# Whipple's Disease with Destructive Arthritis, Abdominal Lymphadenopathy, and Central Nervous System Involvement

MICHAEL C. DeARMENT, TIMOTHY A. WOODWARD, DAVID M. MENKE, PAUL W. BRAZIS, LAURA W. BANCROFT, and SCOTT T. PERSELLIN

***ABSTRACT.*** We describe a patient with Whipple's disease who had an unusual erosive and destructive polyarthritis, massive abdominal lymphadenopathy, asymptomatic central nervous system involvement, and rare manifestations of orbital pseudotumor and orchitis with epididymitis. Taking oral therapy with trimethoprim-sulfamethoxazole he had recurrent flares of orbital pseudotumor, an episode of orchitis with epididymitis, and persistent polymerase chain reaction *T. whipplei*–positive cerebrospinal fluid. Resolution was achieved with a one month course of intravenous ceftriaxone and a 6 month course of azithromycin, and no relapse occurred during 24 months of followup. (J Rheumatol 2003;30:1347–50)

*Key Indexing Terms:*
ARTHRITIS BACTERIAL INFECTION CENTRAL NERVOUS SYSTEM
ORCHITIS WHIPPLE'S DISEASE

Whipple's disease is a rare infectious disease caused by the bacillus *Tropheryma whipplei*. We describe a patient with multisystemic Whipple's disease with a relapsing course requiring an increasingly intensive antibiotic regimen.

## CASE REPORT

A 57-year-old male postal clerk with chronic polyarthritis presented with a one month history of abdominal pain, early satiety, fever, night sweats, and a 30 pound weight loss during the preceding year.

He reported a 10 year history of arthritis beginning with pain, swelling, and morning stiffness of his hands, left knee, and ankle. After initial symptomatic treatment, he was treated with injectable gold. Methotrexate was soon added, but was not tolerated. Hydroxychloroquine was given with gold and prednisone (5–10 mg daily) for about 5 years.

On examination at our institution, he had mild synovitis and limited motion of his wrists, as well as mild synovitis of the bilateral thumb metacarpal phalangeal, ankle, and metatarsal phalangeal joints. Results of abdominal and neurological examination were normal, and he had no palpable adenopathy.

Laboratory studies showed the following values: erythrocyte sedimentation rate 97 mm/h Westergren (reference range 0–22 mm/h), hemoglobin 11.9 g/dl (13.5–17.5 g/dl), albumin 2.25 g/dl (3.5–5.0 g/dl), and globulin 3.35 g/dl (0.7–1.7 g/dl). Tests for rheumatoid factor (RF), antinuclear antibody, and antibodies to extractable nuclear antigens were negative.

Radiographs of the hands showed bilateral carpal collapse with near-complete loss of carpal joint spaces, ankylosis, and erosions (Figures 1A, 1B). Radiographs of the feet showed marked narrowing of tarsal and subtalar joints with arch collapse (Figures 1C, 1D).

Computed tomography (CT) of the abdomen revealed multiple enlarged retroperitoneal, mesenteric, portal, and celiac nodes suggesting lymphoma (Figure 2). CT guided biopsy of the mesenteric lymph nodes revealed lymphatic tissue with macrophages that stained positive with periodic acid–Schiff with diastase digestion (PAS-D) and Gomori methenamine silver (Figure 3). Staining for acid-fast bacilli was negative. Examination of the brain with magnetic resonance imaging was unremarkable. Subsequent analysis of cerebrospinal fluid (CSF) showed pleocytosis, with a white blood cell count of $11.6 \times 10^9$/l (reference range 0–$5 \times 10^9$/l), and polymerase chain reaction (PCR) testing for *T. whipplei* was positive. These results confirmed the diagnosis of Whipple's disease with central nervous system (CSN) involvement.

Treatment was initiated with trimethoprim (160 mg) and sulfamethoxazole (800 mg), orally twice daily. The systemic symptoms and polyarthritis progressively resolved over 6 months. Gold injections were discontinued and the steroid dose was tapered. Prednisone could not be completely discontinued because of recurrence of orbital pseudotumor, characterized by eye pain, swelling, and altered mobility, which responded promptly to higher dose prednisone.

