Cerebral Relapse of Sarcoidlike Whipple’s Disease

F. P. J. Peters, R. S. M. E. Wouters, A. P. de Bruine, and R. W. Stockbrügger

Whipple’s disease, an infection with the recently identified intracellular bacillus *Tropheryma whippelii*, is a systemic disorder that can be life threatening when untreated. In a few patients, the signs and symptoms of the disease are similar to those of sarcoidosis, and this illness is referred to as sarcoidlike Whipple’s disease. This variant must be recognized because patients with sarcoidlike Whipple’s disease must be treated with antibiotics instead of corticosteroids, which would be indicated for patients with true sarcoidosis. We describe a 53-year-old man who had sarcoidlike Whipple’s disease with polyvisceral granulomatous dissemination that was treated with procaine penicillin G and streptomycin followed by doxycycline. His condition initially improved. However, during his 4-month course of treatment he developed a cerebral relapse; this relapse was successfully treated with ceftriaxone and cefixime.

Whipple’s disease was first described in 1907 in a patient with polyarthritis, diarrhea, weight loss, and mesenteric lymphadenopathy [1]. Subsequently, about 617 cases were reported worldwide until 1986 [2]. Whipple’s disease is thus a rare disorder that is frequently characterized by diarrhea, malabsorption, abdominal pain, weight loss, arthralgia, fever, increased skin pigmentation, and lymphadenopathy. Sometimes CNS manifestations (confusion, nystagmus, and ophthalmoplegia) as well as ocular and cardiac manifestations are present [3].

The diagnosis of Whipple’s disease is based mainly on periodic acid–Schiff (PAS) staining or electron microscopy of affected tissue. Recently, a PCR–based assay of the involved tissue has become available [4]. The treatment of choice for Whipple’s disease consists of antibiotics (e.g., co-trimoxazole, tetracycline, streptomycin, procaine penicillin G, and third-generation cephalosporin), which can be life saving.

We describe the case of a patient with an unusual presentation and course of Whipple’s disease. To our knowledge, no patient with sarcoidlike Whipple’s disease involving the CNS has been described. This case represents the third report of successful treatment of a cerebral relapse of Whipple’s disease with cefixime and ceftriaxone [5, 6].

Case Report

A 53-year-old man was admitted to the hospital because of progressive weight loss (24 kg) in the preceding 4 years. His medical history revealed migrating arthritis that had started 8 years before presentation. Because of temporary hypercalcemia (calcium level, 3.16 mmol/L) and an enlarged left inguinal lymph node (biopsy revealed granulomatous adenitis without PAS-positive macrophages), the diagnosis of sarcoidosis was considered and treatment with prednisone (30 mg per day) was started. In the course of this treatment, his clinical condition worsened and diarrhea developed. Further evaluation with a barium follow through of the small intestine showed coarsening of jejunal folds and a pathological appearance of the terminal ileal loop. The diagnosis of Crohn’s disease was suggested, and mesalamine was added to the patient’s therapeutic regimen.

Because of further clinical deterioration, cutaneous hyperpigmentation, proven steatorrhea (42 g every 3 days), and multiple enlarged intraperitoneal and retroperitoneal lymph nodes without fever (figure 1), the diagnosis of Whipple’s disease was considered. A duodenal biopsy showed pathognomonic PAS-positive macrophages in the lamina propria (figure 2). There were no signs of mycobacterial infection (staining of small bowel specimens for acid-fast bacilli was negative).

The patient initially received treatment with procaine penicillin G (600,000 U im twice a day) and streptomycin (1 g im once a day) for 14 days, which was followed by doxycycline (100 mg orally once a day). His clinical condition improved initially with this treatment, but during a 4-month course of treatment he developed neurological symptoms (intermittent ptosis of both eyes as well as myoclonus of the tongue and of the left side of the body).

An MRI of the cerebrum showed a right-sided frontoparietal lesion (figure 3). A cerebral localization of Whipple’s disease was considered. CSF examination, which was negative for PAS-positive macrophages, was the only attempt made to obtain cytological or microbiological proof of the cerebral focus. For 2 months he was treated with co-trimoxazole (960 mg iv for 1 week, followed by orally twice a day); his condition deteriorated after this treatment, so therapy with chloramphenicol (1 g iv three times a day) was started, but he became allergic to this drug. His treatment was then switched to ceftriaxone (2 g iv twice a day for 14 days) and thereafter to oral cefixime, after which his clinical and cerebral condition improved. At
the patient’s last follow-up visit, 14 months after the cerebral relapse and 11 months after cefixime treatment was started, he appeared well and his condition had improved; he had not had a relapse (figure 4).

