Acute Endogenous Endophthalmitis Due to *Bartonella henselae*

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A 45-year-old man presented with progressively worsening vitreitis of 1 week’s duration. Treatment for cat-scratch disease 3 years prior to presentation and persistent vitreitis led to vitrectomy, and analysis of the vitrectomy specimen revealed inflammatory cells and necrotic debris; polymerase-chain-reaction analysis of the vitreous fluid sample, done by use of a novel heminested protocol, demonstrated the presence of *Bartonella henselae* DNA. Treatment with doxycycline led to improvement in the intraocular inflammation but resulted in a poor visual outcome.

Endogenous or metastatic endophthalmitis is typically seen in acutely ill persons but has also been reported in ambulatory patients. A disproportionate number of cases occur in younger persons. Predisposing causes include immunosuppressive therapy, diabetes, lymphoma, iv drug use, and dialysis [1]. We present a case of endophthalmitis due to *Bartonella henselae* in a patient with paroxysmal nocturnal hemoglobinuria, a rare condition characterized by intravascular hemolysis and venous thrombosis.

**Case report.** A 45-year-old white man presented to the University of Illinois at Chicago Uveitis service with a diagnosis of vitreitis. The patient complained of loss of vision in the left eye of 1 week’s duration. He had been treated for iritis with topical prednisolone acetate and homatropine and had been referred for a second opinion when “puffballs” were noted in his vitreous fluid cavity. No pain, redness, or photophobia, was observed, and the patient had no history of ocular trauma. The right eye was asymptomatic.

Examination revealed a visual acuity of 20/20 in the right eye and light perception without projection in the left eye. Intraocular pressures were 16 mm Hg in the right eye and 1 mm Hg in the left eye. The left pupil was nonreactive because of posterior synechiae, and a 3+ reverse afferent pupillary defect was noted. The left eye exhibited 1+ conjunctival injection, medium-sized keratic precipitates, and folds in Descemet’s membrane. The anterior chamber showed 4+ yellow flare and 1+ cells in the anterior chamber with a 1-mm hypopyon. The lens appeared clear. The iris surface (figure 1) and the anterior vitreous fluid showed large clumps of cells and fibrin. The left fundus could not be visualized except for the peculiar yellow glow of the fundus reflex. B-scan ultrasonography disclosed dense vitreitis and choroidal detachment (figure 2). Examination of the right eye revealed nothing remarkable.

The patient’s medical history was significant for paroxysmal nocturnal hemoglobinuria of 3 years’ duration. He had been given a diagnosis of systemic cat-scratch infection in 1994, when he developed fever and neutropenia after being scratched by kittens. Workup done at that time revealed positive antibody titers for *Rochalimaea (Bartonella) henselae* (IgM, 1:80) and negative titers for *Rochalimaea quintana* (IgM, <1:20). The patient was treated with doxycycline, 100 mg administered orally b.i.d. for 1 month, and had convalescent-phase IgG titers of 1:256 for both *R. henselae* and *R. quintana* (IgM for both species, <1:20). No ocular symptoms were present at that time, nor were any systemic recurrences noted during the next few years.

**Figure 1.** Photograph showing yellowish mass over the iris surface. Medium-sized keratic precipitates are present on the inferotemporal cornea.
Diagnostic possibilities at the time of presentation to the uveitis service included acute retinal necrosis, toxoplasmosis, fungal and bacterial endophthalmitis, and malignancy. Laboratory examination revealed a WBC count of 4200 cells/µL with a normal differential count. Mildly elevated bilirubin levels were noted that were consistent with the patient’s diagnosis of paroxysmal hemoglobinuria. In addition, his serum level of lactic dehydrogenase was markedly elevated at 2268 U/L, and his aspartate aminotransferase level was elevated at 268 U/L. The results of all other liver function tests were within normal limits. Urine and blood culture results were negative. Results of fluorescent treponemal antibody absorption and rapid plasma reagin tests were negative. The patient was HIV negative by ELISA. Findings of a chest radiograph were normal, as were those of a CT scan of the head and orbits. Antibody titers for B. henselae were not repeated.

