

Case Report

# Is *Bartonella* a Cause of Primary Sclerosing Cholangitis? A Case Study

Daniel A. Kinderlehrer

668 South Newport Street, Denver, CO 80224, USA; kinderlehrer@gmail.com

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**Abstract:** The etiology of primary sclerosing cholangitis (PSC) is unknown. I present a case which may be indicative of a causal link between *Bartonella* infection and PSC. The patient presented with complaints of abdominal pain and bloody diarrhea. A colonoscopy demonstrated chronic inflammation and changes consistent with ulcerative colitis. Routine laboratory studies revealed elevated liver function tests (LFTs); ultrasound and magnetic resonance imaging (MRI) confirmed the diagnosis of PSC. *Bartonella* serology was positive. It is established that *Bartonella* infection is associated with both gastrointestinal inflammation and autoimmunity; indeed, there is an animal model for *Bartonella*-induced PSC. *Bartonella* is susceptible to treatment with vancomycin and there are case reports and small series that demonstrate that PSC responds to treatment with oral vancomycin. Because of this, it is postulated that at least some cases of PSC may be associated with *Bartonella* infection. The patient in this report was treated with oral vancomycin and, since then, has been in remission for both colitis and PSC. Since vancomycin is not systemically absorbed, the premise is that he suffered from *Bartonella* colitis and an autoimmune reaction to *Bartonella* causing PSC. This premise warrants further study.

**Keywords:** bartonella; primary sclerosing cholangitis; autoimmune; colitis

## 1. Introduction

Primary sclerosing cholangitis (PSC) is a chronic liver disease characterized by a progressive course of cholestasis with inflammation and fibrosis of the intrahepatic and extrahepatic biliary tree. The etiology of PSC is unknown but is postulated to be autoimmune [1]. While immunosuppressive agents have not been effective in the treatment of PSC, antibiotics have shown promise. In particular, vancomycin has demonstrated efficacy in multiple case reports and small series [2].

*Bartonella henselae* (*B. henselae*) is the causative agent of cat scratch disease (CSD) as well as a wide array of systemic infections, including colitis [3]. Arthropod vectors, including *Ixodes* ticks, can transmit *Bartonella* spp., and can co-infect patients with Lyme disease [4,5]. I present a case of a thirteen-year-old immunocompetent male with a previous history of Lyme disease who developed colitis and PSC. He had a positive serology to *B. henselae* and *Bartonella quintana* (*B. quintana*), suggesting the role of *Bartonella* in the pathogenesis of these conditions.

## 2. Case Presentation

This male patient initially presented at nine years of age with multisystem symptoms. At four years of age he developed an Erythema Migrans (EM) rash while in Maryland and was diagnosed by a medical practitioner as having Lyme disease. The patient was put on an antibiotic but discontinued it after four days. Subsequent to this episode, he began complaining of severe leg pains, sleep disturbances and mood swings with dramatic temper tantrums. Gradually, he developed other symptoms, including intermittent knee pains, inguinal pain, back pain, neck pain, and ear pain. He had one episode of

tachycardia with dyspnea and chest pain lasting thirty minutes; the cardiac evaluation was negative. When his handwriting began to deteriorate, his parents brought him in for evaluation.

The family did not own a cat. A review of the systems was otherwise negative and physical examination was unremarkable. Laboratory evaluation was significant for the presence of Lyme Western Blot immunoglobulin G (IgG) bands 39 and 41.