After 6 months of therapy, pain and tenderness developed in the right testicle. Orchitis and epididymitis were documented by ultrasound, with resolution documented 5 months later. Because PCR tests for *T. whipplei* in CSF were persistently positive after 12 months of therapy, the frequency of trimethoprim-sulfamethoxazole administration was increased to 3 times daily. After 19 months of oral therapy with recurrent flares of orbital pseudotumor, he was given ceftriaxone (2 g) intravenously, daily for 1 month, and azithromycin (500 mg) orally, daily for 6 months. PCR findings in CSF became negative after the parenteral therapy and were negative when rechecked 7 and 24 months later.

## DISCUSSION

The clinical spectrum of Whipple's disease has continued to expand since Dr G.H. Whipple's initial case description in 1907[1]. Intermittent migratory oligo- or polyarthritis occurs in nearly all patients with Whipple's disease and is the most

*From the Division of Pulmonary Medicine, Division of Gastroenterology and Hepatology, Department of Laboratory Medicine and Pathology, Department of Ophthalmology, Department of Radiology, and Division of Rheumatology, Mayo Clinic, Jacksonville, Florida, USA.*

*M.C. DeArment, MD, Division of Pulmonary Medicine; T.A. Woodward, MD, Division of Gastroenterology and Hepatology; D.M. Menke, MD, Department of Laboratory Medicine and Pathology; P.W. Brazis, MD, Department of Ophthalmology; L.W. Bancroft, MD, Department of Radiology; S.T. Persellin, MD, Division of Rheumatology.*

*Address reprint requests to Dr. S.T. Persellin, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224.*

