Rheumatic and Musculoskeletal Features of Whipple Disease: A Report of 29 Cases

Marine Meunier, Xavier Puechal, Emmanuel Hoppé, Martin Soubrier, Philippe Dieudé, Jean Marie Berthelot, Paola Caramaschi, Jacques-Eric Gottenberg, Laure Gossec, Jacques Morel, Emilie Maury, Julien Wipff, André Kahan, and Yannick Allanore

ABSTRACT. ***Objective.*** Whipple disease is a rare infection caused by *Tropheryma whipplei*. Although patients commonly complain of osteoarticular involvement, musculoskeletal manifestations have been poorly described. We report cases of Whipple disease with rheumatic symptoms and describe their clinical presentation, modes of diagnosis, and outcomes.

Methods. This retrospective multicenter study included patients with Whipple disease diagnosed and referenced between 1977 and 2011 in 10 rheumatology centers in France and Italy.

Results. Twenty-nine patients were included. The median age was 55 years. The median time to diagnosis from first symptoms was 5 years. Polyarthritis was the most frequent presentation (20/29), and was most often chronic, intermittent (19/29), seronegative (22/23), and nonerosive (22/29). In all cases, the symptoms had led to incorrect diagnosis of inflammatory rheumatic disease and immunosuppressants, including biotherapy, were prescribed in most cases (24/29) without success. The diagnosis of Whipple disease was made by histological analysis, molecular biology tests, or both in 21%, 36%, and 43% of the cases, respectively. Duodenal biopsies were performed in most cases (86%). Synovial biopsies were performed in 18% of cases, but all contributed to diagnosis. The clinical outcomes after antibiotic therapy were good for all patients.

Conclusion. Polyarthritis is the main feature observed in cases of Whipple disease; it is seronegative and associated with general and gastrointestinal symptoms. The molecular analysis of duodenal tissue and/or other tissues remains the method of choice to confirm the diagnosis. Reducing the time to diagnosis is important because severe late systemic and fatal forms of the disease may occur. (J Rheumatol First Release Nov 1 2013; doi:10.3899/jrheum.130328)

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From the Paris Descartes University, Rheumatology A Department and Rheumatology B Department, Cochin Hospital, AP-HP, Paris; Rheumatology Department, Le Mans Hospital; Rheumatology Department, CHU Angers; Rheumatology Department, CHU Clermont-Ferrand; Rheumatology Department, Bichat Hospital, AP-HP, Paris; Rheumatology Department, CHU Nantes; Unità di Reumatologia, Azienda Ospedaliera Universitaria Integrata, Verona, Italy; Rheumatology Department, CHU Strasbourg; and the Rheumatology Department, Teaching Hospital of Lapeyronie and University of Montpellier, France.

M. Meunier, MD, Paris Descartes University, Rheumatology A Department, Cochin Hospital; X. Puechal, MD, Rheumatology Department, Le Mans Hospital; E. Hoppé, MD, Rheumatology Department, CHU Angers; M. Soubrier, PhD, Rheumatology Department, CHU Clermont-Ferrand; P. Dieudé, PhD, Rheumatology Department, Bichat Hospital, AP-HP; J.M. Berthelot, PhD, Rheumatology Department, CHU Nantes; P. Caramaschi, PhD, Unità di Reumatologia, Azienda Ospedaliera Universitaria Integrata; J.E. Gottenberg, PhD, Rheumatology Department, CHU Strasbourg;

L. Gossec, MD, Paris Descartes University, Rheumatology B Department, Cochin Hospital, AP-HP; J. Morel, PhD, Rheumatology Department, Teaching hospital of Lapeyronie and University of Montpellier; E. Maury, MD, Paris Descartes University, Rheumatology A Department, Cochin Hospital; J. Wipff, PhD, Paris Descartes University, Rheumatology A Department, Cochin Hospital; A. Kahan, PhD, Paris Descartes University, Rheumatology A Department, Cochin Hospital; and Y. Allanore, PhD, Paris Descartes University, Rheumatology A Department, Cochin Hospital.

