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EDITORIAL

Whipple's Disease: A Well-Done Outcome to a Rare Disease

Joesph Sellin[1] · **Ian L. P. Beales**[2]

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Looking Back: The History of Whipple's Disease

Whipple's disease (WD) is a condition of which all gastroenterologists likely learn about in medical school, occasionally investigate for, and very rarely see. Despite this rarity, or maybe because of it, there has been a longstanding fascination with the disease. In 1907, Dr. George Hoyt Whipple described a case of arthritis, weight loss, and diarrhea, which when examined *postmortem* was remarkable for prominent periodic acid-Schiff (PAS)-staining foamy macrophages in the small intestinal lamina propria. He hypothesized that there was an underlying disorder of fat metabolism and termed, what would eventually be known as Whipple's disease, intestinal lipodystrophy. The first small bowel biopsy diagnosis of Whipple's was made in 1958; since then, the causative organism has been identified and cultured, its genome sequenced, and new polymerase chain reaction (PCR)-based bacterial identification and immunohistochemical diagnostic tests developed.

Whipple's Disease Today

WD is undoubtedly rare; only a few studies of its prevalence and incidence rate have been performed. Classic Whipple's disease is an illness typically affecting Caucasian populations [1], that is rare in the native Asian and African populations, although genetic carriage is common in these latter populations [2, 3]. The criteria for the diagnosis of WD vary, and the possibility of unrecognized cases must be acknowledged; the most recent studies suggest a prevalence of 3/1,000,000 and an incidence of 0.1–0.6/1,000,000 new cases in Western populations [4]. Some estimates have been as low as 12 new cases per year worldwide.

In this issue of *Digestive Diseases and Sciences*, Hujoel and colleagues describe a case series of Whipple's disease (WD) drawn from clinics in the USA, reporting the clinical and laboratory features in the modern diagnostic era [5]. This current case series was derived from four major referral institutions that collected only 33 cases in 15 years, although elements of referral bias and under-ascertainment may have influenced the numbers. Of the 33 cases identified by Hujoel et al., the diagnosis was made either by PCR analysis of mucosal biopsies in 88% and by PAS-positive staining of intestinal mucosal biopsies in 48%, although not all subjects had both tests performed on all samples. The authors proposed a diagnostic classification of Whipple's disease (see Table 1 in the paper), with three groups: (1) definite classic (small intestinal biopsies positive for both PAS and PCR), (2) probable classic with small intestine positive for PCR or PAS, and (3) localized or extraintestinal with PCR or PAS positivity in a nongastrointestinal tissues and fluids such as plasma and synovial fluid. Classic Whipple's involving the intestine was the most common (55%), but interestingly, localized extraintestinal disease was present in 45% (CNS, joints, heart, eye, and skeletal muscle). Overall, PCR-based tests were positive more frequently (88% of cases), compared with PAS-positive tissue (73%). Antibiotic treatment clinically improved almost three quarters of the studied patients. The most common regimen was intravenous ceftriaxone followed by oral trimethoprim–sulfamethoxazole (TMP-SMX). Given the unlikelihood that there will be any further randomized treatment trials, these collected anecdotal experiences will probably have to suffice for the present.

This is the largest series from the USA, although referral centers in France (142 patients in 10 years) [6] and Germany (191 patients in 13 years) [7] have accrued more patients. Whether this reflects differing epidemiology or referral practices remains unclear.

✉ Ian L. P. Beales
i.beales@uea.ac.uk

Joesph Sellin
sellin@bcm.edu

[1] Professor Emeritus, Division of Gastroenterology, Baylor College of Medicine, Houston, TX 77030, USA

[2] Department of Gastroenterology, Norfolk and Norwich University Hospital, Norwich NR4 7UY, UK

The authors' classification into three types provides a helpful framework for evaluating a rare disease with myriad symptoms and an increasing number of diagnostic tests. Sorting through the classifications can provide a clinician with a strategy regarding how to proceed with a diagnostic evaluation. The authors defined "definite classic" as PAS-positive macrophages in the intestinal lamina propria and positive PCR, an acknowledgment that PAS staining alone may be nonspecific. In actuality, it is much more likely that if a gastroenterologist today encountered PAS-positive small bowel biopsies, the etiology would be mycobacteria avium complex (MAC) rather than WD, especially in an immunocompromised patient. Although immunohistochemistry can be performed, it is unclear how its performance characteristics compare with PCR. Regardless, the current trend is to rely solely on PCR for a positive diagnosis.

Compared with European studies, the overall demographics described by Hujoel, et al. were again similar, with the vast majority of cases occurring in white middle-aged men. Nevertheless, the present report has a relatively larger proportion of localized disease. For instance, in the German study, isolated extraintestinal disease was reported in only 5% of cases [7]. Neurologic–psychological symptoms were noted in almost two-thirds of the US series, but only 22–24% in the European series possibly reflecting specific symptom searching. Even so, 50% of the US patients with neurologic involvement had small bowel involvement histologically or confirmed with PCR, although it is not known whether they were symptomatic.

Only about 10% of this series had the "classic" Whipple's tetrad (fever, diarrhea, abdominal pain, and arthropathy), although partial combinations were much more common. The pathognomonic movement disorder termed oculomasticatory myorhythmia was rare in this series (1/33), as was melanoderma (3/33). Interestingly, despite the emphasis on diarrhea and malabsorption in the historical literature, in many cases there was no systemic evaluation of the gastrointestinal (GI) tract in those with apparently localized disease; although 43% of those with localized disease had no evidence of GI involvement, the rest were not investigated. Concerning small intestinal investigations, all with PAS positivity were also PCR positive, but some cases were PCR positive/PAS negative. The authors do not report whether these PCR-positive cases had normal or abnormal duodenal histology or GI symptoms. Further data on the utility of PCR testing on small bowel biopsies in apparently extraintestinal disease will be interesting.