Discussion

As Whipple’s disease has a varied clinical presentation, the diagnosis cannot be made on the basis of the clinical picture. The most important diagnostic procedure is proximal duodenal biopsy, as most patients with this disease have involvement of the proximal intestine. PAS staining of biopsy material shows foamy macrophages throughout the lamina propria. The same reaction is seen only as a consequence of *Mycobacterium avium* complex infection in patients with AIDS or with histoplasmosis. Whipple’s disease can be differentiated from *M. avium* complex infection by acid-fast staining of histological material, which is positive for patients infected with *M. avium* complex [4]. When there is no intestinal involvement, the diagnosis of

![Figure 1. A CT of the abdomen of a patient with sarcoïd-like Whipple’s disease shows multiple enlarged intraperitoneal and retroperitoneal lymph nodes (arrow).](image1)

![Figure 2. Endoscopic biopsy specimen of the duodenal mucosa of a patient with sarcoïd-like Whipple’s disease. Note the groups of foamy macrophages in A (arrow; stain, hematoxylin-eosin; original magnification, 300×) and the PAS-positive granular material in B (arrow; PAS staining; original magnification, 25×).](image2)
Whipple’s disease can be made only by electron microscopy or PCR of affected tissue (the sequences of bacterial 16S rRNA in infected tissues are amplified) [7, 8].

We have described a patient with a syndrome that resembled sarcoidosis, an unusual manifestation of Whipple’s disease (21 cases of sarcoid-like Whipple’s disease have been reported) [9]. Nine percent of Whipple’s patients have a granulomatous inflammatory reaction in involved tissues [2]. Sometimes the macrophages in a granulomatous inflammatory reaction fail to stain with the PAS method, and a false diagnosis of sarcoidosis is made. To distinguish between Whipple’s disease and sarcoidosis, electron microscopy or the recently developed PCR assay should be performed on infected tissue.

Our patient’s condition initially improved with the recommended combination of antibiotics [10], but he later developed a relapse with neurological manifestations of Whipple’s disease. The neurological signs were probably not induced by a cerebrovascular accident because the symptoms decreased after treatment with a third-generation cephalosporin. The appearance of CNS Whipple’s disease on imaging studies is not specific [11]; thus, in our case the diagnosis was made retrospectively.

The CNS can be affected by Whipple’s disease after treatment with antibiotics (e.g., tetracycline) that do not penetrate uninflamed meninges [5, 12]. In addition, in our patient’s case the previous prednisone treatment might have facilitated the probable cerebral infection by reducing cell-mediated immunity.

Relapse of Whipple’s disease has been reported in 31 of 88 patients after apparently successful treatment [13]. CNS relapse occurred most frequently (13 of the 88 patients). It has been suggested that patients should always initially be treated with
antibiotics that have reliable CNS penetration [5, 13]. However, Cooper et al. [5] described a patient who developed a cerebral relapse during first-line therapy with trimethoprim-sulfamethoxazole, which is known for good CNS penetration. Their patient, like our own, was also successfully treated with cefixime. It is not clear why our patient’s CNS relapse did not resolve with trimethoprim-sulfamethoxazole therapy. It is conceivable that the patient was not compliant with therapy. However, he denied this option. Another explanation is that Tropheryma whippelii could be resistant to trimethoprim-sulfamethoxazole.

In conclusion, it is important to include sarcoïd-like Whipple’s disease in the differential diagnosis for patients with so-called sarcoïdosis since patients with the former disease should be treated with antibiotics whereas patients with sarcoïdosis should be treated with corticosteroids. Sarcoïd-like Whipple’s disease should be considered in the differential diagnosis for patients with so-called sarcoïdosis whose condition does not improve while they are receiving corticosteroid treatment. In such cases the diagnosis is based on PAS staining of any granuloma. If the PAS staining of the granuloma is negative, the specimen should be examined by electron microscopy or PCR. When the diagnosis of Whipple’s disease is made, it is better to use primary CNS-penetrating drugs than to wait for a relapse and then treat it.

References