The patient was treated with oral amoxicillin 500 mg three times daily for six months and symptoms remitted. Four years later, the patient developed fatigue and intermittent abdominal pain with frequent soft bowel movements and some blood in his stools. Three months later, his symptoms worsened and his weight had dropped by four pounds. Investigation at that time revealed:

- Iron deficiency anemia:
  - Hemoglobin = 10.6 g/dL (reference range (RR): 13.5–17.7 g/dL);
  - Hematocrit = 35% (RR: 37–49%);
  - Ferritin = 14 ng/mL (RR: 47–356 ng/mL).
- Increased inflammatory markers:
  - Leukocytosis WBC = 13,600/uL (RR: 4000–11,000/uL);
  - ESR = 41 mm/hr (RR: 0–20 mm/hr);
  - Faecal calprotectin = 188 mg/kg (RR: <50 mg/kg).
- Elevated liver enzymes in a cholestatic pattern:
  - Alkaline phosphatase = 1117 U/L (RR: 98–448 U/L);
  - Aspartate aminotransferase = 121 U/L (RR: 6–38 U/L);
  - Alanine aminotransferase = 207 U/L (RR: 13–63 U/L);
  - Gamma glutamyltransferase = 457 U/L (RR: 6–75 U/L).
- Immunologic testing:
  - Total IgG = 1800 mg/dL (RR: 681–1648);
  - Anti-tissue transglutaminase IgA = 1.9U/mL (RR: 0–19 U/mL);
  - Anti-gliadin antibody IgA = 0.2 (U/mL) (RR: 0–20 U/mL);
  - Antinuclear antibody (ANA) negative (RR: negative);
  - Anticytoplasmic antibody negative (RR: negative);
  - Smooth muscle antibody negative (RR: negative);
  - Anti-liver kidney microsome antibody-1 = 0.8 U (RR: 0–20 U);
  - Myeloperoxidase antibody <0.2 (RR: 0.0–0.9);
  - C-anti-neutrophil cytoplasmic antibody = 1:640 (RR: <1:20).
- Thiopurine S-methyltransferase gene variants: none detected;
- Serological testing of IgG to *Bartonella henselae* and *Bartonella quintana* by enzyme linked immunofluorescence assay (ELISA) were both elevated at 1:256 (RR: non-reactive);
- Serum PCR testing for *Bartonella* species was negative;
- A colonoscopy revealed a diffuse area of moderately congested, erythematous, friable and inflamed mucosa in the rectum, the recto-sigmoid colon, the sigmoid colon, the descending colon and at the splenic flexure (see Figure 1). A biopsy revealed mild active inflammation with mild architectural changes;
- An abdominal ultrasound showed dilation of the distal common bile duct measuring 7.3 mm; hepatic enlargement measuring 17.8 cm sagittally (RR: 8.7–13.7 cm); the liver was mildly echogenic; the remainder of the ultrasound was normal;

- An MRI with magnetic resonance cholangiopancreatography (MRCP) showed slight beading of the common bile duct, common hepatic duct, and proximal hepatic duct; the common bile duct was dilated to 10 mm in width (see Figure 2).