The patient underwent emergent vitrectomy with vitreous fluid biopsy. At the time of surgery, no areas of retinitis were seen, although a focal area of subretinal hemorrhage was noted inferotemporally. Vancomycin (1.0 mg), ceftazidime (2.0 mg) and amphotericin (5 µg) were injected intravitreally. The results of aerobic, anaerobic, fungal, and viral cultures were negative. Results of fluorescent treponemal antibody absorption and rapid plasma reagin tests were negative. The patient was HIV negative by ELISA. Findings of a chest radiograph were normal, as were those of a CT scan of the head and orbits. Antibody titers for B. henselae were not repeated.

The patient underwent another vitrectomy 10 days later because of progressively increasing vitreitis. At the time of surgery, multiple discrete vitreous opacities were noted with no retinal involvement. Vitreous fluid cultures were repeated and showed no growth. Light microscopic examination of the vitrectomy specimen showed a mixture of lymphocytes, polymorphonuclear leukocytes, and necrotic debris. The results of stains for microorganisms, including Warthin-Starry silver stain for Bartonella species were negative. Electron microscopy performed on a centrifuged pellet of the vitreous fluid sample revealed degenerating cellular debris and small, pleomorphic rodlike bacilli (figure 3). Results of cultures of the vitrectomy sample were negative.

The vitreous fluid sample and blood samples were sent for PCR testing for B. henselae. A total of 200 µL of both the vitreous fluid and the blood sample was used for PCR analysis. DNA was isolated from both samples and was tested according to the protocols described by Mouritsen et al. [2]. In brief, DNA was isolated using the IsoQuick DNA extraction kit (Orca Research), which used guanidine lysis, nuclease adsorption, DNA separation, and alcohol precipitation. One microliter of DNA was used in a 10-µL reaction mixture for primary amplification. One microliter of the primary amplification product was used for the template of the secondary, heminested amplification. All amplification was performed with a 1605 rapid air thermocycler (Idaho Technology). The PCR primers that were used were those described by Anderson et al. [3] and have been shown to be capable of differentiating B. henselae from B. quintana. PCR analysis for this organism shows a distinct band at 417 bp for the outer product and at 390 bp for the internal heminested product.

The vitreous fluid sample obtained from this patient exhibited a reproducibly distinct band at 390 bp, confirming the presence of B. henselae DNA in the sample. However, the blood sample did not exhibit a noticeable band at the indicated size (figure 4).

The patient was prescribed orally administered doxycycline, 200 mg b.i.d. After 3 weeks of treatment, his visual acuity improved to counting fingers. At the time of his last examination, 5 months after the initial presentation, his visual acuity was 20/400 in the affected eye. The anterior chamber was deep, with a persistent yellow hue to the aqueous humor. There were still 3+ cells and flare in the anterior chamber, and a dense membrane overlying the optic nerve and macula was present. There was no hypopyon and the vitreous fluid was clear. The patient deferred repeated vitrectomy with membranectomy and was lost to follow-up.
Discussion. After the development of sensitive laboratory techniques to detect B. henselae, many reports in the past decade have described new posterior segment lesions without evidence of retinitis. These include neuroretinitis with or without macular involvement [4–9], acute multifocal retinitis [4, 5, 10–13], intermediate uveitis with retinal vasculitis [5, 13], choroiditis [5, 15], and inflammatory mass of the optic nerve head [5, 16]. Vitreitis has also been a presenting feature of this condition [5–7, 10, 14]. The disease may also manifest in HIV-positive patients [12, 13].

The striking feature in our patient was the rapidly evolving endophthalmitis that included moderate to severe anterior and posterior segment inflammation without evidence of retinitis. Mild to moderate inflammation of the vitreous humor in the absence of retinitis has been described in cat-scratch disease [5–7, 10, 14], but the reported cases have not been as severe as that seen in our patient. It is possible that the choroidal detachment seen in our patient represented choroidal inflammation. However, direct observation of the posterior pole was not possible initially, and no choroidal infiltrates were visualized on direct examination during vitrectomy. At initial presentation, endogenous acute bacterial endophthalmitis from an undetermined source, endogenous fungal infection, acute retinal necrosis, and malignancy were considered in the differential diagnosis but could not be confirmed by culture or pathologic examination.

