Acta Scientific MICROBIOLOGY (ISSN: 2581-3226)

Volume 5 Issue 2 February 2022

Short Communication

Whipple's Disease-An Enigmatic Diagnostic Challenge Despite a Centenary of the Detection of the Etiologic Agent-A Short Communication

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Received: December 29, 2021

Published: January 31, 2022

Whipples disease (WD) represents a chronic infectious disease that was initially detailed by George Whipple in 1907. As per Whipple the intestinal lipodystrophy that was visualized was secondary to the aberrant lipid metabolism as well as not an infection. In 1952 it was thought to be due to bacterial causation along with antibiotic therapy attempt seemed to bring success. Nevertheless, it was only in 1992, that the bacteria got isolated with name of *Tropheryma whipplei* got assigned, whereas in 2001 again the name was altered to *Tropheryma whipplei* that was thought to be the correct spelling [1].

WD is a disease that occurs occasionally, with maximum cases documented in north America as well as Europe. Its incidence is 1-3 /1000, 000 individuals, with average age of manifestation being 55 yrs. It mainly afflicts male population with male: female ratio being 8-4:1. It is correlated with the HLA B 27 haplotype [2,3].

The name of *Tropheryma* got coined from the Greek ''trophe '' that implies nourishment as well as ''eryma'' that implies barrier in view of it influencing the intestine. It is a gram-positive bacillus, that is periodic –acid –Schiff - positive (PAS positive) along with acid fast negative. The bacillus cores existence is with in a plasma membrane, that is enveloped by a cell wall that is made up of three layers. The inner layer possesses polysaccharides which stains PAS positive, a characteristic, whose utilization is done with regards to histological diagnosis [4,5] (Figure 1).

Figure 1: Microscopic detection of *T. whipplei*-infected duodenal mucosa. (Top) Hematoxylin-and-eosin-stained duodenal biopsy specimens with foamy macrophages in the lamina propria (arrows). The specimens were photographed with a 20× (left) and 40× (right) lens objective. (Bottom) Periodic acid-Schiff-diastase (PAS-D)-stained duodenal biopsy specimens with PAS-D-positive granules in the foamy macrophages (arrows). The same duodenal biopsy specimens as those used in the top panels were used here. The specimens were photographed with a 20× (left) and 40× (right) lens objective.

The pathogenesis in detail is not known, however what is understood is the significant part played by the host immunity. Maximum persons contracting *Tropheryma whipplei* remain as asymptomatic carriers or generate immunity which protects them subsequent to a restricted intestinal infection. Just a limited percentage generate chronic disease, which is secondary to aberrant insufficient inadequate immune reaction. This is made up basically of changed macrophage function in addition to dysfunctional type I T cell response. These modes result in intestinal injury as well as along with dissemination of bacteria with systemic influence [4,5].

The idea of this short communication is how despite this disease being known for over a centenary its diagnosis continues to be an enigmatic one. Maximum of the detailed cases of WD are robust disorders that might implicate numerous organs in addition to continuous evolution [6,7]. The Clinical manifestations of WD might be significantly polymorphic. These can be classified as 4 kinds i) Classic Whipples disease ii) localized chronic infections, mainly endocarditis iii) acute infections, like pneumonia, bacteremia, as well as gastroenteritis, iv) carrier state [reviewed in ref no-8].

The commonest symptoms of WD are inclusive of weight reduction, diarrhea along with arthropathy. Although these symptoms might occur concomi tantly, arthropathy might antecede Gastrointestinal symptoms for numerous years. Systemic symptoms like low grade fever occurring intermittently, night sweats along with lymphadenopathy are pretty frequent in case of WD. The other lesser usual symptoms might be inclusive of pulmonary, cardiac, muscle along with central nervous system (CNS) getting implicated [1,7].

With WD being a rare disease in addition to akin clinical presentations might be seen in certain other diseases it is essential to do corroboration with laboratory investigations. The existent criteria with regards to diagnosis need positive outcomes for the PAS positive foamy macrophages in the biopsy of small intestine. Furthermore, the diagnosis can be proved in the PAS positive foamy macrophages in the implicated tissues. Molecular approaches, like quantitative real-time PCR (qPCR).

PCR finding of *T. whipplei* or observation of the particular 16S ribosomal RNA of the bacterium possess greater sensitivity, inspite of turning out to be false positive. More particularly Immunohistochemical staining with antibodies for *T. whipplei* [4,5,8]. Untreated if symptomatic it might prove fatal. The treatment that is advocated at present by UpToDate [9] is dependent on a single, randomized controlled Clinical trial (RCT) that comprised of 40 patients, that got treated with success with the utilization of a single dosage of ceftriaxone 2gdaily or meropenem three dosages of 1g daily that was subsequently followed by oral cotrimoxazole (trimethoprim in combination with sulfonamides) for 12 moths [10]. The alternative therapy is as per figure 2.

Figure 2: Latest proposed therapeutic strategy to treat *T. whipplei* infections. See the text for explanation.

One important thing to realize is there are lot of undiagnosed cases of diarrhea of unexplained etiology where patients keeps on losing weight besides becoming dehydrated with Whipples disease not taken into account as well as in 2021 itself so many case reports of this have appeared. Furthermore even in pyrexia of unkown etiology this should be considered.

The maximum frequent strategies with regards to diagnosis of WD are histopathological examination (HPE), in addition to PCR in view of their being available in maximum laboratories, whereas culture of *T. whipplei* is tough even currently with its availability being existent in minimal laboratories (Figure 3). [11]. Classic Whipples disease is classically associated with histological lesions existent in the duodenum or other small intestinal regions. Despite, histological diagnosis of this bacillus is commonly done with PAS staining, it is not a particular strategy for diagnosis of Whipples disease, as even in patients with infections with other etiologies like *Rhodococcus equii*, Mycobacterium avium intracellulare, *Corynobacterium*, *Bacillus cureus*, Histoplasma, or fungi, PAS positive foamy macrophages can be observed as well [12]. Thus, we are quoting a case report that was published in 2021 with, PAS positive foamy macrophages without any other symptoms as well as no other available molecular methods, hence one needs to be cautious of the differential diagnosis in mind [13] (Figure 4,5).

Figure 3: Schematic representation of the diagnostic algorithm. (A) Diagnostic strategy for classic Whipple's disease (WD). (B) Diagnostic strategy for chronic localized *T. whipplei* infection.

Figure 4: Courtesy ref no-13-Slightly enlarged villi with an accumulation of whitish matter at the tip of the villi of duodenal mucosa.

Figure 5: Courtesy ref no-13-A. Duodenal mucosa with lymphoplasmocytes infiltrate and mucinous material in lamina propria (hematoxylin-eosin stain, ×40); B. PAS-positive inclusions.

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