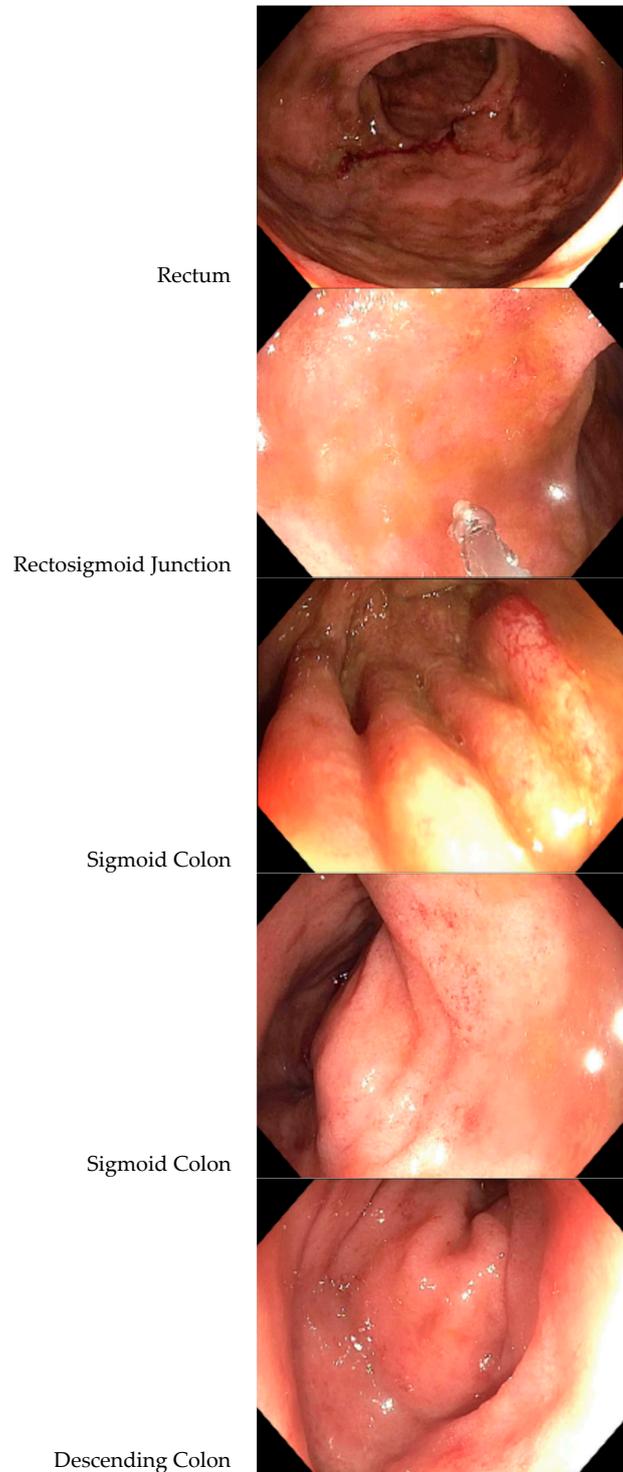
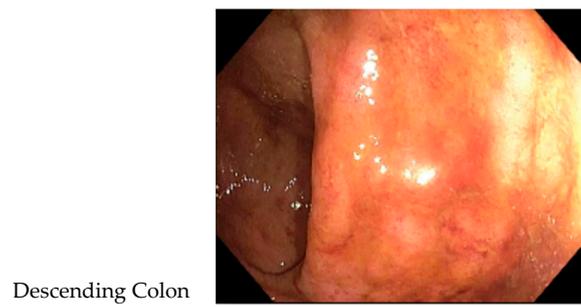
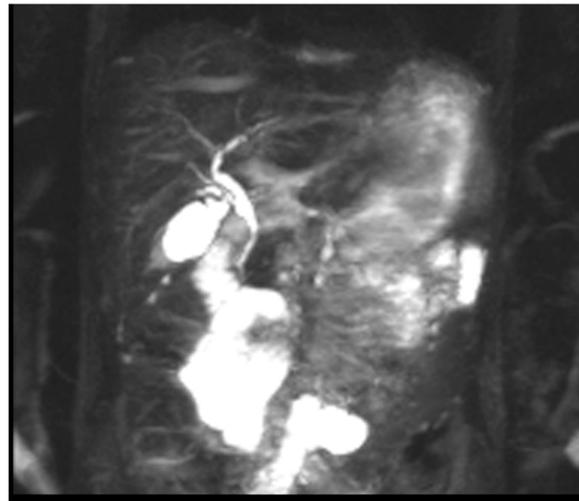


Figure 1. Cont.

