



## *Bartonella henselae*-associated recurrent, bilateral segmental periphlebitis

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### ABSTRACT

**Purpose:** To describe a patient with atypical *Bartonella henselae* (*B. henselae*)-associated ocular inflammation that manifested with recurrent, bilateral segmental periphlebitis.

**Observations:** A 32-year-old White man presented with multiple paracentral scotomata in each eye. Examination revealed mild vitreous cell, segmental sheathing of the retinal veins, and inflammation of the paravenous retina in each eye. Multimodal imaging, including optical coherence tomography as well as widefield fundus autofluorescence, fluorescein angiography, and indocyanine green angiography, was consistent with bilateral, segmental retinal periphlebitis with paravenous inflammation and retinochoroidal scarring. Serology showed elevated *B. henselae* antibody titers, but was otherwise unrevealing, and the patient was diagnosed with presumed *B. henselae*-associated ocular inflammation. Treatment with systemic doxycycline (100 mg PO BID) for four weeks improved the patient's symptoms and posterior uveitis. However, after an asymptomatic period of nearly one year, his bilateral pericentral scotomata recurred and posterior segment examination confirmed new foci of retinal periphlebitis in each eye. Re-treatment with doxycycline (100 mg PO BID) for four weeks again yielded improvement, but one month after completing his antibiotic course, his visual symptoms recurred, and we observed additional areas of periphlebitis and paravenous retinitis with associated branch retinal vein occlusions in each eye. This time a dual antibiotic regimen of doxycycline (100 mg PO BID) and rifampin (300 mg PO BID) was administered for three months, with improvement. Over the next eight years, the patient experienced no further disease relapse, and the previous sites of retinal periphlebitis eventually developed perivenous fibrosis with paravenous retinochoroidal scarring.

**Conclusion:** Rarely, patients with *B. henselae*-associated ocular inflammation develop segmental retinal periphlebitis with or without retinal vein occlusion. This form of ocular bartonellosis can recur, requiring multiple courses of antimicrobial therapy.

## 1. Introduction

*Bartonella henselae* (*B. henselae*) is a facultative intracellular human pathogen that causes a systemic infection known as cat scratch disease (CSD), with between 5 and 15% of affected patients developing ocular involvement.<sup>1</sup> Changes in medical practice and improved diagnostics continue to uncover *B. henselae* as the cause of novel forms of inflammatory ocular disease.<sup>2,3</sup> We report a case of *B. henselae*-associated recurrent, bilateral segmental periphlebitis and branch retinal vein occlusions.

## 2. Case history

A 32-year-old previously healthy White man was referred for evaluation of multiple pericentral scotomata in each eye. He first noted blind spots in his right visual field four weeks prior to presentation, followed one week later by similar symptoms in his left eye. On our examination, best-corrected visual acuity was 20/13 on the right and 20/13-1 on the left. Intraocular pressure was 10 mm Hg on the right and 13 mm Hg on the left. Extraocular motility and confrontational visual fields appeared normal and there was no afferent pupillary defect. Anterior segment examination was unremarkable. However, examination of the posterior

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segment revealed mild vitreous cell, segmental sheathing of retinal veins, and inflammation of the paravenous retina in each eye (Fig. 1). Optical coherence tomography through the lesions showed cells in the posterior hyaloid, hyperreflectivity around the venous wall, and increased retinal thickness and inner retinal hyperreflectivity characteristic of retinitis (Fig. 2). Fundus autofluorescence imaging showed the affected areas to be hypofluorescent centrally with a rim of increased autofluorescence. Fluorescein angiography showed focal leakage from the walls of affected retinal veins and the adjacent

