Chronic Q Fever Hepatitis

Ilia Galperin MD and Jehuda M. van Dijk MD

Department of Geriatrics, Shaare Zedek Medical Center, Jerusalem, Israel

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Q fever is a systemic infection usually caused by inhalation of the rickettsial agent *Coxiella burnetii* or by consumption of infected milk products. Person-to-person transmission is possible but extremely rare. C. *burnetii* has two phases (two antigenic variations) that relate to mutational changes in the lipopolysaccharide: phase 1 is the natural phase found in infected animals and humans, while phase 2 occurs after serial passage in eggs or cell culture. Phase 1 is associated with chronic illness.

Liver involvement is very common in acute and chronic Q fever. Isolated chronic Q fever hepatitis, however, is a very rare disease and little is known about either its natural history or its treatment. Diagnosis of isolated chronic Q fever hepatitis is based on evidence of liver involvement, namely antibody titer of immunoglobulin G >1:1,600 (100% predictive) by immunofluorescence to phase 1 antigen [1], and the exclusion of involvement of other organs. We present here a patient with isolated chronic Q fever hepatitis.

Patient Description

In June 2003 a 69 year old woman was hospitalized for the diagnostic evaluation of prolonged fever. For 2 weeks preceding admission she suffered from a high spiking fever of 39–40°C, severe generalized weakness and diffuse frontal headaches. Before her admission she underwent the following workup: physical examination, which was normal except for severe lassitude and spiking fever; a chest X-ray and abdominal ultrasound, which were normal; and routine blood tests that revealed only mild liver enzymes elevation.

Her past medical history was unremarkable. On admission her physical examination was normal apart from fever (39°C). Laboratory tests revealed the following: hemoglobin 13.6 g/dl, white blood cell count 10,400/mm^3, with 68% neutrophils, 22% lymphocytes and 9.5% monocytes, platelet count 340,000/mm^3 and erythrocyte sedimentation rate 44 mm/hour. Liver enzymes included alkaline phosphatase 122 u/L (normal 38–130 u/L), aspartate aminotransferase 306 u/L (normal 14–36 u/L), alanine aminotransferase 128 u/L (normal 9–52 u/L), gamma-glutamyltransferase 82 u/L (normal 12–43 u/L), lactate dehydrogenase 943 u/L (normal 313–618 u/L), and total bilirubin 1.6 mg/dl (normal 0.2–1.3)

The investigation of the patient's prolonged fever included computed tomography of the entire body, which was normal. Repeated blood and urine cultures were negative. Serum samples obtained near the time of admission were tested by indirect immunofluorescence antibody assay and demonstrated IgG antibodies reactive with *Coxiella burnetii* phase II antigen at reciprocal titers of 1:6,400, Q fever IgG angibody, phase I, 1:400.

In order to exclude endocarditis the patient underwent transthoracic echocardiography and transesophageal echocardiography, which were entirely normal. Although these tests do not completely rule out the possibility of infectious endocarditis, they are currently considered the most sensitive and specific for endocardial involvement (the combination of negative TTE and TEE has a negative predictive value of 95%).

Acute Q fever hepatitis was diagnosed. Doxycycline therapy resulted in partial clinical improvement, with temperature declining to 37.3–37.8°C. The weakness remitted but liver enzymes remained elevated. Further blood samples obtained 2 weeks and 4 weeks after admission demonstrated elevated IgG antibodies to C. *burnetii* phase I antigen [Table]. This confirmed the diagnosis of chronic Q fever [1].

In summary, this patient presented with acute Q fever hepatitis that progressed to chronic Q fever hepatitis. To the previous therapy of doxycycline 100 mg twice daily, ciprofloxacin 500 mg twice daily was added. One month later the patient was afebrile but still had

Q fever serology by microimmunofluorescence with serum samples

Date of hospitalization	7 July 2003	20 July 2003
Q fever IgM Ab phase 1	1:20	1:400
Q fever IgM Ab phase 2	>1:6,400	>1:12,800
Q fever IgG Ab phase 1	1:400	>1:12,800
Q fever IgG Ab phase 2	>1:6400	>1:12,800

Ig = immunoglobulin
TTE = transthoracic echocardiography
TEE = transesophageal echocardiography

some general weakness. The liver function test results remained abnormal. Three months later the patient was asymptomatic without evidence of endocarditis, but liver function tests still revealed slightly abnormal results.

