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CNS Whipple's Disease Heralded by Retinal Vasculitis

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Case Report

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Abstract

Background: Whipple's disease is a rare, chronic, multi-organ, bacterial infection. The most common presenting manifestation of Whipple's disease is gastrointestinal symptoms such as abdominal pain, weight loss, diarrhea, and migratory non-deforming sero negative polyarthralgias. Although neuro-ophthalmologic symptoms are common in CNS Whipple's disease, uveitis as a presenting sign is rare.

Case Report: A 36-year-old black male presented with the initial complaint of left eye vision loss but left against medical advice, only to return nine weeks later with additional symptoms of right eye visual field loss. Ocular examination revealed panuveitis, vasculitis, optic nerve atrophy left eye, and right homonymous hemianopsia of both eyes. Extensive laboratory testings were all negative. A MRI imaging showed large enhancing lesions in the thalamus, temporal and parietal lobes. A brain biopsy revealed periodic acid-Schiff reagent (PAS)-positive intracytoplasmic organisms within multiple macrophages, consistent with Whipple's disease. After two months of antibiotic therapy, the patient's symptoms and MRI findings were markedly improved.

Conclusion: Although rare, Whipple's disease should be considered in any unexplained chronic uveitis especially if accompanied by CNS, gastrointestinal or migratory polyarthralgia symptoms.

Keywords: Whipple's Disease; Panuveitis; Vasculitis; Opticatrophy; Visual field loss; Tropheryma whipplei

Introduction

Whipple's disease, once thought to be an inflammatory disease of the gastrointestinal tract of unknown origin, was first reported in 1895 by Allchin and Hebb but not until 1907 was it recognized as a unique "intestinal lipodystrophy" disease by the pathologist George Hoyt Whipple which later bared his name. The first case of ocular Whipple's disease was reported in 1949. Although the signs and symptoms of Whipple's disease were well known for years the causative bacterium was only successfully identified as Tropheryma whipplei in 1992.

T. whipplei is an actinomycete organism that often appears in environments like soil and animal's wastes. The disease occurs predominantly in middle age Caucasian males and is extremely rare with approximately 1000 reported cases to date [1]. Rickman reported one case of Whipple's disease of the eye without any apparent CNS or gastrointestinal involvement [2]. Most clinical eye manifestations are nonspecific including uveitis, retinal hemorrhage,, papilledema, cornea ulcer, chemosis, glaucoma, epiphora, and optic atrophy, thus making a proper diagnosis is quite difficult leading to delays in treatment and poor prognosis. The purpose of this report is to describe a case of ophthalmic signs and symptoms that can be the first manifestation of Whipple's disease.

Case Report

History

A 36-year-old African American male presented to the emergency department with a one-day history of sudden decreased vision, redness, and pain with eye movement of the left eye. Two months prior, he had been treated for conjunctivitis in the left eye which had resolved. He had a history of untreated hypertension. His social history was positive for tobacco use and employment within the last year as a sewer worker. There was no recent history of travel or trauma. Reviews of systems were negative for abdominal symptoms, headache, weight loss, and arthritis.

Best-corrected visual acuities were 20/10 in the right eye and count fingers at 2 feet in the left eye and no improvement with pinhole. There was a grade 1 afferent pupillary defect on the left eye. Ocular motility and confrontation visual fields were normal in both eyes. Intraocular pressure was 17 mmHg in both eyes via Goldmann tonometry. Right eye anterior segment examination was unremarkable. The left eye had diffuse hyperemia and grade 2+ injection with circumlimbal flush, grade 4+ cells and 2+ flare and a 0.5mm hypopyon. Posterior synechiae were presented at seven and ten o'clock. Dilated fundus examination was normal on the right. Left eye revealed grade 2+ vitreous cells, mild disc edema and vascular sheathing with a frosted branch appearance involving the inferior temporal arcade. Intraretinal and preretinal hemorrhages occupied a two-disc diameter area of necrosis inferior to the optic nerve. Panuveitis OS was made with differential diagnosis of CMV retinitis, sarcoidosis, and TB were suspected. HIV, immune panel, RPR, MHA-TP, ACE, Lysozyme, HLA-B27, and CXR were ordered and admission for further evaluation was recommended; however, the patient declined and left against medical advice.

Nine weeks later, he returned with chief complaint of persistent poor vision on the left and a one-week history of headache with sudden loss of vision of the temporal field on the right. This was preceded by a witnessed black out spell with no shaking, abnormal movements, or incontinence. After awaking he experienced numbness and tingling over his whole right side accompanied by headache and visual loss. Eight weeks prior, he had noted wrist and elbow pain. Four weeks prior, he had trouble with short-term memory and developed paranoid ideation. Patient appeared oriented times three and no slurred speech. He admitted that he has been taking 800 mg Ibuprofen and Tylenol for headaches as needed.