Address correspondence to Professor Y. Allanore, Rheumatology A Department, Cochin Hospital, AP-HP, 27 rue du faubourg St Jacques, Paris, 75014 France. E-mail: yannick.allanore@cch.aphp.fr

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Whipple disease is a very rare chronic multisystemic bacterial infection caused by *Tropheryma whipplei*, mainly affecting middle-aged men. The spectrum of clinical manifestations is very broad[1,2,3] and it is always fatal without antibiotic treatment. The natural course of classic Whipple disease is characterized by 2 stages. An inaugural prodromal stage is inconstant in three-quarters of cases, involving nonspecific symptoms, including joint pain. In the later stage there is weight loss and diarrhea in most cases. The median delay between these 2 stages is 6 years[4]; however, clinical progression may be more rapid in patients under immunosuppressive therapy[5,6]. Joint involvement[2,7,8,9,10,11] is a common feature of Whipple disease (65% to 90%), and begins during the prodromal stage of the disease. It usually develops as a chronic, rheumatoid factor (RF)– negative, intermittent, and nonerosive arthritis. Oligoarthritis seems to be less frequent than polyarthritis and the joints usually affected are the large joints: knees, wrists, and ankles. Presentations mimic rheumatoid arthritis (RA) or, less frequently, spondyloarthritis (SpA) in cases of axial joint involvement[12].

Other manifestations of classic Whipple disease[2,7,8,9,10,13,14,15] are fever (38%); gastrointestinal

symptoms with weight loss (93%); diarrhea (81%); abdominal pain; neuropsychiatric involvement (33%) with diverse manifestations; cardiac involvement (17–55%) with pericarditis, myocarditis, or endocarditis; pulmonary involvement with pleural effusion (14%); pulmonary infiltration; and mediastinal or mesenteric lymph node granulomas (52%).

The diversity of the clinical manifestations explains why diagnosis is often delayed after the first appearance of symptoms.

Diagnosis is mostly confirmed by periodic acid Schiff (PAS) staining and PCR; *T. whipplei* cannot be cultured by traditional methods[2,3,16]. After PAS staining, small-bowel biopsies present magenta inclusions within macrophages of the lamina propria. Biopsies of other tissues, for example lymph nodes, and synovial samples show less specific PAS-stained inclusions. PCR is a more recent diagnostic tool that detects the 16S rRNA gene of *T. whipplei* in various tissue samples and body fluids[17,18].

The aim of our study was to report and describe the clinical patterns in patients with rheumatic presentation of Whipple disease and the diagnostic methods used.

MATERIALS AND METHODS

In our retrospective multicenter observational study, we included patients diagnosed with Whipple disease with a rheumatologic presentation, from 1977 to 2011, in the rheumatology units of 9 French hospitals (in Le Mans, Paris, Limoges, Nantes, Clermont-Ferrand, Strasbourg, Montpellier, and Angers) and 1 Italian hospital (Verona). Diagnosis of Whipple disease was confirmed by the rheumatologists from several of the medical centers participating in the study when patients were found to have a compatible clinical history. Definitive diagnosis was established by PAS staining and/or specific PCR for *T. whipplei* on histological samples.

All medical charts, hospitalization, or consultation reports were collected and the medical data were analyzed centrally. Detailed information including age, sex, delay between first symptoms and diagnosis, rheumatologic misdiagnosis history, and history of immunosuppressive treatment (corticosteroids, disease modifying antirheumatic drugs, and/or biotherapies) were collected.

Characteristics of joint involvement were noted, including arthritis, number of affected joints, symptom evolution with time (signs of inflammation, movement, and symmetry), axial joint involvement, PCR values, RF, anticyclic citrullinated peptide antibodies (anti-CCP), and joint destruction measured by radiograph. The general characteristics were noted and included weight loss, asthenia, fever, gastrointestinal involvement (diarrhea, abdominal pain, and hypoalbuminemia), presence of lymph nodes, and neurologic involvement. The types of biopsies performed included duodenal, on lymph nodes, and synovial samples. The results of analysis of biopsies by histological PAS staining and/or specific PCR for *T. whipplei*, and the results of specific PCR tests on fluids (blood, stool, saliva, and/or cerebrospinal fluid) were also recorded.

RESULTS

Twenty-five of the patients were male and the median age was 55 years (range 30–74). The median time to diagnosis from the appearance of the first symptoms was 5 years (range 1–30). Before the diagnosis of Whipple disease, most of the cases were initially diagnosed as inflammatory arthritis. Previous rheumatologic diagnoses and medical treatments for the 29 patients are shown in Table 1.

Table 1. Previous rheumatologic diagnoses and medical treatments received.

	n (%)
First diagnosis	
Spondyloarthritis	10 (37)
Rheumatoid arthritis, RF-negative	8 (30)
Unexplained polyarthritis	4 (15)
Giant cell arteritis	2 (7)
Still disease	1 (4)
Sarcoidosis	1 (4)
Gout	1 (4)
Previous immunosuppressive treatment	24 (89)
Corticosteroids	15 (56)
DMARD	14 (52)
Biotherapy	8 (30)

DMARD: disease-modifying antirheumatic drugs.

