IDCases 39 (2025) e02178

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Tropheryma whipplei infection presenting as indolent endophthalmitis

Rami Waked [a,*], Jeffrey K. Moore [b], Brandon Winward [c], Sophia Ham [b], Howard W. Hoyt [d], Leyla Azis [a]

[a] *Infectious Diseases, MaineHealth Medical Center, Portland, Maine, USA*
[b] *Ophthalmology, MaineHealth Maine Medical Center, Portland, Maine, USA*
[c] *Ophthalmology, UT Southwestern Medical Center, Dallas, TX, United States*
[d] *Ophthalmology, Pen Bay Medical Center, Rockport, Maine, USA*

ARTICLE INFO

Keywords:
Tropheryma whipplei
Whipple's disease
Polymerase Chain Reaction
RNA
Ribosomal
16S
Endophthalmitis
Anti-Bacterial Agents

ABSTRACT

Tropheryma whipplei (*T. whipplei*) infection can be difficult to diagnose due to its variable clinical manifestations and the limitations of standard diagnostic tests. This case describes a 78-year-old male with blurry vision and floaters in his right eye five months after cataract surgery, along with new onset weight loss and arthralgias. Ophthalmologic examination revealed inflammation and posterior vitritis, and vitreous biopsy identified *T. whipplei* via broad-range bacterial PCR, despite negative vitreous cultures and unremarkable flow cytometry. Gastrointestinal endoscopic and cerebrospinal fluid studies revealed no pathological or molecular evidence of the disease, complicating the diagnosis. Treatment with intravenous ceftriaxone followed by oral trimethoprim-sulfamethoxazole for 12 months resulted in resolution of symptoms and inflammation, with normalization of laboratory markers. This case underscores the diagnostic utility of broad-range bacterial PCR in atypical infections and highlights Whipple infection as a differential diagnosis in ocular presentations. Comprehensive interdisciplinary evaluation was critical for effective management.

Introduction

Whipple's disease, caused by *Tropheryma whipplei* (*T. whipplei*), is a rare multisystemic infection causing diverse clinical manifestations [1]. The classic presentation is characterized by diarrhea, diffuse joint pain and weight loss. Ocular involvement, such as uveitis and retinitis, is a rare presentation [1–5]. Diagnosis of this disease is challenging due to its variable presentations, rarity and ability to mimic other conditions [1]. This case highlights the difficulty diagnosing *T. whipplei* infection and the role of molecular diagnostics in ocular infections.

Case

A 78-year-old male presented to his ophthalmologist with right eye blurry vision and floaters five months following a bilateral cataract surgery. His symptoms started 3 weeks before his presentation and were gradual in onset. He also reported a 4.5-kilogram weight loss associated with loss of appetite for a few weeks. Patient did not report any symptoms of fever, chills, night sweats, diarrhea, steatorrhea, abdominal pain, nausea, vomiting, or other extraocular central nervous system symptoms. His past medical history was significant for rheumatoid arthritis for which he receives daily oral prednisone 5 mg and rituximab infusions every 6 months, as well as remote history of latent tuberculosis treated with 9 months course of isoniazid. His physical examination was unremarkable, with no significant palpable lymphadenopathy, or clinical signs of active arthritis. The right eye exam was notable for inflammation and posterior vitritis. A vitrectomy was performed. Samples were sent for bacterial and fungal gram stain and culture, flow cytometry and broad range bacterial PCR and sequencing (Mayo Clinic Laboratories, Rochester, Minnesota). No acid-fast gram stain or culture was performed.