Comment

Q fever is a worldwide rickettsial zoonosis caused by *Coxiella burnetii*. While the incidence of Q fever varies from country to country, this illness is particularly frequent and well known in France [1]. Chronic Q fever is a very rare disease. For example, in France Q fever endocarditis is estimated at 1 per 1 million inhabitants per year [1], and 0.75 cases per 1 million population per year in Israel.

About 73% of patients suffering from Q fever endocarditis have liver involvement. Although pure chronic Q fever hepatitis is very rare, cases of isolated chronic Q fever hepatitis have been described. In one series only 3 cases of chronic hepatitis were diagnosed from among 92 patients with chronic Q fever [2]. Most of the literature comprises case reports [3,4]. Usually the clinical picture is not specific. The pathologic picture on liver biopsy usually reveals hepatitis with fibrin-ring granulomas and some degree of fatty changes [3].

There are no clinical guidelines concerning the optimal treatment for chronic Q fever hepatitis. Specifically, which antibiotic regimen should be administered, and for how long? It has been suggested that acute Q fever hepatitis may progress to chronic Q fever hepatitis and in some cases to portal tract fibrosis and cirrhosis [5]. Although Atienza et al. [4] described chronic Q fever hepatitis with progressive development of extensive liver fibrosis, most reports did not describe progression to cirrhosis. Thus, there are insufficient data in the literature to show a causal relationship between chronic Q fever hepatitis and cirrhosis.

We wish to emphasize that only controlled studies have been conducted on the treatment of Q fever endocarditis [5] in contrast to chronic Q fever hepatitis. Based on the results of these studies a number of combination drug regimens were suggested. We chose doxycyline and ciprofloxacin with close serologic and clinical follow-up. Despite recommendations in the literature that the optimal treatment of chronic Q fever consists of a combination of doxycyline and hydroxychloroquin, due to difficulty in monitoring hydroxychloroquin blood levels, we decided to treat our patient as described above. Owing to the possibility of relapse of chronic Q fever or resistance to treatment with doxycycline and ciprofloxacin, the regimen with hydroxychloroquin and doxycycline should be considered despite the difficulties in monitoring drug levels [5].

In conclusion, we have presented a case of chronic Q fever hepatitis – a rare and non-specific illness that should be included in the differential diagnosis of any patient with severe general weakness, prolonged fever and mild liver enzymes elevation in whom routine microbiologic investigation is negative.

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Correspondence: Dr I. Galperin, Dept. of Geriatrics, Shaare Zedek Medical Center, P.O. Box 3235, Jerusalem 91031, Israel.
Phone: (972-2) 655-5168
Fax: (972-2) 655-5765
email: helsinki@szmc.org.il

Capsule

Osteoporosis, osteoclasts and marijuana

More than half of individuals age 50 and older are at risk for osteoporosis, a disorder characterized by low bone mass. One of the principal cell types regulating skeletal growth and integrity is the osteoclast, which functions to resorb bone. Several drugs currently in clinical use for osteoporosis, such as the bisphosphonates, act by inhibiting osteoclast activity. A surprising new molecular player in bone growth and remodeling has been identified by Idris et al., who found that mutant mice deficient in cannabinoid type 1 (CB1) receptors have increased bone mass that appears to be caused by aberrant apoptosis (cell death) of osteoclasts. Moreover, mutant female mice were protected against bone loss induced by ovary removal, which is a model of postmenopausal bone loss in women, and this protective effect could be reproduced pharmacologically in wild-type mice by the administration of cannabinoid antagonists. Thus, osteoporosis joins a growing list of human disorders, including obesity and nicotine dependence, that may be treatable by drugs targeting the cannabinoid receptors, a class of proteins originally discovered as the binding sites for the major psychoactive ingredient of marijuana.

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Eitan Israeli