Immunosuppressive therapy was administered to 89% of the patients, including 1 or several biotherapies for 8 patients (30%); 5 patients received 1 course of anti-tumor necrosis factor (TNF) agent; 2 patients received 2 or 3 courses of anti-TNF; and 1 patient received 3 courses of anti-TNF and then was treated with abatacept and rituximab. After the initiation of immunosuppressive therapy, general health, digestive, or joint symptoms deteriorated in 13 patients (54%). Among the 8 patients who received biotherapy, the systemic and joint symptoms worsened in 7, with 1 case showing no change.

Clinical manifestations are shown in Table 2. Joint involvement was mostly chronic, intermittent, and non-destructive polyarthritis, in some cases asymmetrical and migratory. None of the patients were RF-positive or anti-CCP-positive. Specific location of affected joints was available only for 24 patients. The joints most frequently affected were wrists (15/24, 62%), knees (15/24, 62%), elbows (12/24, 50%), ankles (11/24, 46%), and hands (10/24, 42%), and infrequently shoulders (8/24, 33%) and hips (3/24, 12%). Three patients had diffuse joint involvement of both small and large joints. Seven patients had erosive joint damage (4 of these patients had unilateral or bilateral coxitis), 2 had sacroiliitis, and 2 had carpitis (1 of whom had tarsitis).

Extraarticular signs were frequent (Table 2). Six patients presented with neurological symptoms including isolated headache (n = 1), meningitis syndrome (n = 1), cognitive change and behavior dysfunction (n = 3), and ataxia and adynamia (n = 1). Among the patients with rheumatologic symptoms, those with long delays to diagnosis, especially those exceeding 6 years, had fever less frequently (18% vs 29%), but joint damage more frequently (36% vs 12%) than other patients. C-reactive protein levels were frequently elevated, with a median value of 68 mg/l (range 4–184). Extraarticular manifestations and C-reactive protein levels did not differ according to the type of rheumatologic presentation.

Table 2. Characteristics of patients at diagnosis.

Characteristics	n (%)
Joint involvement	
Arthritis vs arthralgia	20 (69) vs 9 (31)
Mono/olig/polyarticular	2 (7)/8 (27)/19 (66)
Intermittent	16 (55)
Migratory	12 (41)
Asymmetric	9 (31)
Axial joint involvement	9 (31)
Destructive arthritis	7 (24)
General involvement	28 (97)
Weight loss	24 (83)
Asthenia	25 (92)
Fever	14 (48)
Gastrointestinal involvement	17 (59)
Diarrhea	16 (55)
Hypoalbuminemia	9 (31)
Abdominal pain	9 (31)
Lymph nodes	8 (28)
Neurologic involvement	6 (24)

Transitory clinical improvements were observed in 2 cases when antibiotics were prescribed for other purposes. The first patient was prescribed cyclines several times for a febrile polyarthritis, a long time before the diagnosis of Whipple disease was made. The second patient was treated with penicillin A and quinolones for inhalation pneumonia during acute febrile confusion that was secondarily related to neuromeningitis localization of Whipple disease.

In this retrospective cohort, diagnosis of Whipple disease was made by histological and/or molecular biology analysis of duodenal, lymph node, synovial, and skin biopsies. Diagnosis was confirmed in 43% (12/28) of cases using a combination of PAS staining and positive *T. whipplei* PCR tests. In 29% (8/28) of cases, PCR tests were positive for *T. whipplei* in at least 2 tissues or fluids. In 3.6% (1/28) of cases, PAS staining was positive in at least 2 tissues or fluids. In 18% (5/28) of cases, 1 tissue stained positive by PAS. In 7% (2/28) of cases, PCR tests were positive for *T. whipplei* in 1 tissue (Table 3). Data were lacking concerning diagnostic method for 1 patient.

Synovial biopsies were performed in 5 patients, and the sensitivity of PAS staining was 50% and that of PCR tests 100% for *T. whipplei* (Table 3). Duodenal biopsies were performed in 86% of cases, and PAS staining had a sensitivity of 68% and PCR 100% for *T. whipplei*. For the 4 patients who did not have duodenal biopsies in the absence of gastrointestinal symptoms, diagnosis was made by histological PAS staining of lymph node biopsies in 2 patients, by *T. whipplei* PCR tests of lymph node and synovial biopsies in 1 patient, and by *T. whipplei* PCR tests in a synovial biopsy alone in 1 patient. Lymph node biopsies were obtained from 4 patients, and both PAS staining and *T. whipplei* PCR tests had sensitivities of 100% (Table 3). In addition, *T. whipplei* PCR tests were performed on blood, stool, and/or saliva from 14 patients: the sensitivities were 50% for blood, 9% for stool, and 70% for saliva samples (Table 3).