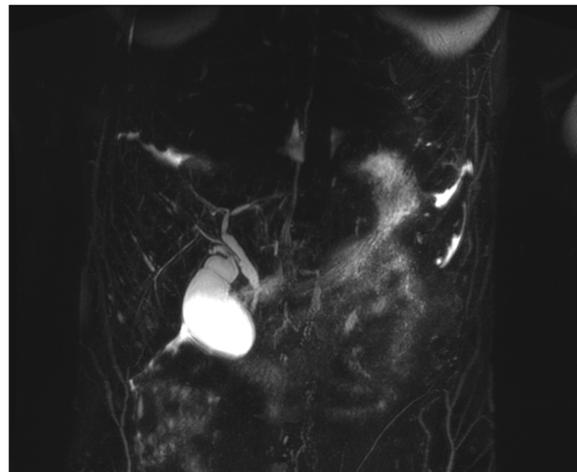


**Figure 1.** Colonoscopy at presentation.



**Figure 2.** Magnetic resonance cholangiopancreatography (MRCP) at presentation.

The patient was treated with mesalamine 400 mg three times daily. His diarrhea slowed but did not resolve and he continued to complain of abdominal pain. After three weeks on mesalamine, he began oral vancomycin 500 mg three times daily. After one month on oral vancomycin, all symptoms remitted. All laboratory abnormalities returned to normal, including faecal calprotectin. A repeat MRCP showed the common bile duct had decreased to 7 mm in width, and beading had decreased (see Figure 3). Repeat *Bartonella* serology and PCR testing of the colonic biopsy is not available.



**Figure 3.** MRCP after one year of treatment.

### 3. Discussion

PSC has an estimated prevalence of 16.2/100,000 in the total adult population; male 22.7/100,000 and female 8.9/100,000 [6]. PSC most often occurs in young males and is associated with a high incidence of inflammatory bowel disease, primarily ulcerative colitis. PSC is complicated by cancer—cholangiocarcinoma, gallbladder carcinoma and colorectal carcinoma—in 13%–14% of patients [7].

The etiology of PSC is unknown, but is postulated to be autoimmune because of its increased frequency with the presence of autoimmune antibodies and autoimmune illnesses, pathological findings of immune cells, particularly lymphocytes, its strong linkage to the histocompatibility complex (HLA) and the prevalence of non-HLA genome-wide single nucleotide polymorphisms [1].

Several therapeutic modalities, including ursodeoxycholic acid and immunosuppressive agents, have failed to alter the course of PSC. While liver transplants may extend lifespan, the recurrence rate is high [1]. However, antibiotics have shown promise. Cox et al. described three adolescent males with PSC and Crohn's disease whose hepatic enzymes and liver biopsies normalized on oral vancomycin [8]. Davies et al. treated fourteen patients with PSC with oral vancomycin, all of whom improved; however, four patients with previously diagnosed cirrhosis showed less improvement than those without cirrhosis [9]. Tabibian et al. randomized thirty-five patients with PSC into four groups: vancomycin 125 mg or 250 mg four times per day and metronidazole 250 mg or 500 mg three times per day; all groups improved but the vancomycin groups showed the greatest improvement [10]. In a triple-blinded, randomized, placebo-controlled trial of twenty-nine patients, of which eighteen were treated with oral vancomycin 125 mg four times daily for twelve weeks, Rahimpour et al. found that vancomycin significantly reduced the PSC Mayo risk scores as well as the levels of alkaline phosphatase [11]. Dao et al. described improvements in both ulcerative colitis and PSC in eight patients, five of whom had undergone liver transplant, when treated with oral vancomycin 125 mg four times daily for 6–8 weeks, after which the dose was tapered but not discontinued; all patients maintained endoscopic response/remission [12]. Tan et al. described the impact of oral vancomycin on seventeen children with ulcerative colitis and PSC, in which they stated: "There was a striking response of colitis with near universal colonic healing" [13]. Additional case reports have cited the efficacy of vancomycin in the treatment of PSC [14–16]. All of these reports are small and predominantly in children or adolescents. Nevertheless, a review article on vancomycin in the treatment of PSC concludes "Vancomycin is one of the most-studied antibiotics in the treatment of PSC with promising results" [2].

Since oral vancomycin is not systemically absorbed, its efficacy has been attributed to working as both an antibiotic and immunomodulator, possibly by modifying the gut microbiome [17,18]. An alternative explanation is that an autoimmune reaction triggered by a *Bartonella* infection in the intestines could precipitate PSC.

