Unexplained dyspnea in a man with recurrent Whipple's disease

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BACKGROUND

- Whipple's disease (WD) is a rare, multi-system infection caused by the gram-positive bacterium *Tropheryma whipplei,* an environmental pathogen found in soil, sewage, and human feces.
- Most exposed will clear the infection or become asymptomatic carriers, with a much smaller proportion developing clinical disease.
- WD classically presents with diarrhea, weight loss, and arthralgias/arthritis, though central nervous system (CNS) and cardiac involvement are also common.

PATIENT CASE

A **65-year-old man** with a history of **Whipple's disease (2004), asthma, and smoking** presented to the emergency department with hypercapnic respiratory failure.

INITIAL PRESENTATION (2004)

- Presented with 2 years of bilateral wrist arthralgias of unknown etiology (treated with hydroxychloroquine) followed by 9 months of migratory arthralgias, weight loss, and progressive neurologic symptoms including insomnia and personality changes.
- Physical examination revealed vertical gaze palsy, myoclonus, ataxia, cognitive impairment (MMSE 23/30), and oculomasticatory myorhythmia, a pathognomonic finding of CNS WD.
- He underwent duodenal biopsy which confirmed WD. TTE revealed thickening of the aortic valve concerning for infective endocarditis.
- He was treated for WD with presumed neurologic and cardiac involvement with 6 weeks of ceftriaxone followed by 12 months of trimethoprim-sulfamethoxazole with improvement.

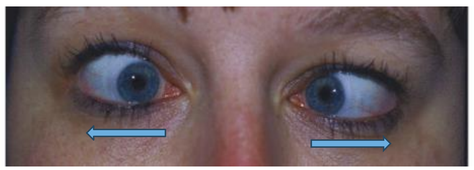


Figure 1. Oculomasticatory myorhythmia: rhythmic convergence-divergence nystagmus with concurrent contractions of the masticatory muscles

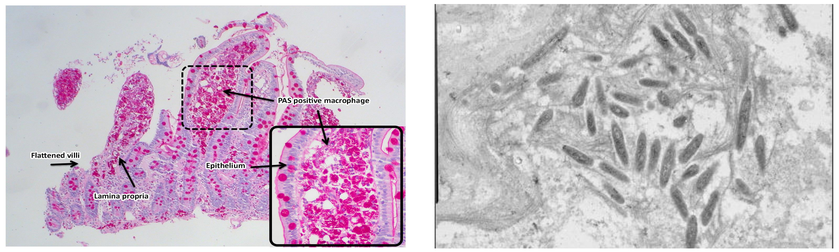


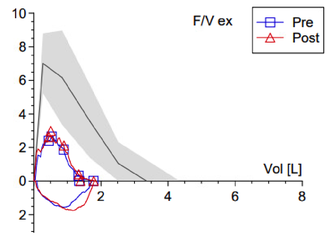
Figure 2. PAS stain (left) and electron microscopy image (right) of duodenal biopsy in patient with WD

ACUTE CARE PRESENTATION (2024)

- In 2024, he re-presented with several months of migratory arthralgias and weight loss. Repeat duodenal biopsy was **PCR positive for *T. whipplei***. TTE demonstrated no evidence of infective endocarditis and CSF PCR was negative. He was started on ceftriaxone 2g IV q24h for presumed recurrence of WD.
- One week later, he presented to the emergency department with progressive dyspnea and orthopnea.
- On examination, he was vitally stable [BP 135/95, HR 92, RR 18, SpO2 96% on room air, afebrile]. There were symmetric vesicular breath sounds with no wheeze. Neurologic examination revealed diffuse fasciculations, muscle atrophy, and hyperreflexia.
- Laboratory investigations revealed a respiratory acidosis (VBG 7.29/67/31). WBC and differential were within normal limits. NT-proBNP was below threshold (<50 ng/L). Chest x-ray was normal. Chest CT demonstrated para-aortic and mediastinal lymphadenopathy raising suspicion for a low-grade lymphoproliferative disorder.
- He was started on BiPAP. His ceftriaxone was increased to 2g IV q12h due to concern for neuromuscular weakness secondary to CNS WD.

INVESTIGATIONS

- Pulmonary function testing revealed reduced TLC, proportional reduction in FEV1 and FVC, and reduced inspiratory muscle strength (MIP) suggestive of diaphragmatic weakness. He was initiated on nocturnal BiPAP.
- EMG/NCS demonstrated diffuse active and chronic denervation in the cervical, thoracic, and lumbosacral regions, concerning for a motor neuron disorder.



CASE RESOLUTION

- Based on physical examination and EMG/NCS, he was diagnosed with an **ALS-like syndrome**, believed to be induced by WD (mediated by immune dysfunction) with other considerations including paraneoplastic syndrome and primary ALS.
- He completed 6 weeks of ceftriaxone and continues on trimethoprim-sulfamethoxazole and doxycycline with the plan for life-long prophylaxis.
- He underwent outpatient endoscopic ultrasound-guided fine needle aspiration biopsy of his paraesophageal lymphadenopathy which was negative for malignancy.
- He is being followed by a neuromuscular specialist and is currently undergoing IVIG therapy with no improvement in symptoms to date.
- If he does not improve after completing IVIG therapy, then a sporadic motor neuron disease such as ALS will be the most likely diagnosis.

CONCLUSIONS

- In cases of respiratory failure without a clear cardiac or pulmonary etiology, neuromuscular weakness should be considered.
- Orthopnea is a cardinal manifestation of diaphragmatic weakness.
- WD can mimic many disease processes (gastrointestinal, rheumatic, and malignant) and while rare, it should be considered, particularly where there is diagnostic uncertainty.
- While this is the first reported case of WD manifesting as an ALS-like syndrome, CNS WD can resemble nearly any neurologic condition; the most common manifestations are cognitive impairment, neuropsychiatric symptoms, and supranuclear ophthalmoplegia.

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