Diagnostic Data

On examination, his vision was 20/20 on the right with some eccentric viewing and 20/200 on the left. A grade 1 afferent pupillary defect was still present on the left. Color vision was 12/12 OD, 1/12 OS. Motility was full and unrestricted. A right homonymous hemianopia was found on confrontation field and confirmed full threshold visual field test (Figure 1).

Humphrey Visual Field 30-2 showed depression consistent with right homonymous hemianopsia on right eye and diffused depression on the left eye consistent with optic atrophy. Intraocular pressures were 20 mmHg OD and 18 mmHg OS. Anterior segment showed normal findings right eye and posterior synechiae at 6 & 9 o'clock in the left eye. Fundus examination revealed normal optic nerve and retina right eye but disc pallor, arteriolar sheathing and attenuation involving the inferior temporal arcade left eye (Figure 2a, 2b, & 2c).

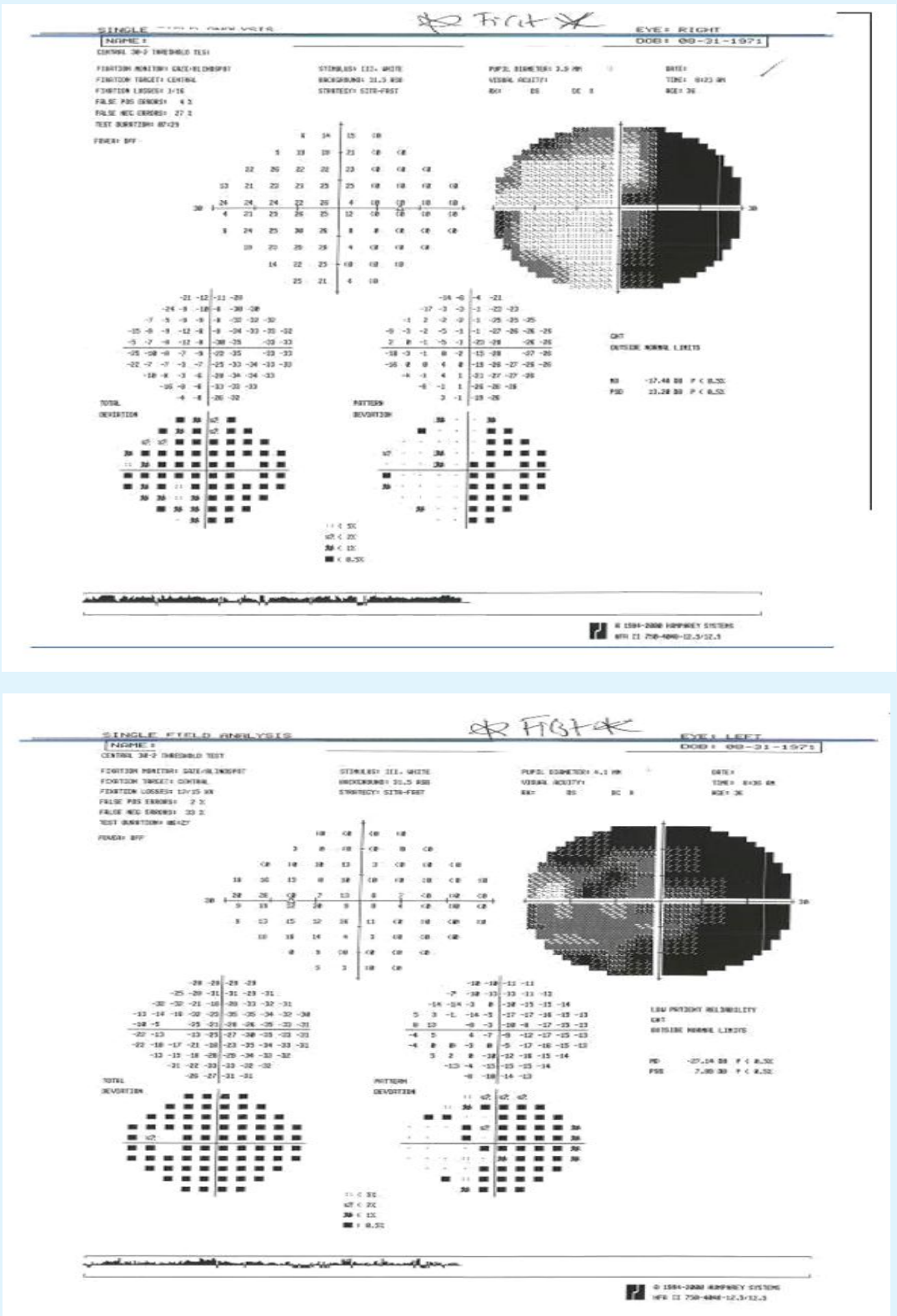


Figure 1: Humphrey Visual Field 30-2 showed depression consistent with right homonymous hemianopsia on right eye and diffused depression on the left eye consistent with optic atrophy.