*Submitted June 13, 2002; revision accepted November 25, 2002.*

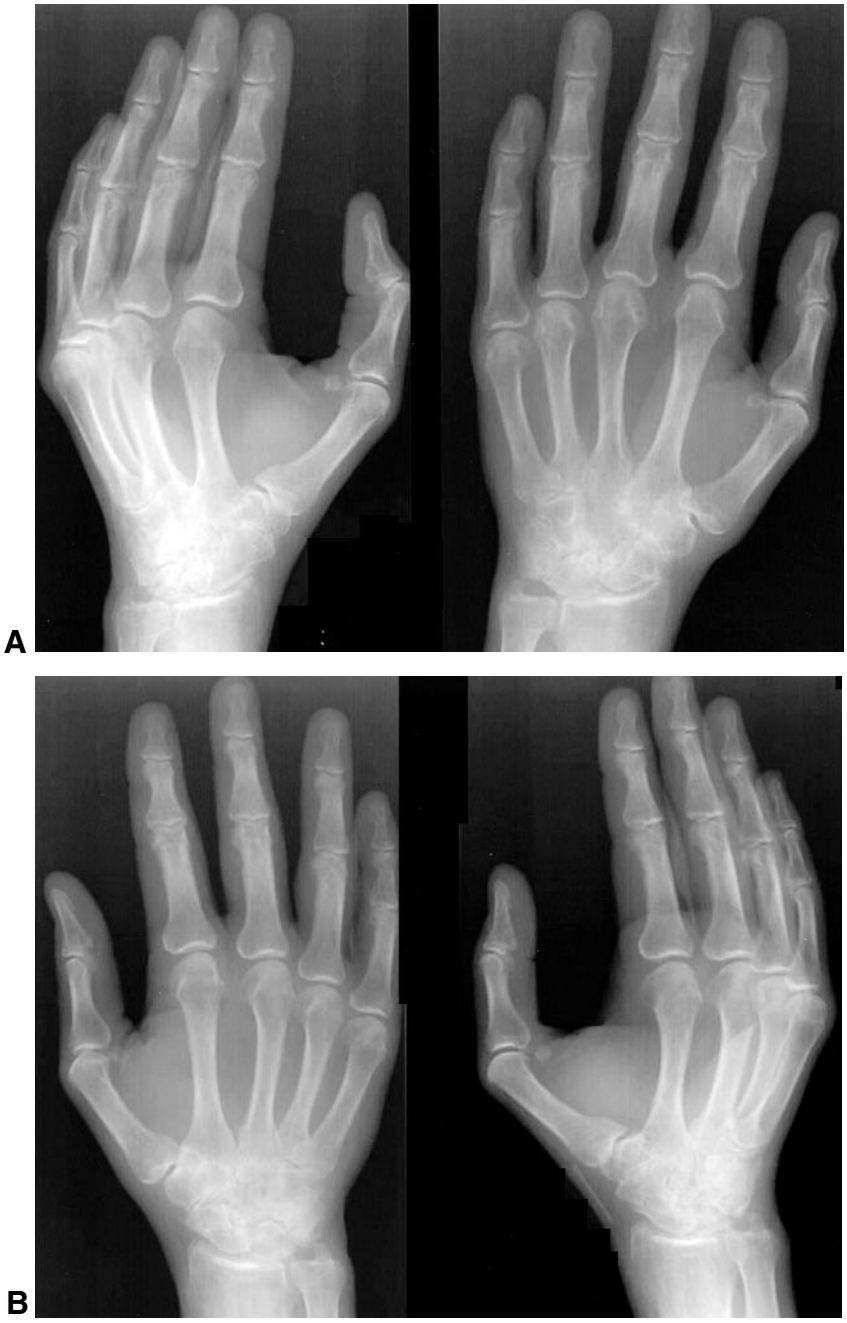


*Figure 1.*

common presenting symptom, preceding the diagnosis by a mean of 6–10 years[2]. Severe, frequent, recurrent self-limited attacks lasting hours to days are typical, mimicking palindromic rheumatism. Joints most commonly affected are knees, ankles, and wrists; less frequently affected are hips, elbows, and small joints of the hands and feet.

Chronic polyarthritis is less common and is usually nondeforming, nonerosive, and seronegative for RF. As in our patient, involvement may be bilateral and symmetric, mimicking rheumatoid arthritis. Subcutaneous nodules are rare and have typical PAS staining with histopathology[3]. Joint radiographs are usually normal; less frequently, they may reveal joint space narrowing, erosions, carpal fusion, and sacroiliitis[4]. Histologic staining, electron microscopy, and PCR of the synovium and synovial fluid have confirmed the presence of *T. whipplei*[5].

CNS involvement has been reported in 10% to 43% of patients with Whipple's disease[6], most frequently with slowly progressive dementia, supranuclear gaze palsy, and myoclonus. CNS disease may be present without identifiable gastrointestinal tract disease[7]. Our patient had persistent asymptomatic CNS involvement identified by PCR

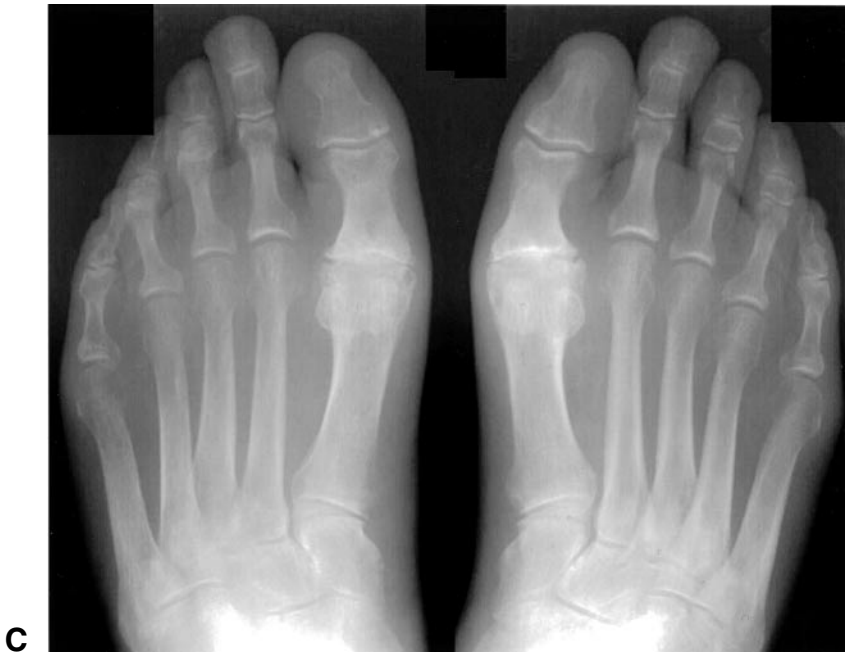


*Figure 1*. Radiographs of extremities of a 57-year-old man with Whipple's disease. A and B, hands. C and D, feet.

