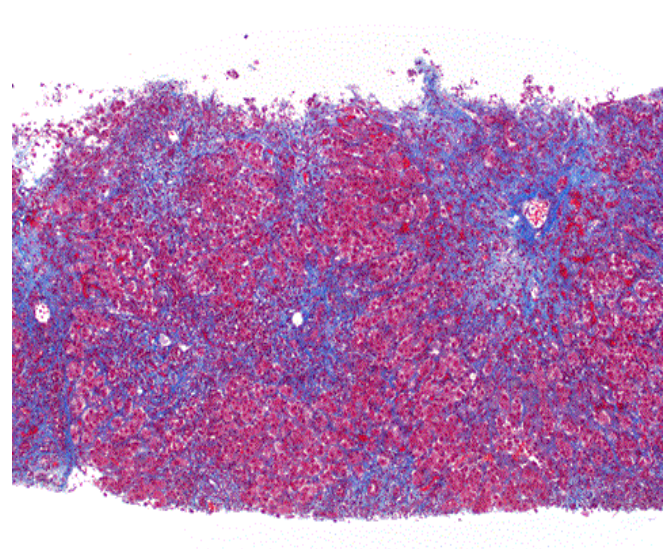
**Table 1** Laboratory results of patients 1 and 2.

	Patient 1					Patient 2			
	10/19/2010	11/6/2010	11/22/2010	11/30/2010	8/25/2011	10/20-25/13	11/6/2013	2/5/2014	5/7/2014
TB	1.7	14.4	9.4	3.8	0.7	13.7	5.7	0.5	0.4
DB	0.5	8.5	6	2	0.2	7.7	2.9	<0.2	<0.2
AST		1,388	1,737	91	113	1,480	274	35	48
ALT		984	1,567	358	146	1,245	495	42	35
ALP		87	121	132	84	108	193	102	71
T Prot			8.8	8.1	7.6	8.5	8.3	7.9	7.9
Ph I IgG		1: 128	1: 128		1: 32	1:8192		1: 4096	1: 4096
Ph II IgG		1:152	1:2048		1:128	1:4096		1: 2048	1: 1024
Ph I IgM		<1:16	<1:16		<1:16	<1:16		<1:16	<1:16
Ph II IgM		<1:16	<1:16		<1:16	<1:16		<1:16	<1:16
AMA	<0.1								
ASMA	Neg		1:1280		1:320				
ANA	Neg		<1:140		1:40	<1:180			
UC-ANCA	Neg		Positive		Positive	Indeterm.			
Actin Ab						133			
PBC Ab						30			
LKM Ab			< 1:10			< 1:10			

TB: total bilirubin (0.2-1.0 mg/dl); DB: direct bilirubin (0-0.2 mg/dl); AST: aspartate aminotransferase (0-40 U/L); ALT: alanine aminotransferase (0-41 U/L); ALP: Alkaline phosphatase (40-129 U/L); T Prot: total protein (6-8 g/dl); AMA: Antimitochondrial antibody (<0.1); ASMA: antismooth-muscle antibody (<1:40); ANA: antinuclear antibody (<1:40); UC ANCA: ulcerative colitis anti-neutrophil cytoplasmic antibody (no range found); LKM: liver-kidney microsomal antibody (<1:10); PBC Ab: primary biliary cirrhosis antibody (0-20 U). Empty cells indicate test was not performed.



**Figure 1** Case 1 H&E image of liver biopsy (600x) demonstrates severely active hepatitis with prominent plasmacytic inflammation (circled).



**Figure 2** Case 1 Trichrome stain of liver biopsy (100x) demonstrates bridging fibrosis and/or necrosis.

discontinued his immunosuppressive medications, with prompt resolution after resumption of immunosuppressant medication, further supported a diagnosis of AIH. He received 3 months of antibiotic therapy and remains on immunosuppressant therapy. Q fever serology 22 months after initiation of antibiotic treatment showed sero-reversion.

## Case 2

A 63 year- old male who lived on and tended to an acreage

adjacent to the Mississippi River noted several weeks of diffuse arthralgia followed by dark urine, fatigue and right upper quadrant abdominal pain. He had no known prior autoimmune or liver disease. He was found to have markedly elevated bilirubin and transaminases as shown (**Table 1**). Complete blood count and basic metabolic panel were unremarkable. Serologies for hepatitis A, B, C, cytomegalovirus and Epstein Barr Virus, *Ehrlichia*, *Anaplasma*, *Bartonella* and *Leptospira* were negative. Blood acetaminophen was undetectable and ceruloplasmin and