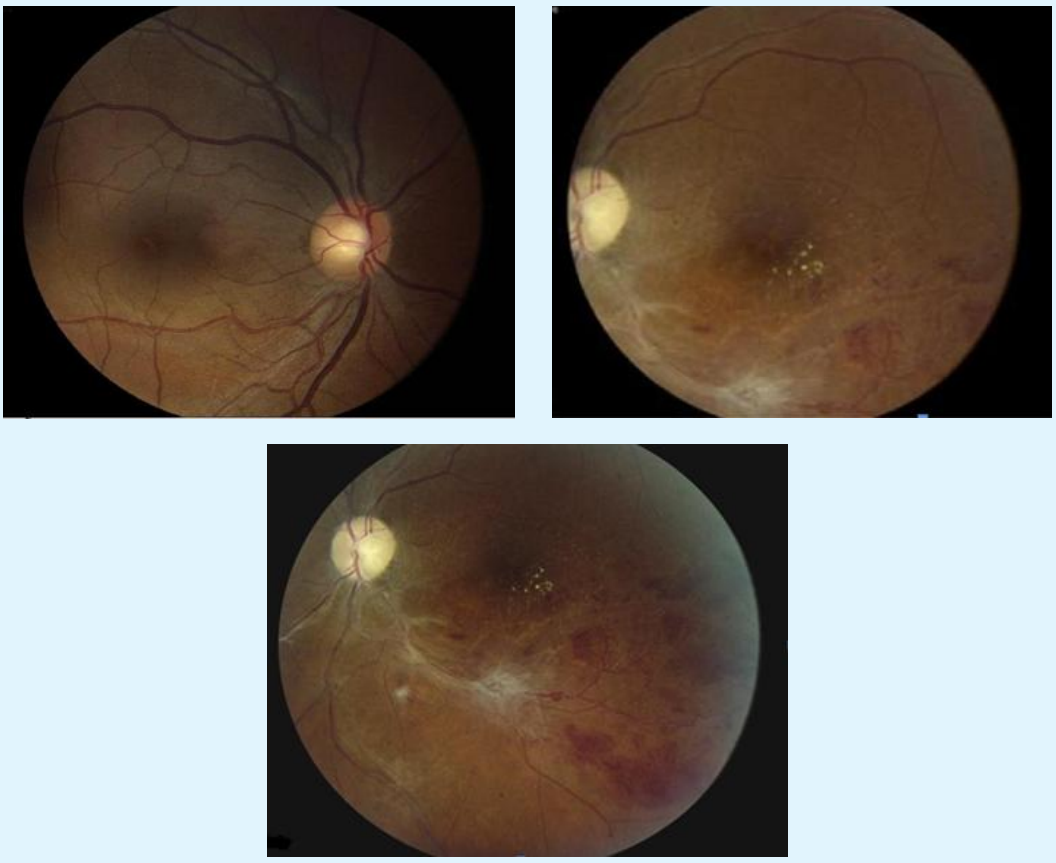


Figure 2a, 2b, 2c: Fundus photos showed normal retina OD but disc pallor, diffuse retinal hemorrhages and exudates involved the macula, arteriolar sheathing and attenuation involving the inferior temporal arcade OS.

Diffuse retinal hemorrhages and exudates involved the macula and inferior temporal retina appeared less active than when originally seen 9 weeks prior. Neurologic examination uncovered a proximal weakness in the right leg. Differential diagnosis of chronic panuveitis left eye secondary to infections or immune-mediated (Table 1) and right temporal homonymous hemianopsia right eye with high suspicion for stroke secondary to uncontrolled hypertension and noncompliance to medication were suspected. Stat laboratory workups, CT scan, and neurology consult were ordered. Head CT scan found a ring enhancing mass with central hypodensity in the left basal ganglia. Sedimentation rate was 89mm/hr. Antithrombin III and Lysosyme were slightly elevated at 148 and 23. ANA, HIV, HLA-B27, Lyme titers, RPR, RF, CXR, and PPD were negative. Differential diagnosis at this point is: metastic or neoplastic disease. ANCA, Bartonella, Brucella, CMV IgG/IgM, Cryptococcus, Coccidioides, MHA-TP, Toxoplasmosis IgG/IgM, West Nile IgG/IgM, Toxocara antibody, and urine Histoplasmosis were ordered and results were negative (Table 2).

Infection	Immune-mediated	Metastic/Neoplastic Masquerader	Syndromes confined primarily to the eye
Lyme disease	Sarcoidosis	Leukemia	Sympathetic ophthalmia
HIV/CMV	Behcet's	Lymphoma	Leber's neuroretinitis
Herpes virus	Ankylosing spondylitis	Syphilis	Acute retinal necrosis
Toxoplasmosis	Reactive arthritis		

Leprosy	Systemic lupus erythematosus		
Tuberculosis	Vogt-Koyanagi-Harada		
Whipple's			
West Nile			
Bartonella			

Table 1*:* Differential diagnose of panuveitis/chronic Vasculitis.

