Whipple disease of the central nervous system: an unusual occurrence in association with acquired immune deficiency syndrome

Case report

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Whipple disease is a multisystem infectious disease caused by Tropheryma whipplei. It commonly affects the gastrointestinal tract causing abdominal discomfort, diarrhea, weight loss and fatigue. Systemic manifestations such as fever, chronic migratory arthralgias, night sweats, and lymphadenopathy are also commonly seen. Tropheryma whipplei is the offending microbe responsible for causing Whipple disease. Central nervous system manifestations are seen in 10–20% of patients with documented Whipple disease.13

Infection of the CNS has been documented in many forms including mass lesions,34 intracranial hypertension,6,32,48 encephalopathy,5,55 ocular and skeletal myoclonus,8,43 and dementia.5,55 Ocular and oculofaciocortical myorhythmia are 2 movement disorder manifestations that are pathognomonic for CNS Whipple disease.25,50,53 Rare reports exist of Whipple disease isolated to the CNS without gastrointestinal tract or systemic manifestations.24 With appropriate antimicrobial treatment, Whipple disease can be cured. However, untreated, this disease often leads rapidly to death.

Acquired immune deficiency syndrome is an acquired profound decrease in the immunity of the body due to infection by the HIV. It was first recognized in 1981 and now affects ~34 million people worldwide. Central nervous system involvement is seen in nearly 50% of cases of HIV infection, usually due to an opportunistic infection. The most common CNS manifestations of AIDS are toxoplasmosis, primary CNS lymphoma, progressive multifocal leukoencephalopathy, and cryptococcal abscess; in fact, all of these are considered AIDS-defining illnesses, signaling the transition from HIV infection to AIDS.

The occurrence of CNS Whipple disease in a patient with HIV/AIDS is extremely unusual. In fact, it has only been reported in the literature once28 and, moreover, that case was not confirmed with electron microscopy. We present the second case of intracranial Whipple disease in a patient with AIDS and the first such case confirmed with electron microscopy. Our case also demonstrates the utility of stereotactic biopsy to obtain a definitive histological diagnosis for the fairly common problem of deep-seated intracranial lesions in the setting of HIV infection; the importance of this is especially apparent in a case such as this when the actual diagnosis was not a part of the routine differential diagnosis.

Case Report

Presentation. This 35-year-old African-American man presented with a 6-month history of intermittent
mass lesions in patients suffering from HIV infection, for initial management of newly diagnosed intracranial abscess, CNS tuberculosis, and metastatic cancer.

Differential Diagnosis. Given the newly diagnosed AIDS status of the patient, the differential diagnoses based on the radiographic findings were toxoplasmosis, primary CNS lymphoma, progressive multifocal leukoencephalopathy, cryptococcal abscess, and viral encephalitis. Other less likely considerations included bacterial abscess, CNS tuberculosis, and metastatic cancer.

Medical Treatment. Based on the standard of care for initial management of newly diagnosed intracranial mass lesions in patients suffering from HIV infection, the patient was empirically started on combination therapy of sulfadiazine and pyrimethamine for a presumptive diagnosis of toxoplasmosis. Despite the 2-week period of antitoxoplasmosis treatment, the patient exhibited no neurological improvement and repeated imaging demonstrated no change in the size of the lesions and, in fact, more surrounding edema was seen.

Biopsy. Because empirical medical treatment failed to elicit a response, we decided to perform a brain biopsy to establish a definitive histological diagnosis. We chose to perform an MR imaging–guided stereotactic biopsy of the right basal ganglion lesion as it was by far the largest and also exhibited the most contrast enhancement. Frozen-section pathology review revealed a nonspecific inflammatory process with a large number of perivascular foamy histiocytes. The second biopsy specimen was evaluated using both permanent histological studies and routine cultures (aerobic/anaerobic/acid fast bacilli/fungal). Permanent section examination confirmed the presence of numerous perivascular foamy histiocytes and mild chronic inflammation. All tissue cultures were negative. The findings of PAS-positive foamy histiocytes raised the possibility of CNS Whipple disease; therefore, electron microscopy was performed. This revealed multiple vacuoles admixed with phagosomes within the cytoplasm of the histiocytes. Within these phagosomes were multiple electron-dense, gram-positive bacillary structures consistent with microorganisms. This constellation of histological findings was consistent with the diagnosis of CNS Whipple disease.

Follow-Up Course. On establishing the histological diagnosis, we instituted appropriate antimicrobial therapy with intravenous penicillin and streptomycin and oral TMP-SMX. The intravenous antibiotics were administered for 2 weeks; repeated neurological examination revealed complete resolution of left-sided face/arm/leg weakness. The patient did, however, suffer 2 focal motor seizures postoperatively, and seizure activity resolved with antiepileptic medication. The long-term treatment plan is to continue the oral TMP-SMX therapy and obtain follow-up MR imaging in 3–6 months (or earlier if symptoms should recur). As the patient is immunocompromised, we decided to continue treatment with TMP-SMX indefinitely. Antiretroviral therapy has also been started. The patient is currently living at home and is able to take care of himself independently.