There were lymphocytes and macrophages but no malignant cells appreciated on cytology by the ocular pathologist. Vitreous bacterial and fungal cultures did not show any growth. Flow cytometry was unremarkable. However, broad spectrum bacterial PCR test was positive for *T. whipplei* (cycle time was 22.74). He had elevated C-reactive protein (CRP) to 45.6 mg/L, and erythrocyte sedimentation rate (ESR) to 58 mm/h. Patient was subsequently referred to infectious disease specialist due to clinical suspicion for Whipple infection. Patient underwent an esophagogastroduodenoscopy (EGD) with biopsies obtained

* Correspondence to: Maine Medical Centre, 22 Bramhall St, Portland, Maine 04102, USA.
E-mail addresses: ramiwaked12@hotmail.com, rami.waked@mainehealth.org (R. Waked).

https://doi.org/10.1016/j.idcr.2025.e02178
Received 12 December 2024; Received in revised form 11 January 2025; Accepted 3 February 2025
Available online 4 February 2025

from esophagogastric junction, duodenum and small bowel all showed no evidence of Whipple's disease. This conclusion was based on negative Periodic acid-Schiff (PAS) staining observed in histology and negative PCR results for *T. whipplei* on the duodenal biopsy. A *T. whipplei* PCR blood test (*T. whipplei*, Molecular Detection, Mayo Clinic Laboratories, Rochester, Minnesota) was negative. Despite the lack of neurologic symptoms and given the concern for Whipple eye disease, a lumbar puncture was also obtained showing no pleocytosis, while aerobic/anaerobic culture remained without growth and cerebrospinal fluid *T. whipplei* PCR was negative (*T. whipplei*, Molecular Detection, Mayo Clinic Laboratories, Rochester, Minnesota). He tested negative for human immunodeficiency virus and treponema pallidum blood serologies.

Given the concern for Whipple endophthalmitis and positive *T. whipplei* PCR in vitreous liquid as well as systemic symptoms of weight loss and arthralgias, he was treated with intravenous ceftriaxone 2 gm daily for two weeks, followed by a 12-month course of oral sulfamethoxazole-trimethoprim 800/160 mg twice daily. He completed the antibiotic course without any complications. While on the antibiotic course, he was closely following with his ophthalmologist and infectious disease specialists. The patient was noted to have marked improvement in his eye exam (Fig. 1) and symptoms, as well as improvement of his appetite, weight gain and resolution of arthralgias. Slit lamp exam of the right eye showed < 5 pigmented vitreous cells per high powered field at one year follow up, down from 20 cells per high-powered field initially. OCT (Optical coherence tomography) revealed an epiretinal membrane without edema. His labs showed normalization of CRP and ESR. The antibiotic was discontinued after 12 months of therapy.

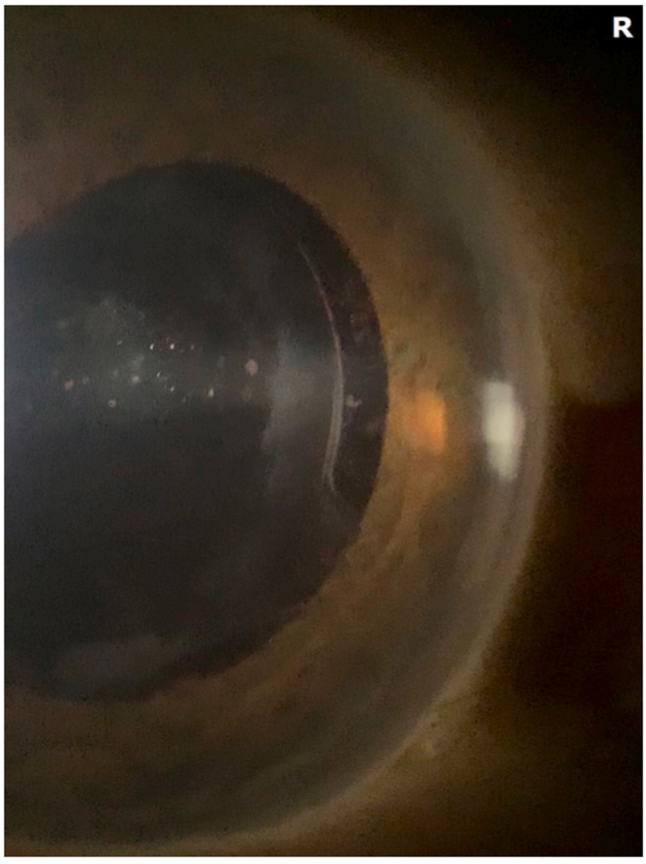

Fig. 1. Anterior segment post vitrectomy. Four and a half months into treatment. Slowly resolving lens precipitates.