Test	Result
ESR	89 (H)
RPR	Negative
ACE	Negative
ANA	Negative
RF	Negative
HLA-B27	Negative
Antithrombin III	148 (H)
MHA-TP	Negative
Lyzosyme	23 (H)
C-Anca	Negative
HIV	Negative
Lyme titer	Negative
Brucella	Negative
Bartonella	Negative
Cryptococcus	Negative
Coccidioides	Negative
CXR	Negative
VZV	Negative
Toxoplasmosis IgG/IgM	Negative
West Nile IgG/IgM	Negative
Urine Histoplasmosis	Negative
Toxocara antibody	Negative
Cardioechogram	Negative
Esophagogastro- duodenalscopy biopsy	Negative T.whipplei
CT of chest, abdomen, & pelvis	Negative lesion

CSF studies	Results
T. whipplei DNA PCR	Negative
Toxo PCR	Negative
Gram stain	Negative
HSV/VZV	Negative
Crypto	Negative
M. Tub	Negative
India Ink	Negative

Table 2: Laboratory tests.

Brain MRI (Figure 3) revealed left thalamic/left medial temporal lobe peripherally enhancing mass/hemorrhage with surrounding T2/FLAIR signal with similar lesion seen in the left posterior parietal lobe. The findings were

"consistent with a possible metastatic lesion or toxoplasmosis given the proper clinical setting." Chest, abdomen, and pelvis CT found no evidence of malignancy. Spinal fluid examination revealed 41 WBC's, normal protein, negative gram Cryptococcal, and Indian ink stain. HSV/VZV, mycobacterium tuberculosis, Toxoplasmosis and *T. Whipplei* spinal fluid PCR were negative. Esophagogastroduodenoscopy (EGD) with biopsy was negative for *T. Whipplei*.

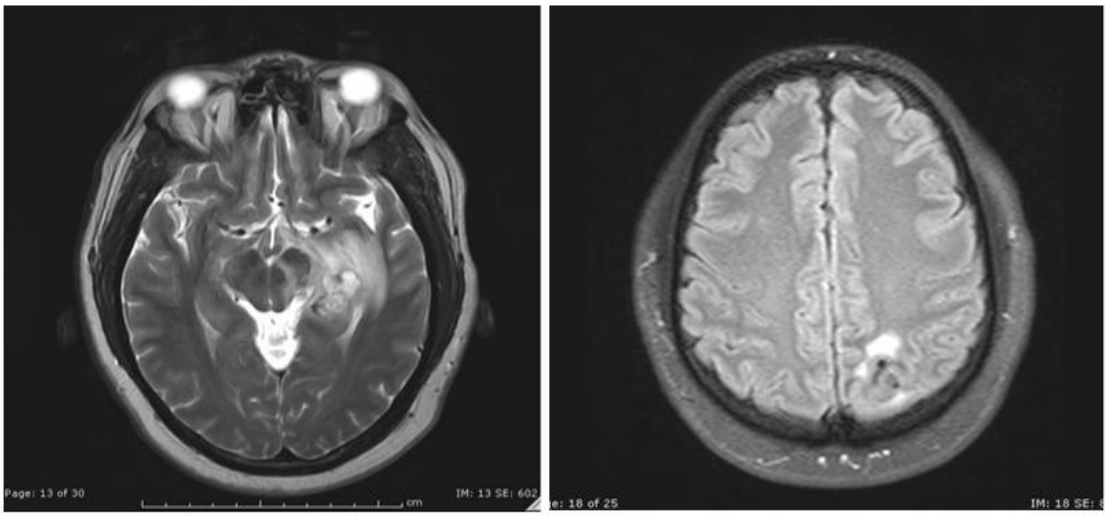


Figure 3a, 3b: Brain MRI showed left thalamic/left medial temporal lobe peripherally enhancing mass with surrounding T2/FLAIR. Similar mass in the left posterior parietal lobe.

Diagnosis

A brain biopsy was performed which revealed foci of reactive changes, combined with the presence of intracytoplasmic periodic acid-Schiff reagent (PAS)-positive organisms within macrophages (Figure 4) which were consistent with a diagnosis of cerebral Whipple's disease (Figure 5). Cultures were not performed.

