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Whipple's disease: a case report and review of literature

Abstract

Whipple's disease is a rare systemic disease. It is caused by a gram-positive infectious bacillus called *Tropheryma whipplei (T. whipplei)*. The common presenting feature is malabsorption, but it can also affect multiple organs as heart, central nervous system (CNS), joints, skin, lungs and vascular system. Presentation can be highly variable but mainly the patients are complaining of weight loss, diarrhea, joint pain, and arthritis, about 15% of patients do not develop these classic symptoms. Endoscopic picture usually shows pale yellow shaggy mucosa with erythematous eroded patches in the duodenum extending up to the jejunum. Definitive diagnosis is made mainly by endoscopic duodenal biopsies that show characteristic foamy macrophages in the lamina propria containing non-acid fast gram positive bacilli that stain red with Periodic acid-Schiff (PAS) stain. Immuno-histochemical staining for antibodies against *T. whipplei* had been used to detect the organism in a variety of tissues. Polymerase chain reaction (PCR) of *T. whipplei* is considered a confirmatory test. We present a case of classic Whipple's disease with review of literature for better understanding of the presentation, methods of diagnosis and treatment of the disease.

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Case report

A 53- years old male presenting with chronic diarrhea of 8months duration, his diarrhea was of large volume, frothy in nature with foul odour. It was not related to a specific type of food, persisted during fasting with no diurnal variations. His condition was also associated with significant weight loss. The condition was associated with low grade fever and arthralgia of his both knee and hip joints. After 2months from the onset of his diarrhea he started to develop dizziness and easy fatigability. Physical examination of the patient was unremarkable apart from the pallor. Work up for diagnosing the cause of his diarrhea was done in the form of repeated stool analysis and culture, complete blood count, liver profile, renal profile, electrolytes, ESR, B2 microglobulins, virology (HIV, HBsAg, antiHCVab) and thyroid profile. All the previously mentioned investigations were normal apart from microcytic hypochromic anemia due to iron deficiency with haemoglobin=7.3mg/dl, serum Fe was 10mg/dl and transferrin saturation was 5%, also he had mild hypoproteinemia with serum total protein of 6.2g/dl and mild hypoalbuminemia with serum albumin of 3g/dl. His ESR was 123 and C-reactive protein (CRP) was 49mg/dl as shown in Table 1. Abdominal ultrasound was completely normal. Attempts of giving empirical medications in the form of metronidazole and quinolones failed to control the condition of the patient. Endoscopic intervention was decided in the form of upper endoscopy and colonoscopy. Total colonoscopy and terminal ileoscopy were done with no abnormality detected. For the upper endoscopy; the duodenal mucosa down to the proximal jejunum was markedly congested with extensive whitish mucosal patches as shown in Figure 1-3. Multiple biopsies were taken; histopathological examination showed focal villous distortion and focal villous erosions. The lamina propria showed mild mono-nuclear cell infiltrate with extensive infiltrate of foamy macrophages with dilated lymphatic spaces as shown in Figure 4. PAS (periodic acid shiff) stain was applied during microscopic examination where the organism was detected as shown in Figure 5. And hence the patient was diagnosed as a case of Whipple's disease (WD). Then treatment was started accordingly in the form of ceftriaxone for 15days followed by trimethoprim-sulfamethoxazole (TMP/SMX) twice a day for 1 to 2years with marked improvement of the patient's condition. The improvement was evident by his laboratory parameters (Table 1) and endoscopic picture (Figure 6).

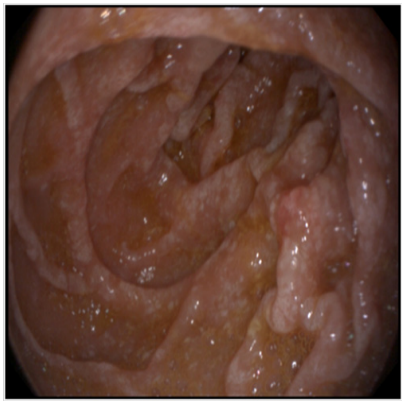

Figure 1 Shaggy mucosa of the duodenum.

