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Review

Whipple's arthritis

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ABSTRACT

Whipple's disease is a chronic systemic infection that is due to the bacterial agent *Tropheryma whipplei* and can be cured by appropriate antibiotic therapy. The typical patient is a middle-aged man. Rheumatologists are in a prime position to handle Whipple's disease. The classical presentation combines weight loss and diarrhea, preceded in three-quarters of patients by a distinctive pattern of joint manifestations that run an intermittent course, at least initially. The mean time from joint symptom onset to the diagnosis of Whipple's disease is 6 years. Either oligoarthritis or chronic polyarthritis with negative tests for rheumatoid factors (RFs) develops. If the diagnosis is missed, progression to chronic septic destructive polyarthritis may occur. Spondyloarthritis has also been reported, as well as a few cases of diskitis or, even more rarely, of hypertrophic osteoarthropathy. In most patients with the classical form of Whipple's disease, periodic acid-Schiff (PAS) staining of duodenal and jejunal biopsies shows macrophagic inclusions that contain bacteria. However, the involvement of the bowel may be undetectable clinically or, less often, histologically, and even PCR testing of bowel biopsies may be negative. Therefore, when nothing points to bowel disease, rheumatologists should consider *T. whipplei* infection in middle-aged men with unexplained intermittent oligoarthritis. PCR testing allows the detection of *T. whipplei* genetic material in joint fluid, saliva, and feces. This test is now a first-line diagnostic investigation, although *T. whipplei* is a rare cause of unexplained RF-negative oligoarthritis or polyarthritis in males. PCR testing can provide an early diagnosis before the development of severe systemic complications, which are still fatal in some cases.

1. Whipple's disease and focal chronic infections due to *Tropheryma whipplei*

Whipple's disease is a rare, chronic, systemic infection due to the bacterial agent *Tropheryma whipplei*. Appropriate antibiotic therapy provides a cure. Gastroduodenal biopsies show typical histological alterations. The incidence of Whipple's disease has been estimated at about 0.5 to $1/10^6$ population. Farmers and individuals exposed to soil and animals may be at highest risk. Among patients with Whipple's disease, 96% are male and 97% Caucasian [1]. Middle-aged men are predominantly affected, with a mean age at joint symptom onset of 40.3 years [2]. The mode of transmission may involve passage of the bacterial agent from the environment into the body through a gastrointestinal portal of entry, followed by fecal-oral transmission. However, person-to-person transmission through the oral-oral route cannot be ruled out.

In addition to classic Whipple's disease, presentations include chronic focal infections with normal gastrointestinal histology such as endocarditis, central nervous system (CNS) involvement, uveitis, arthritis, and diskitis [3]. The current increase in the prevalence of these focal forms is ascribable to the introduction of molecular biology diagnostic methods.

2. *Tropheryma whipplei*

Nearly a century after Whipple's disease was first described [4] and 8 years after the first report of *T. whipplei* detection by amplification of its 16S ribosomal RNA sequence [5], the organism was successfully cultured [6]. Until these recent advances in detection techniques, *T. whipplei* was viewed as an uncommon organism that only very rarely caused disease. Recent evidence indicates that *T. whipplei* is a commensal organism and not an obligate pathogen. In the general population, 1.5% to 7% of individuals are healthy carriers with positive fecal PCR tests [3,7]. A higher prevalence of 12% to 25% has been reported among sewer workers. *T. whipplei* has also been detected in saliva samples from 0.2% to 1.5% of healthy individuals [7], in 0% to 0.26% of duodenal biopsies, and in 0.5% of blood units from healthy donors. Among joint fluid samples from male

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patients with unexplained arthritis and no evidence of Whipple's disease, 1.58% were positive for *T. whipplei* [8].

In addition to systemic and focal chronic infections, *T. whipplei* alone or combined with other organisms may play a role in acute pediatric infections, such as gastroenteritis and transient febrile episodes, and perhaps also in pneumonia in adults [9]. Thus, an episode of acute diarrhea in a young child may indicate primary *T. whipplei* infection, and true Whipple's disease may then develop only in the tiny minority of individuals who have genetic susceptibility factors. This hypothesis is consistent with the high seroprevalence (52%) in apparently healthy adults [9]. In West Africa, there is a distinctive epidemiological picture with perhaps a higher incidence of *T. whipplei* infection.

3. Genetic susceptibility

The very strong male bias and associations with HLA-B27, DRB1*13, and DQB1*06 suggest a role for genetic factors. Exposure to *T. whipplei* seems common, yet only very few individuals experience Whipple's disease, further supporting a role for genetic susceptibility [9]. Reports of relapses of Whipple's disease due to different *T. whipplei* strains also strongly points to genetic susceptibility [10]. The susceptibility factors would seem to be fairly specific of the immune response to *T. whipplei* since, apart from giardiasis, other infections are not seen with increased frequency in patients with Whipple's disease.

