Case Report

A Case of Whipple's Disease: A Very Rare Cause for Rapidly Progressive Dementia

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ABSTRACT

Introduction: Whipple's disease (WD) is a very rare systemic disease caused by the gram-positive bacillus Tropherymawhippleii 1st described in the year 1907. It is a disease with multisystem involvement and high degree of suspicion is needed for diagnosis. However the classical (OMM)oculomasticatory (OFMM)oculofacial-skeletal myorhythmia clubbed with dementia, head ache and other neurologic features should deserve an attempt to confirm whenever possible and therapeutic trial as it is one of the treatable dementias. Males are more affected and probable route of infection is oral though clustering of cases is not reported so far. **Case Report:** 63 year old hypertensive patient presented with abdominal pain, weight loss, dementia, ataxia, extrapyramidal features, falls, up gaze palsy,oculomastigatory skeletal myorhythmia,skin of the face showing nodules which were pigmented and itchy fallowing HAJ pilgrimage.. Investigations for immune mediated,vascul itic,paraneoplastic, sarcoid were noncontributory. Duodenal biopsy showed nonspecific changes. MRI was consistent with changes reported in Whipples. Patient responded to treatment of Whipples disease. **Discussion and Conclusion:** Our patient presented with the typical and unique oculomastigatory myorhythmia clubbed with systemic features of whipplesdisese and showed response to treatment. Limitation of our report we could not do PCR due to lack of availability. This case is being reported for its rarity and to create awareness regarding the typical eye movements.

Key words: *Oculomastigatory dysrhythmia, treatable dementia, Whipple's disease*

INTRODUCTION

Whipple's disease (WD) is a very rare systemic disease caused by the Gram-positive bacillus *Tropheryma whipplei*. In the year 1907, George Hoyt Whipple described a case of intestinal lipodystrophy in a physician who died with a wasting disease. Allchin and Hebb reported a condition called intestinal lymphangiectasia 18 years before the description by Whipple. Morgan in 1961, reviewed the blocks and identified the periodic acid-Schiff (PAS) positive diastase negative,

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Gram-positive material in the macrophage considered probably intracellular.[1] This can be identified in macrophages, intestinal epithelium, endothelial cells of capillaries, lymphocytes, plasma cells, brain, and skin. From small intestine biopsy, 16s RNA gene sequence has been identified. Electron microscope shows a plasma membrane surrounded by two more layers making it trilamellar, and currently, four different genotypic variants are detected.[2]

Only about 1000 cases are so far reported in literature. Males are more affected than females.[3] Patients present with joint pains, fatigue, weight loss, loose stools, abdominal pain, cardiac, pulmonary, cutaneous features, and postmortem evaluation of the index patient revealed in the intestine rod-shaped structures not staining with aniline dyes. The disease is commonly reported from Europe and North America. From India, only two reports are available to our knowledge from patients who visited other nations.[4,5] Biopsy was initially negative and later showed the PAS-positive agents in repeat biopsy.

Pathogenesis

The method of infection not known; probably oral by contaminated material from soil. Defective T-lymphocyte function especially circulating CD11b (integrin alpha) which is important for macrophage activation is affected.[6] Deficiency in the production of interleukin 12 in monocyte and macrophage with reduced capacity to produce interferons and macrophage activation defect is probably the cause of vulnerability for disease.

Pathology

There is generalized cerebral atrophy with 1–2 mm size granulomas in periventricular, subependymal, and diffuse parenchymal regions. These granulomas contain PAS-positive infiltrates with areas of vacuoles and demyelination and infarcts.