A significant proportion (14/19) of the patients had received systemic immunosuppression before the diagnosis of Whipple's disease was made, similar to European studies (up to 76% so treated) [6, 8], probably reflecting treatment of the chronic systematic inflammatory changes, predominantly arthropathy, in patients prior to being specifically diagnosed with Whipple's. It is not clear whether this immunosuppression is a risk factor for clinical Whipple's or an adverse prognosis, but it does reinforce the need for all clinicians to be alert to the protean manifestations of Whipple's.

In this series, antibiotic treatment was very effective; 80% had a clinical response, although follow-up and testing were not systematic. The majority of patients were treated with a traditional ceftriaxone followed by a TMP-SMX regimen. Optimal treatment for the disease remains controversial, in particular if different manifestations require individualized treatments. The one randomized trial showed equivalence between intravenous ceftriaxone and meropenem when followed by 12 months of therapy with TMP-SMX [9], although more recently 3 months of TMP-SMX therapy following up to 2 weeks of ceftriaxone was reported to be as effective as the more traditional 12 months [10]. Molecular analysis has shown that *T whipplei* does not carry the genetic target of trimethoprim and that 40% of cultures derived from European patients are resistant to sulfamethoxazole [11], motivating a change in the European guidelines, now advocating doxycycline and hydroxychloroquine as first-line therapy [12], a combination that is bacteriocidal in vitro [13]. Others have suggested the traditional ceftriaxone TMP-SMX 12-month regimen be followed by lifelong doxycycline [14]. It is not clear whether US strains are significantly different than the ones isolated in Europe. The significance of these in vitro sensitivity tests also needs to be considered; despite the apparent clinical efficacy of the more traditional regimens, in vitro resistance to cephalosporins and carbapenems (usually imipenem) has been reported [13], emphasizing the importance of follow-up in order to ensure treatment success, whichever regimen is used. Preliminary results suggest that duodenal PCR may be useful for follow-up testing. Of 17 cases reported by Ramzan et al [15], 12 had duodenal PCR-positive samples post-treatment and 5 of these had obvious clinical relapse.

Where does this leave busy clinicians? In a case series such as this, working back from a diagnosis, characteristics of Whipple's disease are identifiable. The problem is that these characteristic clinical findings represent common and nonspecific factors. Therefore, a clinician confronted with a patient with joint and abdominal pain would be hard-pressed to think of Whipple's as the first, second, or even third possible diagnosis. The middle-aged, white, and male predominance, though an important clue, is not specific. In patients with significant GI symptoms, although the diagnosis is likely to be made almost by accident when obtaining tissue to investigate other more common diseases, PCR should be used to follow up nonspecific or PAS-positive changes. In other cases, the diagnosis should be considered in cases of blood culture-negative endocarditis or nonresponsive arthropathy. Putatively characteristic neurologic signs can help inform the diagnosis although only one case with such

diagnostic signs was noted in the present series (3%). In those where systemic Whipple's disease is being considered, although a duodenal biopsy is minimally invasive and easily obtained, the sample should be processed for a specific PCR test. Since the optimal antibiotic regimen is unknown, it will be important to determine whether US and European Whipple's disease is intrinsically different using careful follow-up in order to ensure treatment success is essential. It is likely that since further knowledge will be gained primarily from case series, it is hoped that data collection and investigations will be systematic and rigorous.

Looking Forward: Re-appraisal of WD in the Twenty-First Century

There have been significant advances in understanding the ecology of *T whipplei* since the molecular characterization of the bacterium. *T whipplei* appears to be descended from the actinomycetes line, related to what have been termed environmental bacteria (EB) residing in soil or water that concentrate in sewage, forming communities with a large variety of species, explaining in part some of the observation that farmers, sewage plant workers, and others with outdoor professions appear to have a greater risk of WD. Other than humans, there is no known animal host, again similar to EB. These types of bacteria are difficult, if not impossible, to culture using artificial media [16].

With the development of PCR, it is now evident that there is asymptomatic infection and carriage of *T whipplei*. Seroprevalence is surprisingly common given the rarity of clinical WD. Antibodies to *T whipplei* are present in 48–72% of the general European and Asian populations. Detection of *T whipplei* in stool and/or saliva has been reported in 1.5–4% of cases in Europe, with higher rates in at-risk populations such as sewage workers (up to 25%). An informal calculation would suggest that < 0.005% of individuals with evidence of *T whipplei* infection actually develop WD. Given the miniscule incidence of clinically diagnosed WD, infection in and of itself is not sufficient to cause the disease; unique host factors are undoubtedly necessary to produce clinically significant WD. It is not clear at this point whether there are any subclinical manifestations associated with "asymptomatic" or perhaps not so asymptomatic carriage.

The development of sensitive and specific tests for WD certainly aids in its diagnosis but adds layers of complexity to understanding the relationship between the diagnostic tests and the clinical spectrum of disease. What exactly are the connections between PCR positivity and the classical histological changes? Is there some predictable progression from the presence of PCR positivity and the more characteristic small bowel changes, i.e., does PCR positivity alone represent an earlier stage of the disease? Alternatively, is it a variant with different clinical properties? Finally, are EB responsible for other poorly understood diseases? These are important questions, the answers to which will provide a better understanding of WD itself, and perhaps for the contributions of other EB to human health and disease. Nevertheless, given the time and effort involved in collecting and characterizing the present series of 33 patients, these issues are unlikely to be speedily resolved.

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