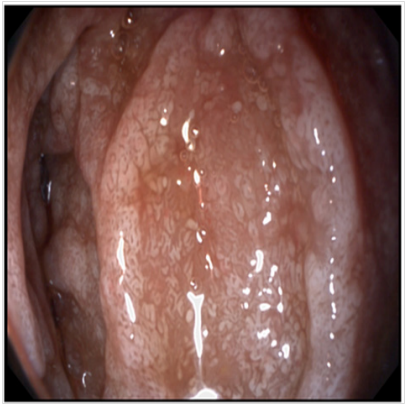

Figure 2 Whitish patches of Whipple's disease.

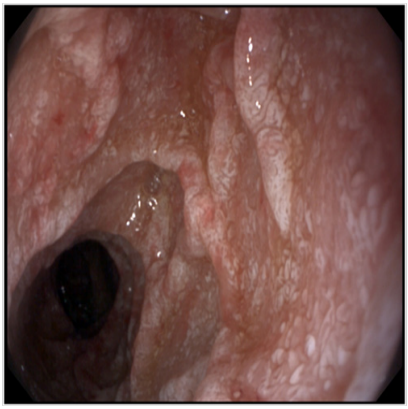

Figure 3 Endoscopic view of Whipple's disease.

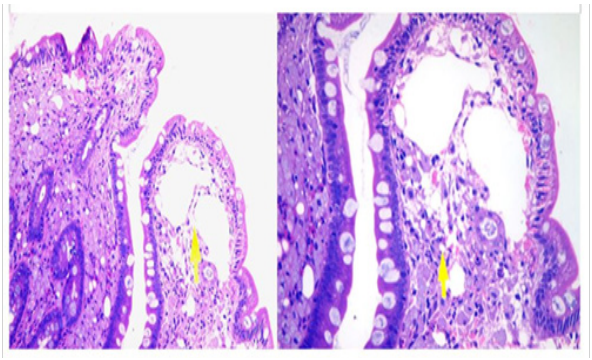

Figure 4 Focal villous distortion and erosion with extensive infiltration of lamina propria with foamy macrophages (arrows).

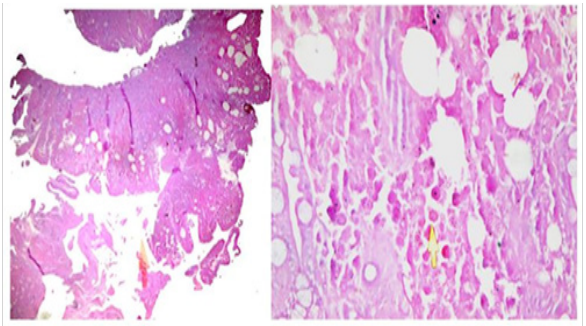

Figure 5 PAS stain showing macrophages with the organism inside (arrows).

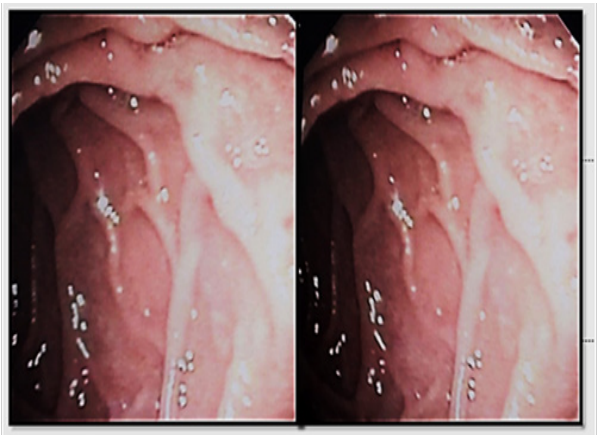

Figure 6 Complete disappearance of the shaggy mucosa of the duodenum after 3months of treatment.