4. Clinical and laboratory manifestations of Whipple's disease

The diagnosis of Whipple's disease is often delayed, for several reasons: the condition is rare, presents a wide spectrum of clinical patterns, and occasionally develops without any clinical or histological evidence of gastrointestinal involvement. The diagnosis must therefore be considered in many clinical situations, even when the classic signs are lacking (Box 1) [9]. In classic Whipple's disease, recurrent arthritis is the first manifestation. Weight loss and diarrhea develop several years later, together with a variety of other clinical manifestations. The typical patient is a middle-aged man. At the time of the diagnosis of classic Whipple's disease, there is usually a variable combination of chronic diarrhea, febrile episodes, weight loss, lymphadenopathy, joint involvement and, less often, neurological, cardiac, and ocular manifestations [9].

4.1. Joint manifestations

Joint manifestations mark the onset of Whipple's disease in three-quarters of patients. The mean time from joint symptom onset to the diagnosis is 6.7 years (range, 0.3–36 years) [2]. Over 80% of patients experience joint symptoms at some point [11–14].

Most patients have intermittent migratory joint symptoms with either oligoarthritis or polyarthritis. The joints are entirely normal between the flares. Arthritis occurs in 41% to 61% of cases, whereas arthralgia is slightly less common, with 26% to 54% of cases [2]. The large joints are predominantly targeted, in the following order of decreasing frequency: knees, wrists, ankles, hips, elbows, and shoulders [2]. The small joints are affected far less often and never in isolation. Gastrointestinal involvement is demonstrated by histological or PCR tests in the vast majority of cases. A few patients, however, have chronic focal joint infection with normal gastrointestinal biopsy specimens, even by PCR [15]. Therefore, unexplained intermittent oligoarthritis or polyarthritis of the large joints in a middle-aged man should suggest Whipple's disease, even in the absence of gastrointestinal manifestations (Box 1) [2,9,16]. Overall, however, among cases of RF-negative polyarthritis or undifferentiated oligoarthritis in males, few seem ascribable to *T. whipplei* infection.

Chronic polyarthritis in a symmetric distribution is less common [2]. The small joints are spared. The inflammation is intermittent at first then becomes continuous. Joint destruction and RFs are absent in the overwhelming majority of patients. Subcutaneous nodules have been reported. Rarely, patients with prolonged untreated Whipple's disease may develop radiological evidence of destruction such as joint space narrowing at the carpal, carpometacarpal, or radiocarpal joints (Fig. 1) or even involvement of the hips with joint space loss and subchonral cysts [2]. These lesions are due to septic arthritis, as shown by the culture of *T. whipplei* from joint fluid cultures [16]. Progression to ankylosis occurs only after many years. The bilateral symmetric radiographic lesions often lead to a mistaken diagnosis of rheumatoid factor-negative rheumatoid arthritis [16]. If missed at this stage, the correct diagnosis is made when gastrointestinal symptoms and weight loss develop eventually. The administration of antibiotic therapy is then followed by a dramatic improvement in the joint manifestations.

Axial involvement is less common than peripheral arthritis [2]. Furthermore, patients with axial disease often also have peripheral arthritis. Syndesmophytes and fusion of the sacroiliac joints and facet joints have been reported.

Box 1: Clinical presentations for which *Tropheryma whipplei* infection should be considered [9].

- Unexplained intermittent arthritis
- Chronic polyarthritis with negative tests for rheumatoid factors and no involvement of the small joints
- Chronic diarrhea
- Prolonged fever of unknown origin
- Unexplained neurological manifestations
- Uveitis
- Endocarditis with negative blood cultures
- Epithelioid and giant-cell granuloma
- Development of extraarticular manifestations (gastrointestinal, cardiac, or neurological symptoms or fever) in a patient receiving biological therapy for polyarthritis

The presence of several manifestations in a middle-aged man increases the likelihood of Whipple's disease.

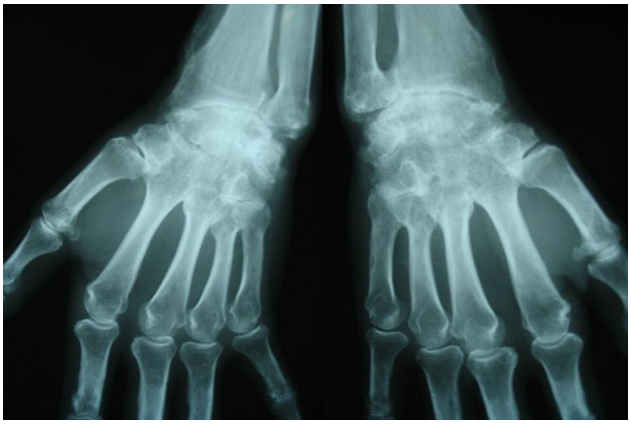

Fig. 1. Polyarthritis with joint destruction in a patient with Whipple's disease: symmetrical ankylosis of the carpal and carpometacarpal joints and bilateral narrowing of the radiocarpal joint space. The metacarpophalangeal joints are not affected (Courtesy of Puéchal et al. [16]).