Therapeutic strategies differed substantially between the different centers and dates of inclusion and were too heterogeneous to allow any relevant analyses. Nevertheless, clinical and biological outcomes for all patients included were good after antibiotic treatment. This suggests that the prognosis for patients with a rheumatic presentation may be good, but this remains to be confirmed by further studies.

DISCUSSION

Our study of 29 patients with a rheumatic presentation of Whipple disease was a multicenter, retrospective study and is epidemiologically comparable to other, previously published ones[2,7,8,9,10,13,14]. Although unexplained, it is well known that the disease manifests primarily in males. Most patients are middle aged and there is usually a long delay between the first symptoms and diagnosis, 5 years in our study. This delay before diagnosis can be explained, at least in part, by the rarity of the disease and that the clinical features evolve over several years with various patterns, in many cases not including gastrointestinal symptoms.

Joint involvement is frequent in Whipple disease (65% to 90%) and is often the first prodromal sign of the disease[3,4]. As a consequence, the main differential diagnoses are inflammatory rheumatoid diseases. In our study, most of the patients were initially suspected to have developed SpA (38%) or RF-negative RA (30%), and more rarely unexplained polyarthritis (15%). The high proportion of incorrect SpA diagnoses is probably due to the proportion of axial involvement (31%). Corticosteroids or immunosuppressive treatments prescribed in this context are ineffective, with rapid clinical aggravation or at least persistence of symptoms[5,6], and some patients may develop other major signs of classic Whipple disease[19,20]. In our study, 89% of patients received an immunosuppressive treatment and 30% of patients received a biotherapy, with a rapid clinical progression in 54% and 88% of these cases, respectively. This underlines the extreme caution required before beginning biotherapy, particularly for unexplained polyarthritis. In all cases, the inefficacy of any such treatment should raise the suspicion of incorrect diagnosis, and the emergence of general or digestive symptoms should be seen as indicators of Whipple disease.

Only half of the patients presented with classic palindromic rheumatism, with attacks of arthritis affecting large joints (intermittent in 55% and migratory in 41% of cases)[8,14,21], whereas the other half developed chronic oligoarthritis or polyarthritis. Possibly, the widespread use of immunosuppressants during the course of Whipple disease may lead to poor outcomes, including an increased risk of chronic arthritis. Indeed, in our study arthritis was

Table 3. Results of diagnostic tools used [periodic acid Schiff (PAS) and PCR] for each patient included.

		n = 28		
Patients	PAS Positive, n = 18	PAS-Negative, n = 7	PCR-Positive, n = 22	PCR-Negative, n = 14
1	Duodenal		Duodenal, blood	CSF
2			Synovial, lymph node	CSF, blood
3	Skin	Duodenal	Duodenal, blood	CSF
4		Duodenal	Duodenal	Blood
5	Duodenal		Duodenal	CSF
6			Synovial	CSF
7		Duodenal	Duodenal, skin	
8		Duodenal	Duodenal, skin, stool, CSF	Blood
9		Duodenal	Duodenal, saliva, stool	Blood, CSF
10	Duodenal	Synovial	Synovial, blood, CSF	
11	Duodenal, synovial, lymph node		Synovial, lymph node	
12	Duodenal, lymph node			
13	Duodenal			
14	Lymph node			
15		Duodenal	Duodenal, stool	Saliva, CSF
16	Duodenal		Duodenal, saliva, stool	CSF
17	Lymph node			
18	Duodenal			
19	Duodenal			
20	Duodenal		Duodenal, blood, stool, saliva	CSF
21	Duodenal		Duodenal, synovial	Blood, stool, saliva, CSF
22			Duodenal, saliva, stool	
23	Duodenal		Duodenal	
24			Duodenal, saliva, stool	
25	Duodenal		Duodenal	Blood, saliva
26	Duodenal		Stool, CSF	
27			Duodenal, blood, saliva, stool	CSF
28	Duodenal		Duodenal, blood, saliva, stool	

CSF: cerebrospinal fluid.

more frequent than noninflammatory arthralgia (69% vs 31%), in accordance with previously published studies[4]. Because of the diversity of the clinical rheumatologic presentation of our 29 patients, it is difficult to describe prototypic presentation of articular Whipple phenotype. Axial joint involvement appears uncommon: 31% of patients in our study and 6% to 40% in a previous study[4]. Sacroiliitis and spondylitis have also been described during Whipple disease[22,23], as well as rare cases of *T. whipplei*-related spondylodiscitis[24].