Discussion

This case is notable as Whipple infection was diagnosed following a positive broad-range bacterial PCR from vitreous fluid, despite the presence of only some of the classic symptoms. The patient had significant weight loss and arthralgias, symptoms that added to the clinical suspicion for this disease. Blood and CSF *T. whipplei* PCR tests were negative, and gastric and duodenal biopsies showed no signs of the disease. A rheumatoid arthritis flare was considered less likely due to the absence of typical signs of active disease, such as joint swelling. Additionally, the patient's systemic symptoms, including weight loss and the detection of *T. whipplei* in the vitreous sample, pointed toward an infectious etiology. The marked improvement in inflammatory markers, as well as both visual symptoms and arthralgia, following antibiotic therapy, further supported the diagnosis.

Whipple disease is caused by *T. whipplei*, a gram-positive bacillus. This organism is ubiquitous in the environment and has been isolated in stool samples in 1–11 % of asymptomatic individuals and detected in saliva in 0.2 % of healthy patients [6,7]. Whipple's disease is rare and typically progresses slowly over many years or even decades due to insidious replication [1]. It is unclear why certain individuals are more likely to develop the disease. A study conducted in Europe has demonstrated a correlation between the HLA alleles DRB1 * 13 and DQB1 * 06 and Whipple's disease [8]. Immunosuppressive treatment for arthropathy, as in this patient, may accelerate the progression from prodromal symptoms to classic Whipple's disease or trigger intestinal symptoms [1].

While classic Whipple's disease is characterized by malabsorption, chronic diarrhea, weight loss and joint symptoms, the clinical spectrum of disease has significantly expanded to include various distinct disease manifestations [1]. There are localized forms that affect extra-intestinal organs without involving the digestive tract, acute self-limiting infections, and asymptomatic carriers [1,6,7]. Neurologic symptoms may occur in 10–40 percent of Whipple's disease cases, with higher incidence in untreated patients [9]. Endocarditis caused by *T. whipplei* is also possible and is one of the most common causes of culture-negative endocarditis [10]. This case report may be better described as localized *T. whipplei* eye infection with systemic manifestations rather than classic Whipple's disease, which typically involves gastrointestinal pathology. This classification acknowledges the atypical presentation while highlighting the systemic elements observed in this patient.

Most commonly, Whipple's disease diagnosis is made from duodenal biopsies [1]. Despite significant infiltration by *T. whipplei*, the duodenum often appears normal during endoscopy, though it may exhibit pale yellow mucosa, dilated villi, and lymph vessel ectasia. Multiple biopsies from various duodenal sites are recommended due to the patchy distribution of this disease [1,9]. Detection of foamy macrophages with PAS-positive particles in the lamina propria of the duodenum (or other areas) is standard. Ziehl-Neelsen staining helps differentiate *T. whipplei* from acid-fast mycobacteria. Most patients, even those with few gastrointestinal symptoms, have positive duodenal histology [2]. PAS-negative staining does not rule out Whipple's disease, but reduces its likelihood [1]. PAS-positive macrophages can persist long after successful treatment [1]. *T. whipplei*-specific immunohistochemistry is crucial because it can detect the bacteria before typical PAS-positive macrophages appear and may help differentiate atypical mycobacteria and nonspecific PAS staining [11].

T. whipplei specific PCR is useful when clinical suspicion is high with inconclusive histopathology [12]. PCR results are reliable if confirmed by sequencing or by testing multiple *T. whipplei* target genes to avoid false positives [12]. If PCR results are negative but histology is suspicious, prior antibiotic treatment should be considered as it may reduce bacterial load, affecting the PCR results [1,13]. A PCR cycle threshold value below 30 in duodenal biopsies is highly specific for diagnosing Whipple's disease, indicating a high bacterial load [13]. Broad-range bacterial PCR, used in this case, utilizes amplification primers