Although the diagnosis of cat-scratch disease is often straightforward, given the proper clinical presentation, laboratory diagnosis of unusual cases may be challenging. For our patient, light microscopic examination and culture of the vitreous fluid aspirate were not helpful in establishing the diagnosis. This is not surprising, because the organism is fastidious and difficult to culture [17]. Demonstration of the organisms by histopathologic examination may also be difficult, especially in vitreous fluid biopsy specimens that yield only a small amount of tissue. Measurement of antibody titers by indirect immunofluorescence [5–7, 18] EIAs [19] and, more recently, by use of PCR to detect bacterial DNA [2, 3, 13, 20] have been used to make or confirm the diagnosis of systemic and ocular involvement in cat-scratch disease. In this patient, the presence of bacilli on electron microscopy and the positive PCR result of the second vitreous fluid sample confirmed the diagnosis of cat-scratch disease. The negative results of PCR analysis of our patient’s blood samples may be attributed to transient bacteremia that occurred at the time of ocular inoculation. Because PCR was performed on the blood samples a few weeks after the initial presentation, the level of bacteremia may no longer have been sufficient to elicit a positive PCR result. Also, the levels of bacilli in the ocular fluid probably were much greater and thereby increased the possibility of a positive PCR result.

Furthermore, the negative PCR results for the blood sample suggests that the positive PCR result for the vitreous fluid sample was not the result of contamination by blood and reflected the true presence of Bartonella DNA in the vitreous fluid. The PCR test developed by one of the coauthors of this study (L.M.) can detect DNA in the organism in both fresh and formalin-fixed, paraffin-embedded samples and is probably ideal for use with intraocular specimens for which number of tests need to be performed on a limited sample [2]. Indirect immunofluorescent antibody titers may be helpful in establishing the cause of localized ocular inflammation [5, 6, 9]. However, the intraocular titer required for positivity has yet to be determined [21]. Although such titers were available for our patient while he had systemic infection and were considered positive, titers were not obtained during the recent episode.

Most patients with posterior-segment manifestations of cat-scratch disease have concurrent systemic manifestations or signs that precede ocular findings by only several weeks [4–16]. An unusual feature of this patient was the long interval between the development of systemic symptoms and the onset of acute ocular inflammation. Relapses of treated B. henselae infections have been described and might be the reason for the long interval [22]. The relationship, if any, between the paroxysmal nocturnal hemoglobinuria in this patient and the relapse of infection is uncertain. Patients with paroxysmal nocturnal hemoglobinuria may develop neutropenia that might, in theory, allow for recrudescence of systemic bacteremia [23]. At presentation, this patient had mild neutropenia, but he did not display a level of neutropenia that is usually considered to predispose to infection. One interesting finding in this patient...
that is likely related to the paroxysmal nocturnal hemoglobinuria is the yellow color of the ocular fluids. We presumed this to be due to the presence of a high bilirubin level in the aqueous humor due to high serum bilirubin levels and breakdown of the blood-aqueous barrier.

Regimens used to treat ocular *B. henselae* infection include minocycline, doxycycline, rifampin, ciprofloxacin, trimethoprim-sulfamethoxazole, tetracycline, and erythromycin [5, 6, 13, 24]. Our patient demonstrated a marked decrease in inflammation with prolonged doxycycline therapy. However, the intravitreal injection of antibiotics also may have played a role.

The visual outcome of patients with posterior segment involvement with and without treatment is generally good, with up to 74% patients recovering excellent vision [5]. Causes of poor vision included disc granulomas, choroiditis, and vascular occlusive events [5]. The poor vision of the patient who we studied, could be attributed to a combination of factors. The presence of an afferent pupillary defect suggested optic nerve involvement that could not be directly visualized because of the extensive vitreous fluid infiltrate. Extensive retinal degeneration caused by prolonged vitreous fluid inflammation and residual preretinal membranes could also have contributed to the poor vision of this patient.

The rickettsia *B. henselae* has been associated with a growing list of ocular inflammatory signs. Our case report suggests that acute endogenous endophthalmitis may be an additional presentation of *B. henselae* infection and that *Bartonella* species should be considered in the differential diagnosis of endophthalmitis of unknown etiology. The elucidation of a previous involvement that could not be directly visualized because of the extensive vitreous fluid infiltrate. Extensive retinal degeneration caused by prolonged vitreous fluid inflammation and residual preretinal membranes could also have contributed to the poor vision of this patient.

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References