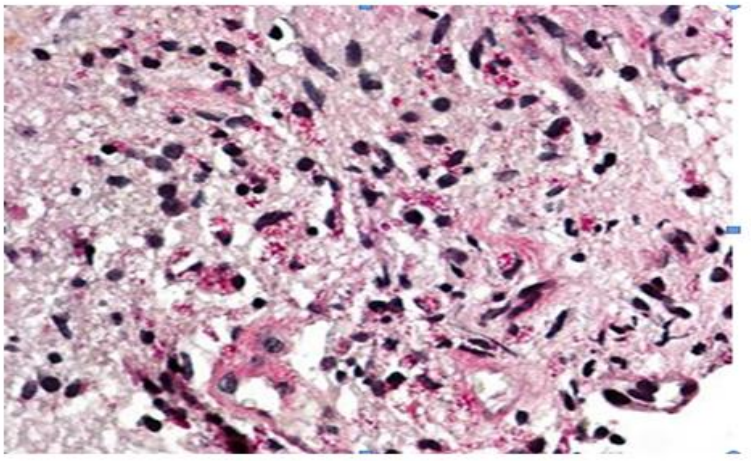


Figure 4: Brain biopsy revealed (+) Periodic acid-Schiff reagent (PAS) intracytoplasmic organisms within multiple macrophages.

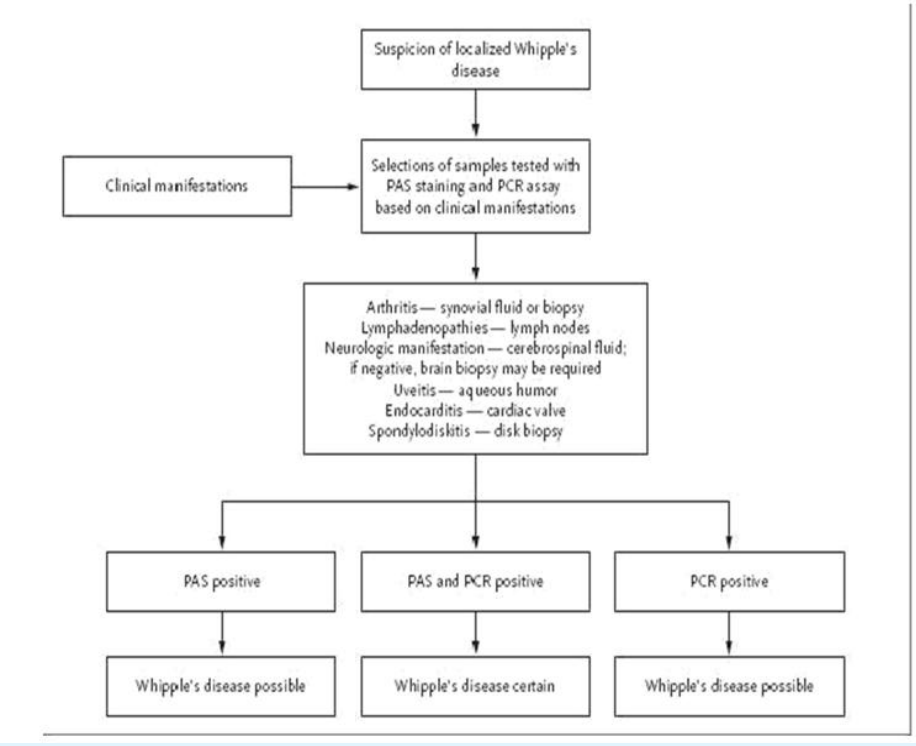


Figure 5: Step in diagnosis.

Treatment and Follow-up

The patient was treated with IV Rocephin for a total of four weeks followed by double strength Bactrim. Repeated MRI scan a month after treatment (Figure 6).

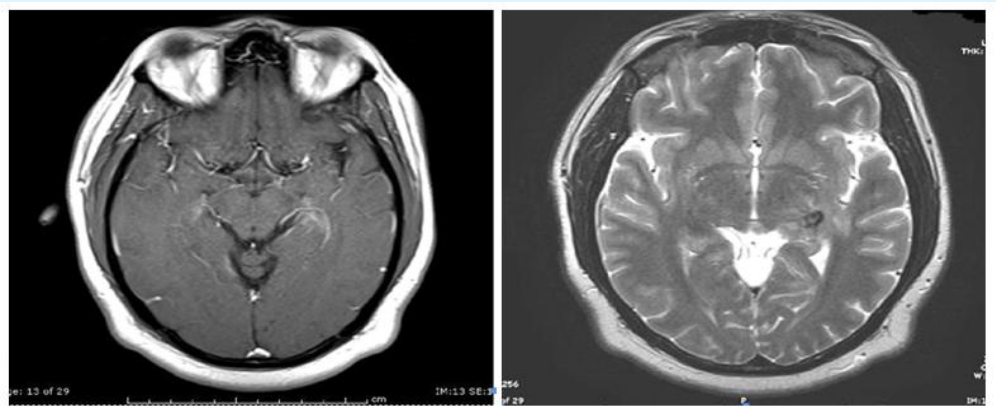


Figure 6a, 6b: Four weeks after treatment, a repeated MRI scan showed significant improvement of the left thalamus, left posterior parietal and left medial temporal lobe lesions.