targeting the bacterial 16S rRNA gene to detect a wide array of bacteria. Post-amplification, the identification of bacteria is conducted by sequencing the amplified DNA and comparing the results to established databases [14]. This test identifies bacteria from sterile sites and is useful for detecting fastidious or slow-growing bacteria, especially after prior antibiotic treatment. False positive results can occur if specimens are contaminated with bacterial nucleic acids from the environment or patient microbiota [14]. However, in this case, a false positive was unlikely due to the patient's systemic and ophthalmologic symptoms and their resolution after antibiotic therapy. The negative *T. whipplei* blood PCR test does not rule out this disease and its clinical utility has not yet been defined [13].

It is recommended to obtain CSF *T. whipplei* PCR testing due to asymptomatic neurologic infection in up to 50 % of patients [1,2]. In a case series of patients with classic Whipple's disease, *T. whipplei* CSF PCR study was positive in 47 % of cases [2]. In our case, CSF studies were performed due to the patient's eye infection. The negative *T. whipplei* CSF PCR aligned with patient's absence of central nervous system symptoms. Patients with localized infection should have specimens collected from clinically affected sites to check for PAS-positive cells followed by PCR analysis to confirm the diagnosis, particularly in immunosuppressed patients and sterile body fluid specimens [1,15].

T. whipplei can mimic various illnesses across multiple organs, posing a diagnostic challenge. Ocular involvement is rare and directed molecular diagnostics for *T. whipplei* in ocular tissues are lacking [3]. In addition, ocular involvement is usually a late presentation in the disease, and typically appears after gastrointestinal and joint symptoms [16]. Only a few cases of ocular Whipple infection have been reported in the literature and they were detected by molecular testing [3–5,16–19]. The most common manifestations of ocular involvement include uveitis, retinitis, and optic neuritis [5,16].

Antibiotic treatment often leads to rapid symptom improvement, with diarrhea and fever resolving in days to weeks and other symptoms improving within weeks [1]. A standard regimen includes a two-week course of intravenous ceftriaxone followed by 12 months of oral Co-trimoxazole. Co-trimoxazole is preferred over tetracycline and is effective, especially for central nervous system disease [1]. A 2010 trial showed that initial therapy with ceftriaxone or meropenem, followed by 12 months of co-trimoxazole, achieved 93 % sustained remission [20]. Alternative regimen includes doxycycline and hydroxychloroquine. Some patients may experience relapses or intolerance to co-trimoxazole.

This case highlights the diagnostic challenges and treatment for Whipple eye infection, emphasizing the importance of comprehensive testing and interdisciplinary care in managing complex Whipple presentations.

Ethical approval

Not applicable.

Fundings

This study did not receive any funding.

CRediT authorship contribution statement

Hoyt Howard W.: Writing – review & editing. **Ham Sophia:** Writing – review & editing. **Azis Leyla:** Writing – review & editing. **Winward Brandon:** Writing – review & editing. **Moore Jeffrey K.:** Writing – review & editing. **Waked Rami:** Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank Dr Daniel Diekema for reviewing this case.

Consent

Written informed consent was obtained from the patient. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