Table 1 Abnormal laboratory parameters of the patient and 3months follow up

Laboratory tests	Findings	3 Months follow up	Normal references
Haemoglobin	7.2	13	(13-17)g/dl
MCV	74.2	91.5	(81-100)pg
MCHC	30.2	34.7	(31-35)g/dl
Serum iron	10	22	(65-75)ug/dl
Transferrin saturation	3%	11%	19%-50%
B2 micro globulins	0.2	--	(0.07-0.18)
ESR	123	72	(up to 15)mm/hr
CRP	49	6	(less than 1)mg/dl
Serum total protein	6.2	8	(6.6-8.3)g/dl
Serum albumin	3	4.6	(3.5-5.2)g/dl

Discussion and review of literature

Epidemiology

Whipple's disease (WD) is a rare condition. Few epidemiologic studies showed its annual incidence is less than 1 per 1,000,000 per annum.[1] It is has a specific predilection for middle aged white males, about 86% with male-to-female ratio: approximately 8-9:1.[2] There is a slight increase in the rate of women being diagnosed as Whipple's disease in recent years. It occurs predominantly in those of Caucasian ethnicity, suggesting a genetic predisposition in that population. The disease is mainly diagnosed in the middle age (median 49years), however some studies showed that the age of diagnosis had shifted recently to older age. This could be attributed to the increasing use of antibiotics to un related conditions had led to a delay in the onset of WD[3] and this also can also be seen in our patient.

Microbiology and genome

Whipple's disease is caused by a gram-positive infectious bacillus called *Tropheryma Whipplei. T. whipplei* is an actinomycete that can be isolated from various types of specimens, as infected heart valves, duodenal biopsy specimens, ocular vitreous fluid, cerebrospinal fluid (CSF), synovial fluid, blood, mesenteric lymph node tissue, muscle tissue, and feces.[4] The genome of *T. whipplei* is quite small for a bacterium it consists of approximately 926,000 base pairs and is the smallest of all known actinomycete genomes.[5] Besides its bacterial doubling times ranges between 28hours and 4days, which is considered among the slowest recorded time for any medically relevant bacterium in the laboratory.[6] This could explain the late onset of symptoms disease and the difficulty in obtaining culture of the organism. *T. whipplei* lacks various metabolic capabilities in carbohydrate, energy metabolism and aminoacid biosynthesis.[7] Thus, the organism is highly dependent on nutrients from its host environment. The proposed extracellular location of the bacteria in patients with intestinal WD, is in the villus tips below the intestinal basement membrane, which is a site of rich influx of nutrients, and would seem consistent with its requirements.[8]

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Pathology and immunology

T. whipplei is commensal bacteria of humans, so a healthy asymptomatic carrier state is present and WD occurs in only a small subset of persons.[9] *T. whipplei* has the capability of invading the mucosa of the proximal small intestine where it's located extracellular and just below the epithelial basement membrane of the lamina propria.[10] From the intestinal mucosa, bacteria are thought to spread via lymphatics into mesenteric and mediastinal lymph nodes and into the systemic circulation causing the extra-intestinal manifestations.[11]

Individuals who are most susceptible to the disease are those with decreased ability to perform intracellular degradation of ingested pathogens or particles, particularly in the macrophages. Several studies indicate that defective T-lymphocyte (particularly TH1 population) function may be an important predisposing factor for the disease.[12] In particular circulating cells that are CD11b (integrin alpha), are reduced in susceptible individuals. CD11b has a vital role in activation of macrophages to destroy intracellular ingested *T. whipplei* bacteria.[11] The clinical manifestations of the disease are mainly caused by infiltration of the tissues by *T. whippeli* where the immune system reacts by incorporating the organisms into tissue macrophages "foamy macrophages".[13] Consequent malabsorption associated with Whipple's disease is believed to be secondary to the disruption of normal villous function due to infiltration of the lamina propria of the small bowel with these foamy macrophages. Patients with arthralgia had been found to have the organism in their synovial tissues.[14] The organisms had been detected in the heart valves of patients with cardiac Whipple's disease[15] and in the CNS of patients with neurological disease. Rarely, the organism can be seen in the lungs of affected patients.[16] These foamy macrophages can be easily seen infiltrating this tissues using light microscopy, especially when PAS stain is used for the histological sections.[3]

Clinical features

There are many different forms of presentation of WD, but it is mainly an intestinal disease with wide range of symptoms. It can range from abdominal pain, anorexia, distension, flatulence, diarrhea, weight loss, steatorrhea and rarely can be a cause of gastrointestinal bleeding. It can cause also extra intestinal manifestations in the form of[17,18] intermittent low grade fever, chronic cough, skin hyperpigmentation (50%), polyarthralgia (transient, episodic, may be prodromal symptom), generalized lymphadenopathy, anemia, hypoalbuminemia, edema and rarely clotting abnormalities.