Showed significant improvement of the left thalamus, left posterior parietal and left medial temporal lobe lesions. At the same time, ophthalmologic examination found no change in visual acuity or ocular symptoms but new pre-retinal hemorrhages were noted (Figure 7a & b).

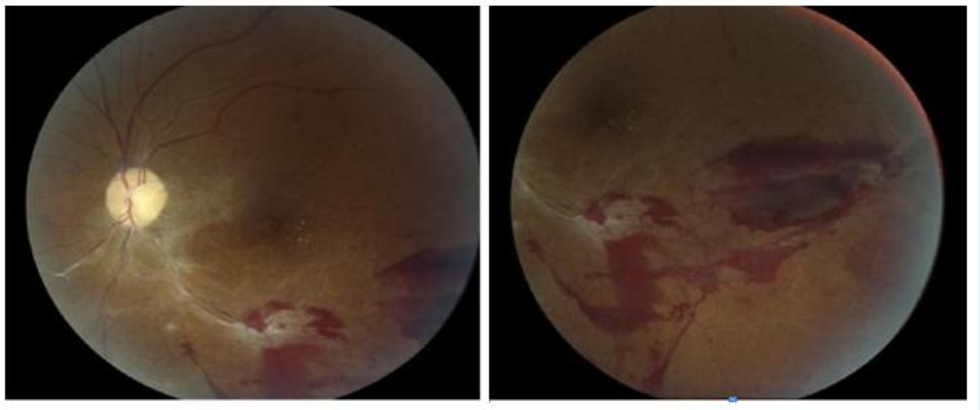
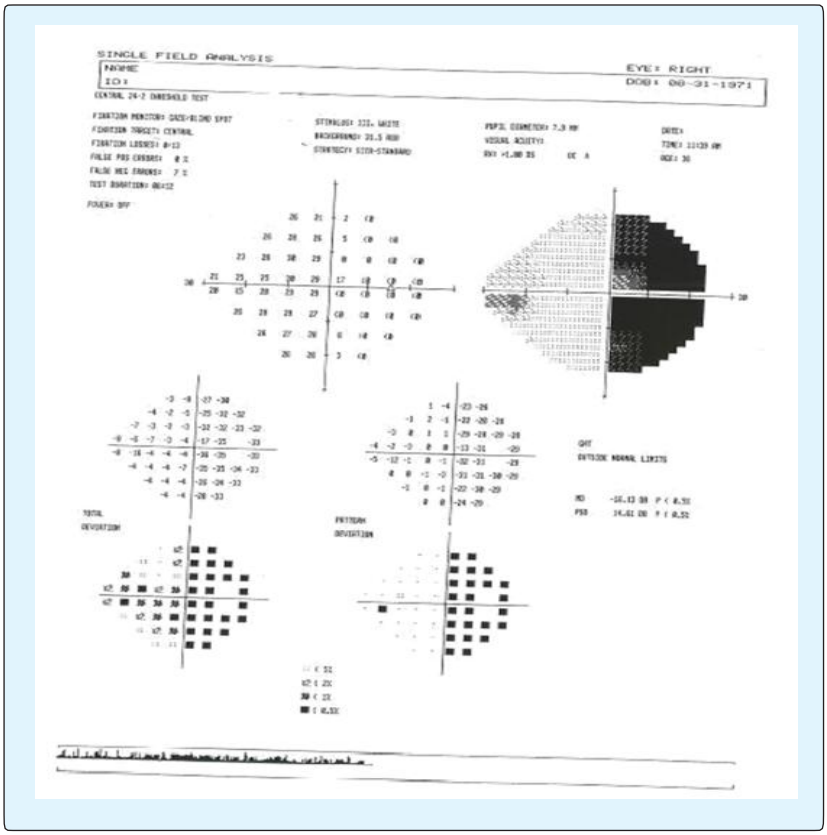


Figure 7a, 7b: OS had new pre - retinal hemorrhages at 4 weeks post-treatment.

One month later, a right homonymous hemianopia OD and generalized depression OS remained on full threshold visual field test but pre-retinal hemorrhage was improved (Figure 8 & 9).