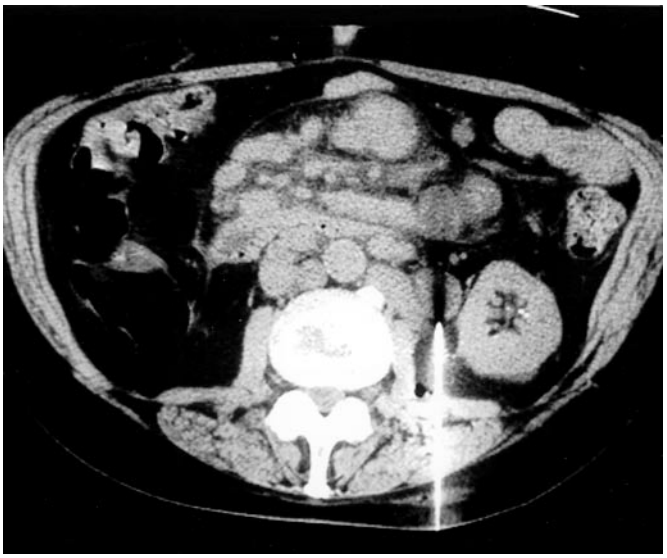

*Figure 2*. Computed tomography scan of the abdomen.

testing of CSF. Systematic PCR testing of CSF is needed to evaluate the hypothesis that CNS involvement may be nearly universal in Whipple's disease[8].

Our patient developed clinical orchitis and epididymitis, confirmed by testicular ultrasound examination. This is a rare manifestation, likely representing disease relapse. *T. whipplei* has been identified in the testis postmortem in 2 patients with Whipple's disease[9], and epididymitis was found in one patient[10].

Our patient had recurrent flares of orbital pseudotumor before diagnosis of Whipple's disease. Recurrent flares after initial antibiotic therapy, with positive PCR testing of CSF, were consistent with disease relapse. This is also consistent with reports of orbital pseudotumor occurring in patients