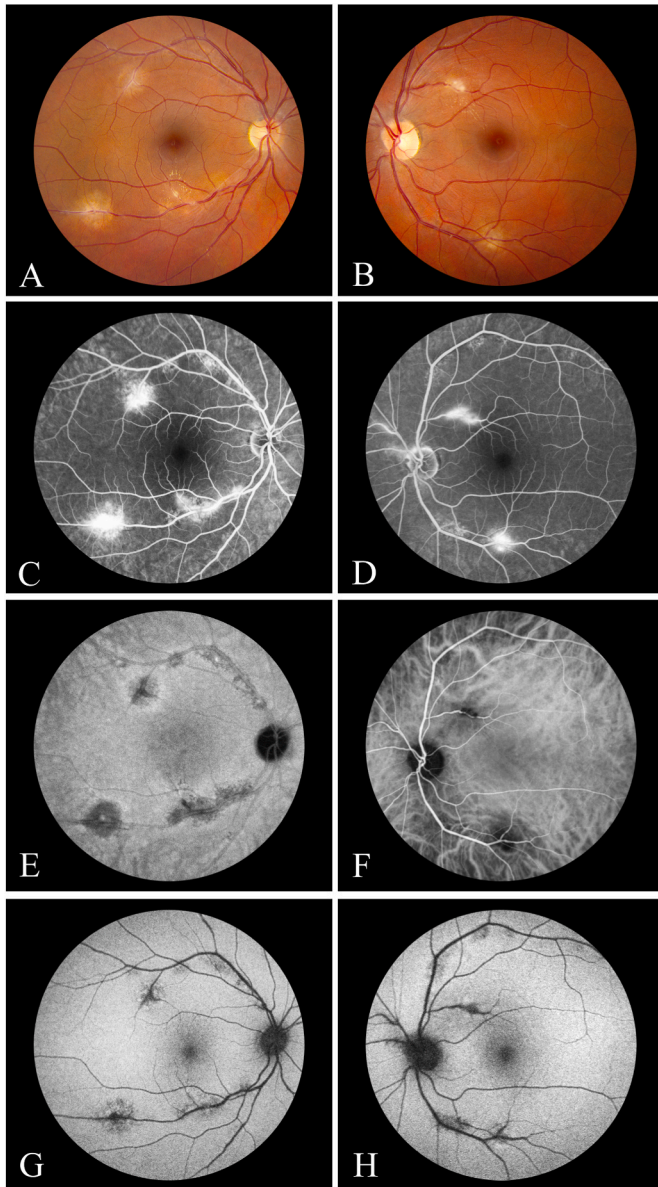
paravenous retina (Fig. 1). Indocyanine green angiography showed hypofluorescence of the choroid adjacent to areas of periphlebitis (Fig. 1). Serologic workup for syphilis, tuberculosis, sarcoidosis, anti-neutrophil cytoplasm antibody-related vasculitides, toxoplasmosis, and human immunodeficiency virus was negative, but elevated IgG *B. henselae* antibody titers (1:64) were detected. The patient was diagnosed with presumed ocular bartonellosis and treated with systemic doxycycline (100 mg PO BID) without systemic corticosteroids for four weeks, with improvement. After an asymptomatic period of nearly one year, this patient experienced recurrent bilateral pericentral scotomata, and we found new foci of retinal periphlebitis in each eye. He was retreated with doxycycline (100 mg PO BID) alone for four weeks, which again led to clinical and symptomatic improvement. However, one month after completing the course of antibiotics, the patient's visual symptoms recurred, and repeat examination identified additional areas of segmental retinal periphlebitis, this time associated with intraretinal hemorrhages, hard exudation, and cotton wool spots suggestive of branch retinal vein occlusion in each eye. A dual oral antibiotic regimen consisting of doxycycline (100 mg PO BID) and rifampin (300 mg PO BID) without systemic corticosteroids was administered and maintained for three months, resulting in resolution of his symptoms and his retinal findings. Repeat examinations of this patient's posterior segment over the next eight years found no evidence of recurrent posterior uveitis, but he developed bilateral, segmental perivenous fibrosis with surrounding retinochoroidal atrophy at the previous sites of periphlebitis (Fig. 3).