alpha 1 antitrypsin levels were normal. Abdominal computed tomography and right upper quadrant ultrasound showed possible cirrhosis with hepatosplenomegaly without biliary dilation. Liver biopsy showed severe active hepatitis with sheets of plasma cells consistent with autoimmune etiology with bridging necrosis. Autoimmune evaluation revealed strongly positive anti-actin antibodies, indeterminate ANCA and negative ANA titers. Primary biliary cirrhosis antibodies were also mildly elevated. On hospital day 4, a diagnosis of probable AIH was made according to the International Autoimmune Hepatitis Group scoring system [1]. He was started on prednisone 60 milligrams daily. Shortly after discharge, Q fever serologies returned and were consistent with chronic Q fever (**Table 1**). Transesophageal echocardiography did not reveal vegetations or significant valvular dysfunction. Over the next several months, transaminases and bilirubin levels normalized. Because of continued elevated Q fever antibody titers and persistent fatigue, antibiotic therapy directed against *Coxiella burnetii* was begun approximately 15 months after the diagnosis of AIH.

## Discussion

*C. burnetii*, an obligate intracellular gram-negative coccobacillus, is the cause of Q fever. The organism is acquired primarily through inhalation of aerosols from contaminated soil or excreta of infected animals. The most common clinical manifestations of acute infection are flu-like illness, pneumonia, and hepatitis. The last is typically associated with fibrin ring granulomas on histology and *Coxiella* antigens can be demonstrated by immunohistochemistry.

Q fever is usually diagnosed by serologic methods. A four-fold rise in Phase II IgG in paired sera provides very high specificity for the diagnosis of acute Q fever [2]. Chronic Q fever is usually diagnosed by high-titer Phase I IgG ( $\geq 1:800$  by microimmunofluorescence) and at these levels has a 98% positive predictive value for chronic Q fever [3,4]. The patient described in Case 1 met serologic criteria for acute Q fever, and patient 2 met criteria for chronic Q fever.

Acute infection by *Coxiella burnetii* has been associated with the production of a range of autoantibodies, including antiphospholipid and antimitochondrial antibodies, ANA, and ASMA [4-6]. The frequency of autoantibodies in some reports of Q fever is very notable: in one study 54% of acutely-infected patients developed at least one of 6 specified autoantibodies, including 29% with ASMA; similarly 67% of chronically-infected patients developed autoantibodies, including 26% with ASMA [7]. However, it is unclear whether the Q-fever-associated autoantibodies are epiphenomena or have a pathogenic role in autoimmune illness. Evidence that the autoimmune features of *Coxiella* infection may be clinically significant includes a recent report of serologically-diagnosed autoimmune liver disease that occurred more than a year after the diagnosis of Q fever by serology. Close to the time of Q fever diagnosis the liver biopsy showed usual changes of *Coxiella*-associated hepatitis, but the following year with persistent liver function test abnormalities, autoimmune serologies were found to be positive [8]. A more remote report describes a patient with acute Q fever and positive

ASMA whose fever resolved only after addition of steroids to the antibiotics, but no liver biopsy was performed [9].

Viruses have primarily been entertained as triggers for autoimmune hepatitis [10]. Theories for viral pathogenesis include molecular mimicry involving viral epitopes similar to liver antigens, the exposure of normally-sequestered self-antigens or the induction of inflammatory cytokine production with increased antigen presentation [11]. Local organ inflammation caused by direct infection is proposed to facilitate the transition from autoimmunity to autoimmune disease [12].

Though the sequence of immune phenomena has been difficult to chart, AIH likely involves an environmental agent that triggers a cascade of T-cell mediated necroinflammation and fibrosis directed at host liver antigens in genetically predisposed hosts. T-regulatory cells are reduced in number and function in the disease [13]. In Type 1 AIH, the more common form, autoantibodies detected include ANA, ASMA, perinuclear antineutrophil antibody and anti-actin antibody. Though the autoantibodies are a hallmark of the disease, the liver antigen(s) targeted by the immune response is not well-defined. A murine model of AIH indicates that an epitope of cytochrome P450IID6 is closely involved with autoimmunity, and studies in human AIH implicate the asialoglycoprotein receptor and soluble liver antigen as targets for autoreactive T cells [14-16].

The possibility that primary autoimmune antibodies led to false-positive *Coxiella* serology in our patients needs to be considered. Though rheumatoid factor can confound Q fever serologic results, to our knowledge other autoantibodies have not been reported to cause false-positive Q fever serologies. It is unlikely that the Q fever serologies were falsely positive due to an alternate infection given the high titers and the lack of antibodies against related organisms which are reported to share cross-reactive antibodies such as *Bartonella* or *Ehrlichia* [17,18].