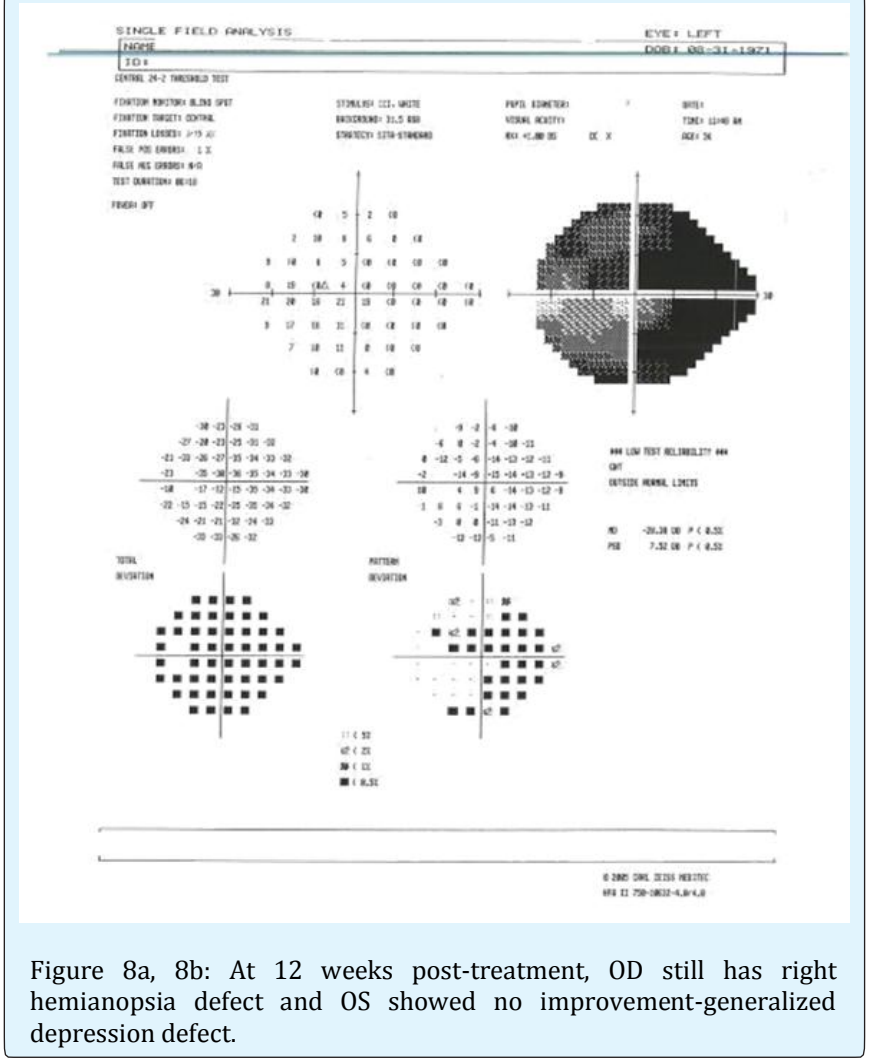


Figure 8a, 8b: At 12 weeks post-treatment, OD still has right hemianopsia defect and OS showed no improvement-generalized depression defect.

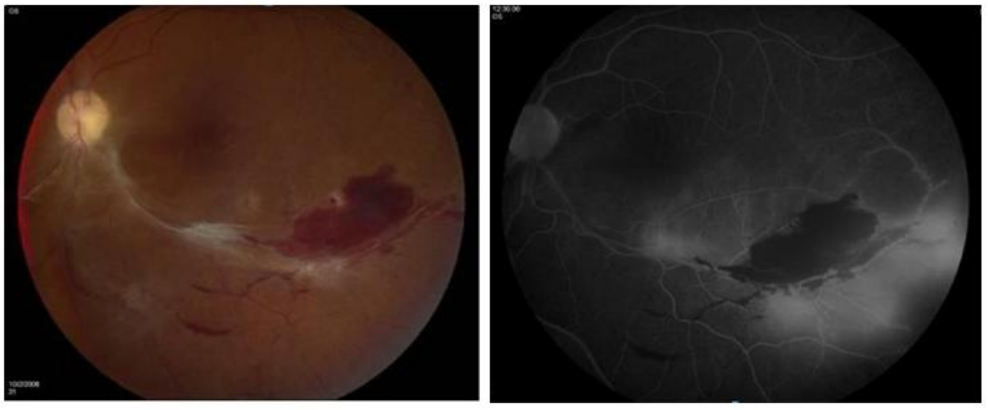


Figure 9a, 9b: At 12 week's post-treatment, pre-retinal hemorrhage OS improved.

Discussion

Whipple's disease is a rare, chronic, multi-organ, bacterial infection that primarily involves the gastrointestinal tract and its lymphatic drainage in middle age men. The most common presenting manifestations of Whipple's disease are weight loss, diarrhea, migratory non-deforming seronegative polyarthralgias and abdominal pain. Extra intestinal involvement is found primarily in the central nervous system, lungs, and heart, although other sites including the eye may be affected. Ocular inflammation may occur alone or with gastrointestinal, neurologic, or other systemic manifestations (Table3).