### 3. Discussion

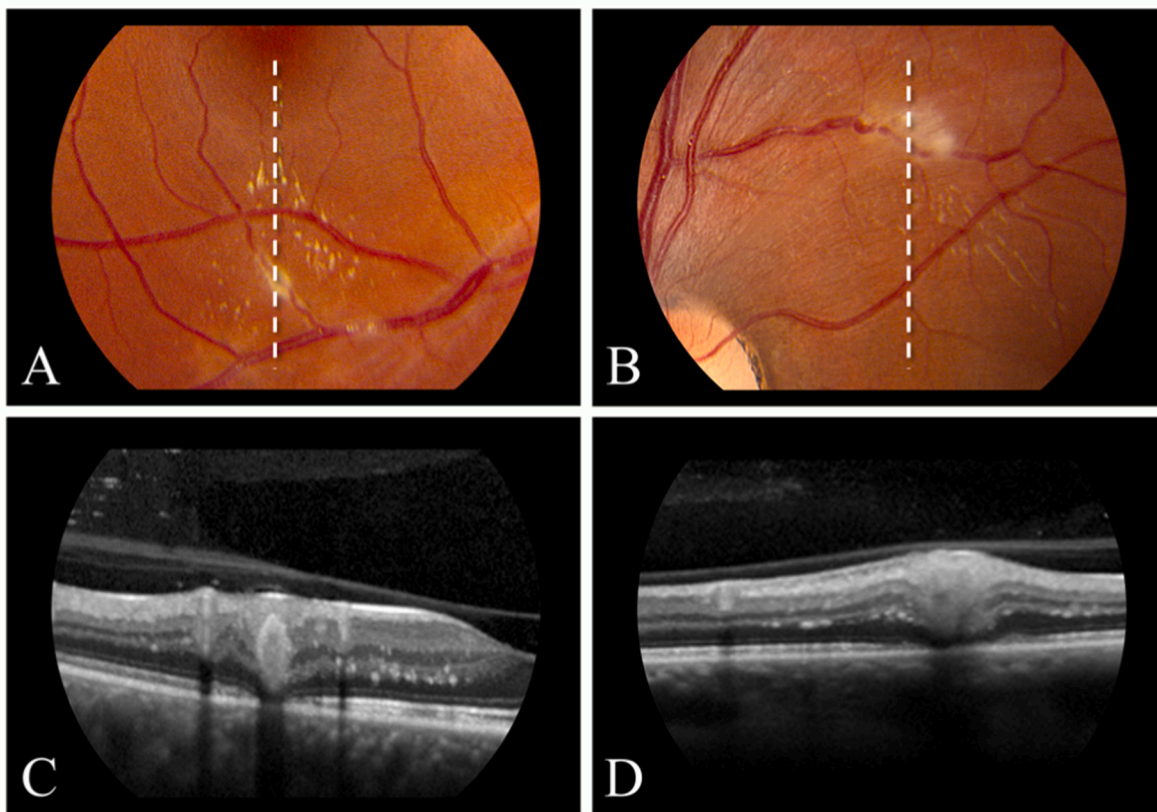
A man with bilateral pericentral scotomata was found to have multifocal, segmental retinal periphlebitis in each eye. Systemic laboratory evaluation detected the presence of antibodies against *B. henselae*. While the patient's symptoms and findings improved transiently following treatment with doxycycline alone, sustained improvement required prolonged treatment with both doxycycline and rifampin. Serial examination and multimodal imaging revealed that this form of posterior uveitis first affects the retinal veins and then the adjacent paravenous retina, posing a risk of branch retinal vein occlusion, and affected areas ultimately develop perivenous fibrosis and paravenous retinochoroidal scarring.

The species *B. henselae*, the most common cause of ocular bartonellosis in humans, is known to incite a wide spectrum of intraocular inflammation. While Parinaud's oculoglandular syndrome, neuroretinitis, multifocal retinitis, and retinal artery occlusion are the common manifestations, patients with *B. henselae*-associated ocular inflammation have also been reported to have iridocyclitis, vitritis, focal retinochoroiditis, branch retinal vein occlusion secondary to vasculitis, disc edema with peripapillary serous retinal detachment, focal optic neuropathy without papillitis, helioid unifocal choroiditis, retinal vasoproliferative lesions, solid, elevated mass lesions affecting the retina, choroid, and optic disc, and bilateral perivascular chorioretinal lesions.<sup>1,4-8</sup> Of note, Chang et al. described a case of isolated, focal phlebitis caused by *B. henselae*.<sup>9</sup>

To our knowledge, only one other case of *B. henselae*-associated ocular inflammation resulting in bilateral perivenous fibrosis with paravenous retinochoroidal lesions has been reported.<sup>7</sup> Sahin described a patient with such findings in the absence of active uveitis, and because a systemic work up only showed elevated IgG *B. henselae* titers, the patient was diagnosed with *B. henselae*-associated ocular disease.<sup>7</sup> Given the appearance of our patient's eventual perivenous fibrosis and retinochoroidal scarring, the two cases appear quite similar. Curi et al. have described a more extensive and severe form *B. henselae*-associated segmental phlebitis with retinochoroiditis in an HIV positive patient.<sup>10</sup> We show through multimodal imaging and longitudinal follow up that this form of *B. henselae*-associated posterior uveitis begins primarily as a segmental periphlebitis (Figs. 1 and 2) with subsequent involvement of the adjacent paravenous retina (Fig. 3).