Discussion

Presentation

Whipple disease was first described in 1907 by Dr. George Whipple at Johns Hopkins. The index case was...
that of a 36-year-old medical missionary with fever, migratory polyarthritis, diarrhea, weight loss, abdominal pain, erythema nodosum, and mesenteric adenopathy. Postmortem examination revealed fatty deposits throughout the body, especially in the intestinal tract and lymph nodes. Therefore, the disease was initially referred to by Whipple as “intestinal lipodystrophy.” Subsequently, Black-Schaffer found, via PAS staining, that the deposits within macrophages were actually glycoproteins and not lipids as originally thought.13 In 1992, Relman and colleagues,43 using molecular genetic techniques, identified the causative bacterium as a gram-positive actinomycete, which they named \textit{Tropheryma whippleii}. The bacterium has never been successfully cultured.

Whipple disease is a rare, multisystem, chronic granulomatous disease mainly affecting middle-aged white males. It typically involves multiple organ systems, such as the gastrointestinal tract, joints, the heart, and mesentery. There is a significant male predominance (up to 6:1) and the peak age of diagnosis is in the 6th decade of life.17 Common systemic findings include diarrhea, weight loss, arthralgias, fever of unknown origin, and rash. On detailed investigation, one often notes that migratory arthralgias often precede the gastrointestinal symptoms by many years.52 On physical examination, peripheral edema, rash, ascites, lymphadenopathy, hyperpigmentation, pulmonary infiltrates, and hepatosplenomegaly may all be seen. Anemia, elevated erythrocyte sedimentation rate, hypocalcemia, and abnormal liver function tests are frequent laboratory abnormalities.

Symptomatic CNS involvement is seen in 10–20% of cases.13 In fact, isolated CNS involvement without systemic abnormalities has been documented in several case reports.12,13,14,17,23,30,34,40,44,52,58 Clinically silent involvement of the CNS has been reported in 40–60% of cases, and these cases were historically discovered only in postmortem studies. Neurological symptoms are variable and may or may not reflect the anatomical location of the lesion. Common neurological findings include dementia, supranuclear gaze palsy, myoclonus, ataxia, hypothalamic dysfunction, altered sensorium, cognitive changes, personality changes, parkinsonism, seizures, and aseptic meningitis.5,13,21,22,31,35,48,50,51,53 Acute increased intracranial pressure has also been reported in association with CNS Whipple disease.33 Oculofaciococular myorhythmia are involuntary movement disorders thought to be pathognomonic for Whipple disease involving the CNS. The former consists of a slow pendular nystagmus associated with synchronous opening and closing of the jaw, whereas the latter differs only in that it also involves nonfacial skeletal muscles.22,35,51,53,58 The concurrent finding of ophthalmoplegia, dementia, and myoclonus is a triad highly suggestive of intracranial Whipple disease, but this triad is only seen in ~ 20% of cases.13

\textbf{Imaging and Workup}

As with most infectious processes affecting the CNS, the neuroimaging findings are nonspecific.21 Imaging evidence of infection may be seen as multiple intracranial masses, a focal mass, cerebritis, meningeal infiltration, or ependymal enhancement. On MR imaging, lesions are most often hyperintense on T2-weighted sequences and enhance diffusely. Ring-enhancing lesions have also been documented. Focal lesions commonly affect the basal ganglia, cerebellum, insula, cingulate gyrus, hypothalamus, and medial temporal lobes.

Evaluation of CSF has also not led to the establishment of any pathognomonic findings. Mild pleocytosis and elevated protein are common nonspecific findings. The finding of “Sieracki” cells, which stain positively for PAS, have also been reported in the CSF evaluation of Whipple disease.57 Given such nonspecific imaging, laboratory, and CSF

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findings, diagnosis of CNS Whipple disease is difficult and depends heavily on histopathology.

**Intervention**

Stereotactic biopsy of intracranial mass lesions in patients with AIDS is a fairly common procedure. To our knowledge, this is only the second reported case of intracranial Whipple disease diagnosed with stereotactic biopsy; Mendel et al. reported the first case of intracranial Whipple disease that was diagnosed using this method; their patient was, however, not immunocompromised. Gildenberg and associates published the largest series of stereotactic biopsy procedures of intracranial AIDS-associated lesions. In their report, 250 stereotactic brain biopsies were performed for diagnostic purposes in patients with AIDS. Whipple disease was not diagnosed in any of these cases. Our case illustrates that Whipple disease, although rare, should be included on the list of differential diagnoses in AIDS patients with intracranial masses. Because these lesions are often deep seated, small, and/or ill defined, stereotactic biopsy is often needed to obtain an accurate diagnosis.