Ophthalmic (4)	Systemic	Neurologic
Uveitis/Panuveitis,Vitritis	Diarrhea (80%)	Supranuclear ophthalmoplegia
Papilledema	Weightloss	Cognitive impairment
Retinal hemorrhage, cappillary occlusion	Migratory non-deforming seronegative polyarthralgias (70%)	Oculomasticatory myohythmia=Pathognomonic (4)
Corneaulcer	Arthritis	Ataxia
Chemosis,	Lymphadenopathies	Upper motor neuron disorders
Glaucoma	Spondilodiskitis	Headaches
Optic atrophy	Endocarditis	Dementia
Epiphora	Fever?chill	Meningitis
Retinal Vasculitis	Increased skin pigmentation	Seizures & somnolence
Exudates/Hypopyon	Chronic nonproductive cough	Myoclonus
Superficial punctate Keratitis	Pleural effusion/chest pain	

Table 3: Signs and symptoms of Whipple's.

The classic Whipple's disease affects the gastrointestinal tract causing diarrhea, weight loss, and migratory arthritis. Approximately 33% of patients presented with neurologic signs of cognitive impairment and supranuclear ophthalmoplegia [3]. Although less common, oculomasticatory myorhythmia is pathognomonic of the disease. Central nervous system (CNS) involvement can present in classic Whipple's in recurrence of the disease or in isolation [3]. Less common is the findings of cardiac and ophthalmic signs.

Roughly 15% of patients with Whipple's disease do not have the classic signs and symptoms of the disease. Members within this group can present with isolated neurologic, ocular or both findings without histologic evidence of intestinal involvement [3]. The most common neurologic findings are cognitive impairment, supranuclear ophthalmoplegia, ataxia, and upper motor neuron disorders. Oculomasticatory myorhythamia, (consisting of pendular mystagmus or smooth vergent mystagmus associated with tongue and mandibular myoclonus) although less common is pathognomonic for the disease [4].

Chan, et al, reported 77 cases of neurologic Whipple's with four involving the CNS only, 10 with CNS and ocular findings, and 21 cases of isolated ocular involvement [4]. Ophthalmic signs and symptoms can be the first manifestation of

Whipple's disease as described in the case presented here. Intraocular signs include: vasculitis with vitreous, hemorrhages, exudates, capillary occlusion, vitritis, panuveitis, and optic atrophy [4]. The presence of micro-organisms in the retina of patient's with a diagnosis of Whipple's disease has been proven in several instances [1,5]. More recently the presence of *T. whipplei* in the retina and vitreous has been established by diagnostic polymerase chain reaction (PCR) [4].

The exact pathophysiology of Whipple's disease is unknown. There are predisposing factors such as male sex, positive HLA-B27, and occupational exposure to sewage material. One possibility is fecal oral transmission followed by invasion of tissues in those patients whose immune system is compromised in a manner yet to be defined. A proposed mechanism is due to defective macrophages given their abundance in infected tissues [3,6]. Recommended criteria for a definitive diagnosis of Whipple's disease are PAS staining of intracytoplasmic inclusions within macrophages and positive PCR for *T. whipplei* [3]. PAS staining is non-specific [3] and can be

present in *Mycobacerium avium* and Histoplasmosis disease processes.

PCR may also be negative in denocarditis and CNS Whipple's disease [7-9].

In this case, the combination of PAS positive intracytoplasmic macrophage inclusions on brain biopsy, an otherwise negative workup, together with the ocular findings strongly suggested Whipple's disease. Marked improvements of the brain lesions and systemic symptoms with IV Ceftriaxone lead to a definitive diagnosis of Whipple's disease. Although brain lesions cleared and ocular symptoms improved, permanent optic atrophy and the visual defect remained (Figure 7). Ocular signs appeared to worsen slightly after one month of treatment. However, two months later, the vasculitis showed signs of resolution (Figure 8). It is possible that retinal involvement in this case was due to an immune hypersensitivity reaction without the actual presence of organisms in the retina [5,10].

CNS involvement is a feared complication with a poor prognosis [11] and recurrences are common even after an initial response to antibiotics [1]. Re-infection is also a real concern in treated patients given that *T. whipplei* is common in the environment and these patients may have a predisposing immune defect [5,11,12]. Treatment for CNS and Ocular Whipple's disease remains unclear. Current recommendations include four weeks of IV ceftriaxone followed by 1-2 years of oral double strength Trimethoprim/Sulfamethoxazole (Bactrim) which was first proposed for its ability to penetrate the blood brain barrier [13]. But even with antibiotic treatment, CNS Whipple's tends to relapse.

Conclusion

In summary, we presented a patient who initially sought medical attention for ocular complaints and was later found to have CNS Whipple's disease diagnosed by a brain biopsy. He was treated with IV ceftriaxone and oral Trimethoprim/Sulfamethoxazole with improvement of both CNS and systemic symptoms. Although rare, Whipple's disease should be considered in any unexplained chronic uveitis especially if accompanied by CNS, gastro-intestinal, or migratory polyarthralgia sysmptoms.

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