References

[1] Marth T, Moos V, Müller C, Biagi F, Schneider T. Tropheryma whipplei infection and whipple's disease. Lancet Infect Dis 2016 Mar 1;16(3):e13–22.
[2] Lagier JC, Lepidi H, Raoult D, Fenollar F. Systemic tropheryma whipplei: clinical presentation of 142 patients with infections diagnosed or confirmed in a reference center. Med 2010 Sep;89(5):337–45.
[3] Gonzales JA, Doan T, VanZante A, Stewart JM, Sura A, Reddy A, et al. Detection of tropheryma whipplei genome from the aqueous humor by metagenomic sequencing. Ann Intern Med 2021 Sep 21;174(9):1329–30.
[4] Chan RY, Yannuzzi LA, Foster CS. Ocular whipple's disease: earlier definitive diagnosis. Ophthalmology 2001 Dec;108(12):2225–31.
[5] Touitou V, Fenollar F, Cassoux N, Merle-Beral H, LeHoang P, Amoura Z, et al. Ocular whipple's disease: therapeutic strategy and long-term follow-up. Ophthalmology 2012 Jul 1;119(7):1465–9.
[6] Fenollar F, Trani M, Davoust B, Salle B, Birg ML, Rolain JM, et al. Prevalence of asymptomatic tropheryma whipplei carriage among humans and nonhuman primates. J Infect Dis 2008 Mar 15;197(6):880–7.
[7] Fenollar F, Laouira S, Lepidi H, Rolain JM, Raoult D. Value of tropheryma whipplei quantitative polymerase chain reaction assay for the diagnosis of whipple disease: usefulness of saliva and stool specimens for first-line screening. Clin Infect Dis 2008 Sep 1;47(5):659–67.
[8] Martinetti M, Biagi F, Badulli C, Feurle GE, Müller C, Moos V, et al. The HLA alleles DRB1* 13 and DQB1* 06 are associated to whipple's disease. Gastroenterology 2009 Jun;136(7):2289–94.
[9] Ectors N, Geboes K, De Vos R, Heidbuchel H, Rutgeerts P, Desmet V, et al. Whipple's disease: a histological, immunocytochemical and electronmicroscopic study of the immune response in the small intestinal mucosa. Histopathology 1992 Jul;21(1):1–12.
[10] Geissdörfer W, Moos V, Moter A, Loddenkemper C, Jansen A, Tandler R, et al. High frequency of tropheryma whipplei in culture-negative endocarditis. J Clin Microbiol 2012 Feb;50(2):216–22.
[11] Baisden BL, Lepidi H, Raoult D, Argani P, Yardley JH, Dumler JS. Diagnosis of Wihipple disease by immunohistochemical analysis: a sensitive and specific method for the detection of Tropheryma whipplei (the Whipple bacillus) in paraffin-embedded tissue. Am J Clin Pathol 2002 Nov;118(5):742–8.
[12] Moter A, Schmiedel D, Petrich A, Wiessner A, Kikhney J, Schneider T, et al. Validation of an rpoB gene PCR assay for detection of tropheryma whipplei: 10 years' experience in a National reference laboratory. J Clin Microbiol 2013 Nov;51 (11):3858–61.
[13] Meyer S, Puéchal X, Quesne G, Marques I, Jamet A, Ferroni A. Contribution of PCR to differential diagnosis between patients with whipple disease and tropheryma whipplei carriers. J Clin Microbiol 2023 Feb 22;61(2):e0145722.
[14] Liesman RM, Pritt BS, Maleszewski JJ, Patel R. Laboratory diagnosis of infective endocarditis. J Clin Microbiol 2017 Sep;55(9):2599–608.
[15] Marth T. Complicated Whipple's disease and endocarditis following tumor necrosis factor inhibitors. World J Cardiol 2014 Dec 26;6(12):1278–84.
[16] Testi I, Tognon MS, Gupta V. Ocular whipple disease: report of three cases. Ocul Immunol Inflamm 2019 Oct 3;27(7):1117–20.
[17] Campagnolo M, Tognon S, Pompanin S, Sattin A, Cagnin A, Briani C. Whipple's disease without gastrointestinal symptoms: a challenging diagnosis. J Neurol 2016 Aug;263(8):1657–8.
[18] Hujoel IA, Johnson DH, Lebwohl B, Leffler D, Kupfer S, Wu TT, et al. Tropheryma whipplei Infection (Whipple Disease) in the USA. Dig Dis Sci 2019 Jan;64(1): 213–23.
[19] Loiseau V, Chopin MC, Antoine P, Landrieux M, Moritz F. Bilateral panuveitis in Whipple's disease: case report. J Fr Ophtalmol 2024 Aug 3;47(8):104262.
[20] Feurle GE, Moos V, Bläker H, Loddenkemper C, Moter A, Stroux A, et al. Intravenous ceftriaxone, followed by 12 or three months of oral treatment with trimethoprim-sulfamethoxazole in whipple's disease. J Infect 2013 Mar;66(3): 263–70.