Cardiac involvement can occur in the form of pericarditis, myocarditis and endocarditis denoted by isolation of the organism from the cardiac valves. Endocarditis may be encountered as part of intestinal or systemic disease and it may occur in the setting of blood culture negative endocarditis.[19,20]

Central nervous system (CNS) involvement occurs in 10-40% of the patients. It can be in the form of headache, confusion, dementia, ophthalmoplegia, characteristic myoclonus as oculomasticatorymyorhythmia (convergent eye movements with simultaneous chewing movements), gait abnormalities, seizures and finally coma.[21,22] Ocular involvement can be in the form of uveitis, vitritis, keratitis, retinitis, and retinal hemorrhages.[23]

Pulmonary involvement can be in the form of pleural effusion, mediastinal widening (due to lymphadenopathy).[16] Skin involvement apart from hyperpigmentation is very rare; it may be related to the malnutrition or an immune reaction to *T. whipplei* leading to conditions in the form of eczematous plaques, psoriasis and erythema nodosum.[24]

Diagnosis

Diagnosis is made from duodenal biopsy, taken by upper endoscopy, which reveals pale yellow shaggy mucosa with erythematous eroded patches in patients with classic intestinal Whipple's disease[25] and this is seen in our patient. Histopathological examination of the duodenal biopsies shows infiltration of the lamina propria with PAS-positive macrophages with intracellular clumps of *T. whipplei*.[3] Immunohistochemical staining for antibodies against *T. whipplei* has been used to detect the organism in a variety of tissues, and a PCR-based assay is also available.[26] Electron microscopy can be diagnostic showing coccobacillary bodies that represent the *T. whippeli* organism. Histologic examination with routine H&E and PAS stains is usually sufficient to reach a diagnosis, however, it is recommended that PAS-positive histologic findings to be confirmed with other methods when establishing the diagnosis of WD.[25,26]

PCR based assay can be used as a confirmatory test if performed on intestinal samples. It can also aid in the diagnosis of extra intestinal involvement if PCR of the blood, vitreous fluid, synovial fluid, heart valves, or cerebrospinal fluid is done.[27,28]

Treatment

The initial response of WD to antibiotic treatment usually is prompt; however there is a high incidence of relapse rate about 40%.[29] So treatment is divided into two phases, the first phase is the induction phase for 14days followed by maintenance phase for at least 1 or 2years is associated with the least relapse rate. The drugs that could be given in the induction phase; ceftriaxone 2gram intra venous (IV) once or twice daily for 14days, Meropenem 1gram three times a day, or penicillin G 6-24 units daily in divided doses plus streptomycin 1gram once daily intramuscular.[30]

For the maintenance drugs: trimethoprim-sulfamethoxazole (TMP/SMX) in a dose of 160mg/800mg orally for one to two years is the gold standard specially in cases of CNS involvement.[30,31] Other maintenance drugs could be used as Doxycycline 100mg orally twice daily+hydroxychloroquine but relapse could be a problem then.[31] The regimen used was ceftriaxone 2gram daily for 14days followed by TMP/SMX for 1-2years. Threemonths after therapy, marked improvement of his symptoms, laboratory parameters and endoscopic picture could be seen.

To conclude, Whipple's disease is a systemic disease not only an intestinal one. It should be taken into consideration in cases of chronic diarrhea when other differential diagnosis fails to explain the cause, even in non-endemic areas. Better understanding of the organism, variable presentations, methods of diagnosis and proper treatment can lead to prompt diagnosis and prevent the disease relapses.

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Conflict of interest

The author declares no conflict of interest.

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