*Bartonella* is a small, aerobic, intracellular gram-negative pleomorphic bacillus. The bacillus is difficult to grow; hence, culture is not recommended [19]. A polymerase chain reaction (PCR) in blood or tissue specimens is the most definitive way to diagnose bartonellosis; however, this method lacks sensitivity (43%–76%) [20]. Serological testing by either indirect immunofluorescent assay (IFA) or ELISA is the standard tool to diagnose *B. henselae*, although increased sensitivity of antibody assays is associated with decreased specificity [21]. Giladi et al. reported 77% sensitivity of the second of the paired samples IgG by ELISA in patients with CSD documented by positive PCR [22]. Sander et al. reported 100% positive IgG serology in patients with CSD, but also found 30% of controls were seropositive [23]. There is no data on the sensitivity or specificity of serologic testing in patients with *Bartonella* infections acquired via tick transmission. *Bartonella* spp. other than *B. henselae* and *B. quintana* have caused infection in humans [24], which may account for false negative serologies when testing for only the above two *Bartonella* spp.

While it is not known how this patient became infected with *Bartonella*, it is notable that a variety of arthropod vectors may be implicated. *B. henselae* is the causative agent of cat scratch disease (CSD),

transmitted via the cat flea. It is well established that *Bartonella* spp. can also be transmitted by sandflies and lice [25] and, while the transmission of *Bartonella* spp. via a tick vector has been debated, there is direct evidence that *B. henselae* can be transmitted via the *Ixodes* tick [4,5]. Co-occurrence of *Bartonella* spp. with known tick-borne pathogens, such as *Borrelia burgdorferi* (*B. burgdorferi*) *sensu lato* may not be uncommon. Adelson et al. surveyed *Ixodes* ticks in northern New Jersey and found *B. burgdorferi* present in 35% of ticks while 34% harbored *Bartonella* spp. [26]. Additional studies have confirmed the high incidence of *Bartonella* spp. in *Ixodes* ticks [27,28]. Several case studies of patients with *B. burgdorferi* infection of the central nervous system after tick bites have demonstrated concurrent *Bartonella* seropositivity confirmed by detection of *Bartonella* spp. DNA in their blood [29,30].

*Bartonella* spp. are responsible for a wide spectrum of clinical illness in humans, including disseminated infection and septicemia, neurological, cardiovascular, ocular, musculoskeletal, and cutaneous disease [31]. In addition, *B. henselae* can infect the gastrointestinal tract and cause ulcerative colitis [3,32].

*Bartonella* can also induce autoimmune disease [33]. *Bartonella* has been associated with autoimmune thyroiditis [34], autoimmune hemolytic anemia [35], juvenile rheumatoid arthritis [36], IgA nephropathy [37,38], arthropathies [39–41], polyneuropathy [40,42], Guillain-Barré syndrome [43], chronic vasculitis [37,42], immune thrombocytopenic purpura [44], transverse myelitis [45] and Henoch-Schönlein purpura [46,47].

The pathogenesis of autoimmune diseases involves the interplay of genetic and environmental factors [48]. The pathogenic mechanism(s) by which *Bartonella* causes autoimmune disorders may be caused by cross-reactivity or molecular mimicry [49], polyclonal T cell activation by bacterial antigens [50], activation of the classical complement cascade-producing proinflammatory cytokines [51], or the formation of immune complexes which precipitate in various tissues, resulting in an inflammatory response [52]. *Bartonella* can induce cellular immune stimulation resulting in granuloma formation and lymphocyte and neutrophil accumulations in various tissues [53].

There are no previous reports of an association between *Bartonella* infection and PSC in humans, but there are in cats. Kordeck et al. reported the results of inoculating eighteen specific pathogen-free cats that were culture and serologically negative for *Bartonella* with the blood or urine of cats infected with *B. henselae* and/or *Bartonella clarridgeiae* (*B. clarridgeiae*). Thirteen cats were euthanized and nine had evidence of cholangitis/pericholangitis with lymphocytic infiltration and plasma cells [54]. These pathological findings are the same as in patients with PSC.