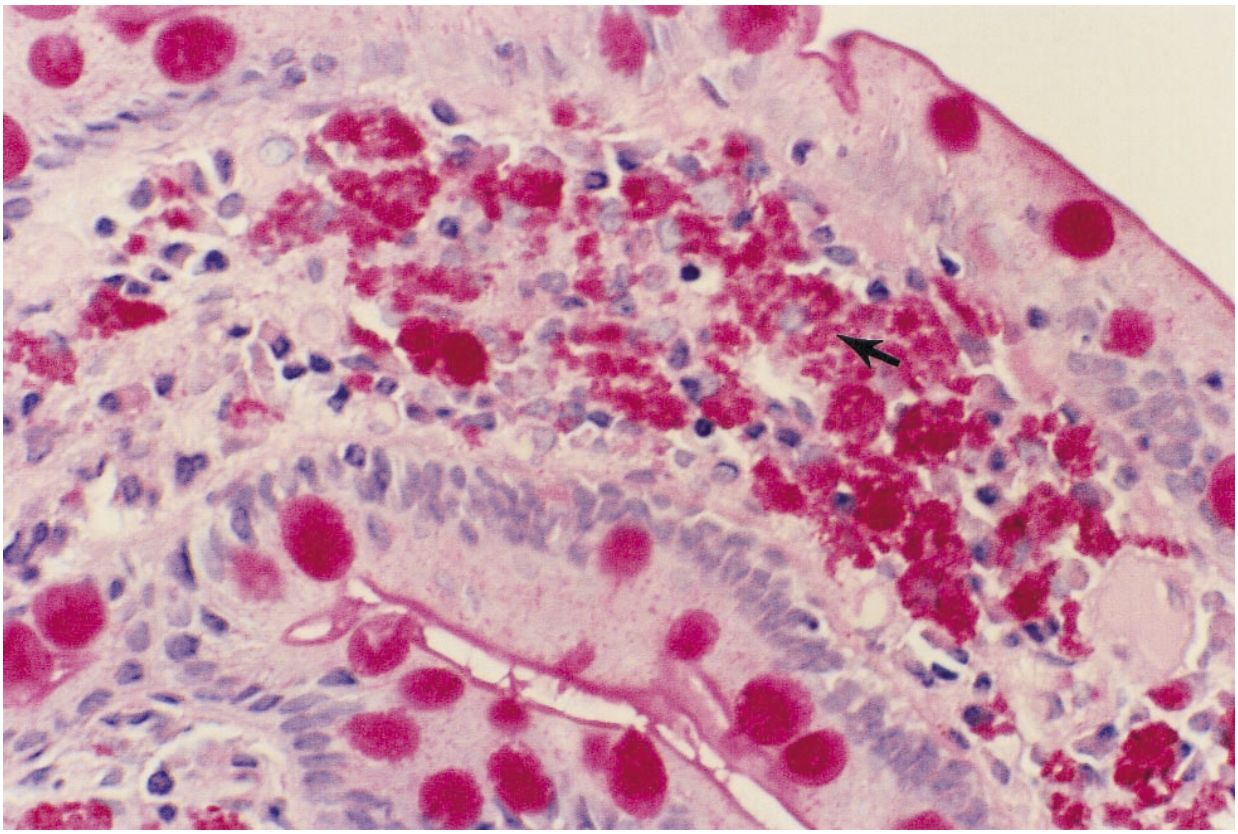

*Figure 3*. Lymphatic tissue from CT guided needle biopsy of the mesenteric lymph nodes. Histiocyte filled with bacteria (arrow). (Periodic acid–Schiff with diastase digestion and Gomori methenamine silver staining; original magnification ×400.)

with coexisting orchitis and epididymitis, suggesting both are indicators of relapse[10,11].

Whipple's disease is a curable infection caused by a bacterium with known antibiotic sensitivities. Clinical resolution of systemic symptoms and diarrhea occurs within days — and of arthritis, within weeks — of initiating appropriate antibiotic therapy. Current antibiotic recommendations are empirical. In view of the high rate of initial asymptomatic CNS involvement and late CNS relapses[6], an initial intensive antibiotic regimen for all patients with Whipple's disease should include agents that cross the blood-brain barrier. Initial treatment with ceftriaxone (2 g, intravenously twice daily for one month) and streptomycin (1 g, intravenously daily for 2 weeks) is commonly recommended[12]. This would be followed by a one year course of daily oral cefixime (400 mg) or twice-daily trimethoprim (160 mg) and sulfamethoxazole (800 mg) for chronic therapy. PCR testing of CSF, with continued monitoring if initial results are positive for *T. whipplei,* may help monitor effectiveness of treatment in resolving CNS involvement[6].

## REFERENCES


1. Whipple GH. A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. Johns Hopkins Hosp Bull 1907; 18:382-91.
2. Puechal X. Whipple disease and arthritis. Curr Opin Rheumatol 2001;13:74-9.
3. Paulley JW. A case of Whipple's disease (intestinal lipodystrophy). Gastroenterology 1952;22:128-33.
4. Scheib JS, Quinet RJ. Whipple's disease with axial and peripheral joint destruction. South Med J 1990;83:684-7.
5. O'Duffy JD, Griffing WL, Li CY, Abdelmalek MF, Persing DH. Whipple's arthritis: direct detection of *Tropheryma whippelii* in synovial fluid and tissue. Arthritis Rheum 1999;42:812-7.
6. Dutly F, Altwegg M. Whipple's disease and "Tropheryma Whippelii." Clin Microbiol Rev 2001;14:561-83.
7. Feurle GE, Volk B, Waldherr R. Cerebral Whipple's disease with negative jejunal histology. N Engl J Med 1979;300:907-8.
8. Dobbins WO III. Whipple's disease [editorial]. Mayo Clin Proc 1988;63:623-4.
9. James TN, Bulkley BH, McAllister HA Jr, Kent SP. Testicular lesions in Whipple's disease. J Lab Clin Med 1985;105:359-67.
10. Middlekauff HR, Fang MA, Hahn BH. Polyarteritis nodosa of the epididymis in a patient with Whipple's disease. J Rheumatol 1987;14:1193-5.
11. Orssaud C, Poisson M, Gardeur D. Orbital myositis, recurrence of Whipple's disease [French]. J Fr Ophtalmol 1992;15:205-8.
12. Schnider PJ, Reisinger EC, Berger T, Krejs GJ, Auff E. Treatment guidelines in central nervous system Whipple's disease [letter]. Ann Neurol 1997;41:561-2.