Clinical features

CNS involvement is reported in 20%–40% which includes dementia, headache, eye movement disorder, myoclonus, oculomasticatory myorhythmia (OMM), oculofacial-skeletal myorhythmia[7] which is pathognomonic in addition to other involuntary movements, epilepsy, cerebellar ataxia, dementia, ophthalmoplegia, vertical gaze palsy, sleep changes, decreased or altered appetite due to hypothalamic involvement and meningitis, and cortical blindness are reported.[8] OMM characterized by pendular convergent-divergent oscillations of the eyes, synchronous with involuntary rhythmic contraction of the muscles of mastication at a rate of 1/s. Headache, depression, confusion, and involuntary movements are not uncommon generally. Peripheral nerves and spinal cord are less involved. Uveitis, keratitis, optic neuritis, and papilledema are also seen.

Skin changes reported are hypopigmentation and pigmentation change, nodules, vesicles resembling dermatitis herpetiformis, etc.

Cardiac changes: Culture-negative endocarditis, myocarditis, cardiac failure, sudden death, etc.

Pulmonary changes are cough and pleural effusion.

Diagnosis

Diagnosis is based on the clinical features and demonstration of PAS-positive diastase-resistant granules in the macrophages of the small intestine or species-specific polymerase chain reaction (PCR) using different sequences of the *T. whipplei* genome. This organism shows phylogenetic affiliation to actinomycetes clade.[9] It is nonacid fast weakly Gram-positive rod-shaped bacilli. 1–2 μ length, thick walled, and its inner wall stains with PAS dyes. 16s RNA gene sequence was isolated from intestine and later from pleural fluids, cardiac tissue, brain tissue, cerebrospinal fluid (CSF), and vitreous.[10-12] Culturing is reported by using interleukin to deactivate macrophages. Currently available diagnostic tools are PAS staining, electron microscopy and genomic detection in biopsy materials, aspirated fluids, etc. Culture, monoclonal or polyclonal antibody, and serology might become available in future.

CASE REPORT

A 63-year-old male was admitted with a history of diabetes mellitus of 20-year duration and ischemic heart disease. He was keeping good health and could successfully complete his Hajj pilgrimage. However, few months after returning from pilgrimage, the patient experienced bouts of abdominal colic which was suspected to be cholecystitis but could not be confirmed. The patient continued to have very poor appetite, abdominal pain, loose stools, loss of about 7 kg weight in 1 year, fatigue, and headache. He later developed slowness of gait and falls. He had also developed feeling of the subjective weakness of the left side of the body, tendency to lose balance, slurring of speech, involuntary movement of eye, face, limbs, and swallowing difficulty in the form of coughing while swallowing. He lacked initiative to do work, had forgetfulness for recent events, visual hallucinations which were formed nonstereotyped, recurrent and patient lacked insight that the images are hallucinatory and was treated as Parkinson's disease at regional hospital with no improvement. As the patient was steadily deteriorating, he was brought to our center. At

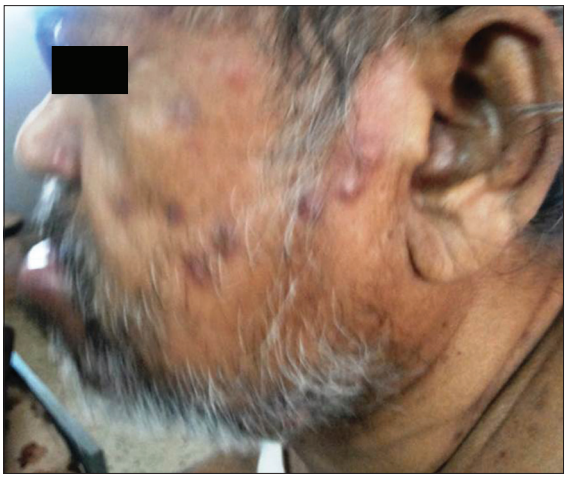

Figure 1: Puckered skin lesions of Whipple's disease

the time of admission, the patient had a HMSE score of 19. The patient had involuntary closing and opening of each eye in disconjugate arrhythmic manner, eyebrow lifting movements, dyskinesia movements of upper lips, cheek, as well as mild elevation of shoulders and twisting of trunk infrequently [Video 1]. He had skew deviation of eyes with saccadic initiation defect, broken saccades, slow vertical saccades, and multiple saccadic oscillations. He had a tendency to stoop forward, swaying while walking, with two person support, anteroposterior trunk movement while sitting, mild finger-nose incoordination, and completely illegible effortless speech diagnosed as mixed dysarthria with drooling and choking on and off. Poor respiratory support while speaking, poor lip seal, slowness of tongue movements, his general examination revealed itchy skin lesions over scalp, cheek, nose, and chin. The lesions were scaly, had nodularity with pigmentation and serous ooze. They were slightly tender [Figure 1].