The case presented here suggests, but does not prove, the causal association of *Bartonella* in the pathogenesis of PSC. The patient had a well-documented case of Lyme disease, with a history of an EM rash in an endemic area for Lyme disease treated inadequately and followed by multisystem symptoms and a Western Blot IgG positive for bands 39 and 41. Band 39 is highly specific for *B. burgdorferi* [55]. While this patient's Western Blot did not meet the Centers for Disease Control and Prevention (CDC) criteria for reporting Lyme disease, the CDC criteria are intended for surveillance purposes only, and are not intended to make a clinical diagnosis [56,57].

When the patient was initially treated for infection with *B. burgdorferi*, he may have been co-infected with a *Bartonella* infection via the same tick vector. The history of severe mood swings is particularly suggestive of infection with *Bartonella* [58]. Treatment of *B. burgdorferi* infection with amoxicillin could suppress a *Bartonella* infection without eradicating the microbe, since *Bartonella* is somewhat susceptible to beta-lactam antibiotics [59]. In any case, three years later, positive antibody titers in this patient documented exposure to *Bartonella* spp. when he developed colitis and PSC. The hepatic ultrasound showed echogenic areas that could represent granulomas associated with *Bartonella* infection [53]. *Bartonella* spp. have high *in vitro* susceptibilities to vancomycin [59] and could treat *Bartonella* colitis. Since oral vancomycin is not systemically absorbed, the implication is that treating the infection reversed an autoimmune response that resulted in PSC.

Several investigators have posited that vancomycin's capacity to treat PSC is due, in part, to its action as an immunomodulator. [18] While the impact of vancomycin on patients with PSC leads

to decreased inflammatory parameters [11,18], vancomycin could also mitigate inflammation if it is treating the microbial trigger of an autoimmune reaction. Howden et al. demonstrated that the development of low-level vancomycin resistance in methicillin resistant *Staphylococcus aureus* is associated with changes in nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) and decreased tumor necrosis factor-alpha (TNF- $\alpha$ ) [60]; however, this decrease in the host pro-inflammatory response to infection is not evidence that vancomycin is an immune modulator. Furthermore, multiple trials of immunosuppressive therapy with glucocorticoids and several chemotherapeutic agents have not led to improvement in patients with PSC [1]. The findings in this patient are consistent with *B. henselae* as a cause of colitis and as the trigger of an autoimmune response resulting in PSC.

#### 4. Conclusions

This case raises the possibility that *Bartonella* infection in the colon could trigger an autoimmune response leading to PSC. Given the serious morbidity and mortality of this illness, the implications are significant for promoting future research. Further studies, such as PCR testing of serum and tissue samples, as well as testing of patients with PSC for *Bartonella* spp. compared with a control population, would help determine the role of *Bartonella* in the etiology of PSC.

**Conflicts of Interest:** The author declares no conflict of interest.

#### Abbreviations

PSC	Primary sclerosing cholangitis
LFT	Liver function test
HLA	Histocompatibility-complex
CSD	Cat scratch disease
EM	Erythema migrans
IgG	Immunoglobulin G
IFA	Indirect immunofluorescence assay
MRI	Magnetic resonance imaging
MRCP	Magnetic resonance cholangiopancreatography
ELISA	Enzyme linked immunoassay
CDC	Centers for Disease Control and Prevention
RR	Reference range
<i>B. henselae</i>	<i>Bartonella henselae</i>
<i>B. quintana</i>	<i>Bartonella quintana</i>
<i>B. burgdorferi</i>	<i>Borrelia burgdorferi</i>
<i>B. clarridgeiae</i>	<i>Bartonella clarridgeiae</i>
NF- $\kappa$ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
TNF- $\alpha$	Tumor necrosis factor-alpha

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