**Fig. 1.** Color fundus photographs (A and B): Fundus photographs of the right (A) and left (B) eyes showing segmental sheathing of retinal veins with adjacent retinitis, retinochoroidal scarring, and lipid exudation. Fluorescein angiography (FA; C and D): FA of the right (C) and left (D) eyes showing leakage at sites of segmental periphlebitis and retinitis/retinochoroidal scarring. Indocyanine green angiography (ICGA; E and F): ICGA of the right (E) and left (F) eyes showing focal areas of hypofluorescence corresponding to sites of segmental periphlebitis and adjacent retinitis/retinochoroidal scarring. Fundus autofluorescence (FAF; G and H): FAF of the right (G) and left (H) eyes showing focal areas of mottled hyper- and hypofluorescence corresponding to sites of paravenous retinitis/retinochoroidal scarring adjacent to the segments of retinal veins with periphlebitis. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



**Fig. 2.** Color fundus photograph of the right (A) and left (B) eyes with orientation lines for the corresponding vertical Spectral domain optical coherence tomography (SD-OCT) scans (C and D, respectively) showing retinal periphlebitis with adjacent retinitis and exudation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)



**Fig. 3.** Pseudocolor fundus photographs of the right (A) and left (B) eyes taken eight years after presentation showing stable, focal paravenous retinochoroidal atrophy adjacent to areas of resolved segmental retinal periphlebitis.

Knowledge regarding the pathogenesis of *B. henselae*-associated ocular inflammation remains lacking, but *in vitro* studies have uncovered the abilities and tendencies of this organism, providing clues on how it causes disease. Following typical intradermal inoculation, *Bartonella* enter a nonbacteremic phase of infection known as the primary niche, wherein the activity of the bacteria remains largely unknown.<sup>3</sup> *In vitro* studies show that *B. henselae* can invade diverse cell types such as endothelial cells, endothelial progenitor cells, epithelial cells, hematopoietic progenitor cells, and monocytes/macrophages, and it remains possible that one or all of these cell types are involved early on.<sup>3</sup> From the primary niche, the organism seeds the bloodstream and then infects erythrocytes to enable vector transmission. Overall, *B. henselae* appears to be an intravascular, intra-erythrocytic, and endotheliotropic organism with the ability to manipulate a wide variety of cell types, which may explain the diverse possible manifestations of CSD.<sup>3</sup>

Retinal periphlebitis can be observed in a wide variety of eye diseases, making a thorough history and evaluation essential in discerning the correct etiology. The earliest descriptions of preferential inflammation around retinal veins were in patients with tuberculosis, tertiary syphilis, sarcoidosis, multiple sclerosis, Eales disease, human immunodeficiency virus, and early endophthalmitis.<sup>11–18</sup> Kleiner and colleagues then described acute frosted retinal periphlebitis in three patients without any discernible systemic etiology.<sup>19</sup> More recently, retinal periphlebitis has been reported in patients with cytomegalovirus retinitis, melanoma-associated retinopathy, cancer-associated retinopathy, herpes zoster sine herpette, and CSD.<sup>8,20–23</sup>

#### 4. Conclusion

In summary, posterior uveitis manifesting as bilateral, segmental



retinal periphlebitis with adjacent paravenous retinitis can develop in select patients with ocular inflammation arising from *B. henselae* infection. Patients with otherwise unexplained retinal periphlebitis should be asked about risk factors for CSD and should be tested for the presence of *B. henselae* antibodies. Our patient's inflammation recurred and required multiple course of treatment with doxycycline, but ultimately showed sustained response to combined doxycycline and rifampin.

### Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

### Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Written consent to publish potentially identifying information, such as details or the case and photographs, was obtained from the patient(s) or their legal guardian(s).

### Authorship

All listed authors meet the ICMJE criteria.

We attest that all authors contributed significantly to the creation of this manuscript, each having fulfilled criteria as established by the ICMJE.

We confirm that the manuscript has been read and approved by all named authors.

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The authors have no financial or non-financial conflicts pertinent to the information presented in this manuscript.

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