In summary, we report two patients who had serologic evidence of acute (Case 1) or chronic (Case 2) Q fever, who were also diagnosed with AIH. The clinical sequence for Case 1 is compatible with AIH triggered by acute Q fever. His use of alcohol prior to the diagnosis of liver disease may be a confounding factor for some of the inflammation and fibrosis noted on biopsy, though the abundance of plasma cells and other laboratory features supported the predominance of an autoimmune process. The patient described in Case 2 was diagnosed near-simultaneously with AIH and chronic Q fever. Given that this second patient's clinical course improved with immunosuppression alone it is not clear that active *Coxiella* infection of the liver was present at the time of the diagnosis of AIH. Our cases indicate that infection by *Coxiella burnetii* can be associated with clinical autoimmune disease, and that infection may possibly trigger clinically-significant autoimmunity. Though causation of AIH by *Coxiella* infection cannot be proved by such a limited number of reports, we suggest that in patients with autoimmune hepatitis and an appropriate exposure history, Q fever serologic testing should be considered to better-understand the association with AIH. Alternately, if the hepatitis in Q fever does not improve

with antibiotic treatment, autoimmune liver disease should be considered.

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## References

- 1 Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, et al. (1999) International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 31: 929-938.
- 2 Parker NR, Barralet JH, Bell AM (2006) Q fever. *Lancet* 367: 679-688.
- 3 Maurin M, Raoult D (1999) Q fever. *Clin Microbiol Rev* 12: 518-553.
- 4 Fournier PE, Marrie TJ, Raoult D (1998) Diagnosis of Q fever. *J Clin Microbiol* 36: 1823-1834.
- 5 Selva A, Ordi-Ros J, Cucurull E, Monegal F (1995) [Antiphospholipid antibodies and Q fever]. *Med Clin (Barc)* 105: 359.
- 6 Elouaer-Blanc L, André C, Zafrani ES, Saint-Marc Girardin MF, Gouault-Heilmann M, et al. (1984) [Anti-mitochondria antibodies with an anti-M aspect, in Q fever]. *Gastroenterol Clin Biol* 8: 980.
- 7 Camacho MT, Outschoorn I, Tellez A, Sequí J (2005) Autoantibody profiles in the sera of patients with Q fever: characterization of antigens by immunofluorescence, immunoblot and sequence analysis. *J Autoimmune Dis* 2: 10.
- 8 Kaech C, Pache I, Raoult D, Greub G (2009) *Coxiella burnetii* as a possible cause of autoimmune liver disease: a case report. *J Med Case Rep* 3: 8870.
- 9 Levy P, Raoult D, Razongles JJ (1989) Q-fever and autoimmunity. *Eur J Epidemiol* 5: 447-453.
- 10 Krawitt EL (2006) Autoimmune hepatitis. *N Engl J Med* 354: 54-66.
- 11 Kamradt T, Göggel R, Erb KJ (2005) Induction, exacerbation and inhibition of allergic and autoimmune diseases by infection. *Trends Immunol* 26: 260-267.
- 12 Christen U, Mc Gavern DB, Luster AD, von Herrath MG, Oldstone MB (2003) Among CXCR3 chemokines, IFN-gamma-inducible protein of 10 kDa (CXC chemokine ligand (CXCL) 10) but not monokine induced by IFN-gamma (CXCL9) imprints a pattern for the subsequent development of autoimmune disease. *J Immunol* 171: 6838-6845.
- 13 Makol A, Watt KD, Chowdhary VR (2011) Autoimmune hepatitis: a review of current diagnosis and treatment. *Hepat Res Treat* 2011: 390916.
- 14 Löhr H, Treichel U, Poralla T, Manns M, Meyer zum Büschenfelde KH (1992) Liver-infiltrating T helper cells in autoimmune chronic active hepatitis stimulate the production of autoantibodies against the human asialoglycoprotein receptor in vitro. *Clin Exp Immunol* 88: 45-49.
- 15 Löhr HF, Schlaak JF, Lohse AW, Böcher WO, Arenz M, et al. (1996) Autoreactive CD4+ LKM-specific and anticlonotypic T-cell responses in LKM-1 antibody-positive autoimmune hepatitis. *Hepatology* 24: 1416-1421.
- 16 Wies I, Brunner S, Henninger J, Herkel J, Kanzler S, et al. (2000) Identification of target antigen for SLA/LP autoantibodies in autoimmune hepatitis. *Lancet* 355: 1510-1515.
- 17 La Scola B, Raoult D (1996) Serological cross-reactions between *Bartonella quintana*, *Bartonella henselae*, and *Coxiella burnetii*. *J Clin Microbiol* 34: 2270-2274.
- 18 Graham JV, Baden L, Tsiodras S, Karchmer AW (2000) Q fever endocarditis associated with extensive serological cross-reactivity. *Clin Infect Dis* 30: 609-610.