Radiological destruction was present in 24% of our patients and certainly contributed to diagnostic errors and delays. Joint damage, even if uncommon, has been described during Whipple disease without any clear explanation of its mechanisms[4,7,21,22,23,25,26]. However, direct visualization of synovial tissues and synovial fluid culture led to the suggestion that Whipple disease may be associated with the presence of the bacterium in the joint itself, as a kind of septic arthritis[25,27,28]. Probably because of the precocity of joint involvement in the natural course of Whipple disease, the extraarticular manifestations in our patients differed from those described in previously published studies, with less diarrhea (55% reported in our study vs 81% in previously published studies), weight loss (83% vs 93%), lymph node involvement (28% vs 52%), and neurological involvement (24% vs 33%)[2]. Moreover, patients with systemic impairment were more rapidly diagnosed, at a stage when destructive arthritis is less frequent.

Genetic factors predisposing to Whipple disease may be suggested by the predominance of males and the increased frequency of the HLA-B27 antigen among affected patients[29,30], although no consistent causative relationship has been found to date[31].

Untreated Whipple disease leads to severe outcomes, and therefore early diagnosis is important. In our study, duodenal biopsies were performed in 86% of the patients and contributed to diagnosis in all of these cases; the sensitivity for PAS staining was 68% and of PCR tests 100%. Thus, duodenal biopsy should always be obtained if Whipple disease is suspected, even in the absence of gastrointestinal symptoms. Depending on the clinical manifestations, other samples should be tested, such as lymph nodes, synovial fluid, and skin tissue[2,7,9,25,32]. In our study, duodenal biopsies were not obtained from the 4 patients who did not have digestive symptoms. For 5 patients, diagnosis was made by histological PAS staining with duodenal or lymph node biopsies, although

PAS-positive inclusions within cells are nonspecific and positive results are found in various other infectious diseases, such as those caused by *Mycobacterium avium*-intracellulare, *Rhodococcus equi*, *Bacillus cereus*, and histoplasma[3,33,34]. When suspected, diagnosis should be confirmed by PCR tests for *T. whipplei* on the same or other tissue samples[2]. In our study, the diagnosis for 2 patients was based solely on *T. whipplei* PCR tests — one with a synovial biopsy and the second with a duodenal biopsy, without PAS staining or sampling other sites. However, *T. whipplei* PCR results should be interpreted with particular caution in the absence of other diagnostic tests, because false positive results do occur (albeit rarely), mainly owing to contamination[35,36,37] or asymptomatic carriers[38]. Positive *T. whipplei* PCR tests associated with negative PAS staining should be interpreted after confirmation by testing a second PCR target in the same or another tissue sample[2]. For 8 patients, diagnosis of Whipple disease was made by *T. whipplei* PCR tests of samples from 2 sites (duodenal, lymph node, skin, and synovial biopsies; and stool and cerebrospinal fluid samples), allowing a confident diagnosis.

Quantitative *T. whipplei* PCR analysis of saliva and stool specimens can be performed as a first-line noninvasive screening for classical Whipple disease[38]. When both are positive, the positive predictive value for Whipple diagnosis is 95.2%, and therefore duodenal biopsies should be performed to confirm diagnosis.

Our study has several limitations and its retrospective design is the first. The diversity of the diagnostic methods may have been accentuated by the length of the inclusion period (1977 to 2011); consequently, the delays until diagnosis may have been affected by the evolution of diagnostic techniques. This is mainly true for PCR, which only became available in 1997[17]. Also, the number of patients included was small, partly due to the rarity of the disease, and consequently it was not possible to distinguish different major forms of disease course, particularly among the cases with rheumatic presentation. The retrospective design may also have been biased by selective reporting of positive results, artificially increasing the apparent sensitivity of the methods used. However, our study gives a realistic overview of the diagnostic approach to Whipple disease, especially for patients with an initial rheumatic presentation.

Our retrospective multicenter study, including 29 patients with a rheumatic presentation of Whipple disease, illustrates the diversity of clinical manifestations and diagnostic approaches. RF-negative polyarthritis associated with extraarticular signs such as fever and general and gastrointestinal symptoms are suggestive of Whipple disease. Failure to respond to immunosuppressive treatment given in cases of unclassified arthritis is also strongly suggestive. In cases of Whipple disease, early diagnosis is critical to improve the outcome. Rheumatologic involvement is a common early event that, if investigated appropriately, may allow early diagnosis and consequently suitable therapy.

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