Investigations

Investigations showed normal routine blood counts, liver functions, renal functions, and thyroid functions. Vasculitic workup, HIV, Venereal Disease Research Laboratory, and ultrasound abdomen were normal. Vitamin B12 levels were low 188.11 pg/ml. CSF showed chloride 121, sugar 154, protein 72, and cells 3. India ink preparation and culture were normal. PCR for WD could not be done due to lack of availability. N-methyl-D-aspartate, voltage-gated potassium channel, (glutamic acid dehydragenase) anti-GAD turned negative. The cardiac evaluation reported apical hypokinesia. Duodenal biopsy showed lamina propria showing focal lymphoplasmacytic cell collections and few histiocytes. Grams-stain, PAS, and GMS did not reveal any bacilli.

Magnetic resonance imaging: T1 and T2 images showed multiple areas of signal changes in the left middle cerebellar peduncle, midbrain, cerebellum, with diffuse cerebral and cerebellar atrophy; creatine peak was seen in the area of signal change [Figure 2]. DOPA uptake scan showed poor uptake in putamen.

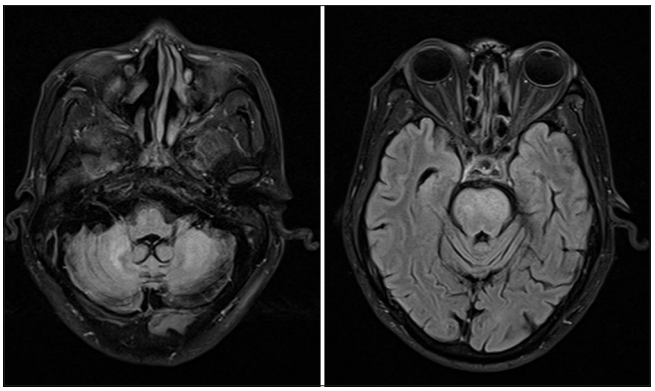

Figure 2: Magnetic resonance imaging shows diffuse cerebral atrophy with fluid attenuated inversion recovery hyperintensities in the brain stem and cerebellum

Course in the hospital and follow-up

In view of the typical phenotype, the patient was treated with injection ceftriaxone 2 g twice a day for 2 weeks. Trimethoprim-sulfamethoxazole twice a day, doxycycline 100 mg a day, Vitamin B12 injections and other drugs he was on for Parkinson's disease were withdrawn.

Follow-up at 3 months

The patient slowly showed signs of improvement, his clarity of speech and swallowing improved; he could walk with one person support [Video 2]. His abdominal symptoms improved and skin lesions improved. On telephonic inquiry, it was learned from relatives that the patient passed away due to pneumonia 5 months later.

DISCUSSION

Our patient had the combination of multiaxial neurologic involvement with oculomasticatory skeletal myorhythmia, abdominal pain and skin changes, skeletal changes, weight loss and radiological features suggestive, and the patient showed response to treatment for WD. Duodenal biopsy can be normal in neurowhipples but we could not confirm with PCR due to lack of availability of the test. Investigation for other causes including sarcoid is negative.

CONCLUSION

This case phenotypically, radiologically, and by way of therapeutic response is consistent with WD. Therefore is being presented to improve insight into the diagnosis in the presence of the above phenotype. It being one

of the treatable dementias early diagnosis is important for good results.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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