**Pathological Findings**

The definitive diagnosis of CNS Whipple disease continues to be based on histopathological findings. An inflammatory reaction combining gliosis and vasculitis is seen replacing normal cortex and white matter. Characteristic foamy macrophages are often seen, and their presence should heighten the clinical suspicion of Whipple disease. Perivascular mononuclear cells and gemistocytic astrocytes are also commonly seen and usually outnumber the more characteristic foamy macrophages. Within the foamy macrophage can be found PAS-positive, diastase-resistant granules.

Both Chears and Ashworth and Yardley and Hendrix initially described the characteristic electron microscopic findings associated with Whipple disease in 1961. Both groups described findings from intestinal mucosa, but these findings have subsequently been seen on evaluation of affected neural tissue. The rod-shaped microbes measure 1.5–2.5 µm long and 0.25 µm wide and contain a trilaminar plasma membrane. They are surrounded by a 6.08-nm cytoplasmic membrane and a 20-nm cell wall. The bacilli can be seen within the PAS-positive granules of the foamy macrophages.

Polymerase chain reaction amplification assays have also been developed to identify the 16S RNA specific for *Tropheryma whippelii*. Some studies have also suggested that polymerase chain reaction of tissue and CSF may be a modality with which to monitor response to therapy. Often, as in our case, histopathological results will be diagnostic, rendering further confirmation with polymerase chain reaction unnecessary.

**Treatment**

Prior to antibiotic treatment of Whipple disease, 211
cases were fatal. With antimicrobial treatment, the disease is usually curable. However, the prognosis is worse if the CNS is involved initially or at the time of relapse. The initial recommendation for treatment was 2 weeks of intravenous penicillin and streptomycin followed by a 1-year course of oral tetracycline. However, in the context of an intact blood-brain barrier, this combination may not be expected to achieve therapeutic concentrations in the CNS. In 1984, Ryser and coworkers presented a case report in which there was complete reversal of Whipple disease–associated dementia with the long-term use of oral TMP-SMX. This is likely due to the fact that TMP-SMX readily penetrates normal meninges, reaches effective levels within lymphocytes, is well absorbed orally, and can be used safely for a long time. The regimen of intravenous penicillin/streptomycin for 2 weeks followed by oral TMP-SMX for 1 year was also demonstrated to be effective in preventing CNS relapses. This was an important finding given the extremely poor outcomes commonly noted in patients with CNS relapses. Ceftriaxone has also been demonstrated to be effective; its ability to penetrate the blood-brain barrier may, in fact, make it a more ideal first-line antibiotic agent. Long-term treatment for at least 1 year is recommended for CNS Whipple disease.

**Association With AIDS**

The association between immune deficiency and Whipple disease has been a controversial topic without definitive conclusion to date. This is an obvious question in our case given the simultaneous occurrence of AIDS and Whipple disease. In 1981, Dobbins demonstrated a pattern of cell-mediated immune deficiency in which there was a diminished response of lymphocytes to the mitogen, phytohemagglutinin. Defective macrophage processing of bacterial antigens (thus leading to the glycoprotein or mucopolysaccharide that stains PAS positive) was also observed. This finding was also noted in a separate case report of 1 patient described in 1985 by Bjerkenes et al. Phagocytosis, intracellular killing, and antigen presentation were found to be normal in this patient, but the level of intracellular degradation was significantly lower. That this was a cell-mediated phenomenon was confirmed in this study, as a combination of the patient’s serum and control lymphocytes did not reproduce the results. There was also a depressed delayed hypersensitivity reaction in all those tested in these reports. Interestingly, there was no humoral immune deficiency observed in either of these reports. There has also been a reported association noted between HLA-B27 (human leukocyte antigen B*27) and Whipple disease, as it tends to occur more commonly (28%) than in the general population (10%). However, despite these abnormal cell-mediated responses in conjunction with Whipple disease, it is not a commonly diagnosed disorder among immunosuppressed patients. The aforementioned associations, however, make it difficult to ignore the likely immune-mediated nature of the disease and certainly raise the question of whether Whipple disease is perhaps an opportunistic infection.

In 1986, Jankovic described a case of Whipple disease affecting the CNS in a patient with AIDS. Although clinically and histologically consistent with Whipple disease, this case was not confirmed with electron microscopy. Autran et al. also described a case of a Haitian woman with AIDS in whom Whipple disease was diagnosed, but this infection was later found to be caused by *Mycobacterium avium-intracellulare*. Other reports have described infections in AIDS patients which mimic Whipple disease; the majority of these were found to be due to *Mycobacterium avium-intracellulare* or *Rhodococcus equi*. In 1995, Maiwald et al. were able to detect *Tropheryma whippelii* DNA in a patient with AIDS, but the patient had no CNS involvement. To our knowledge, ours is the first report of electron microscopy–confirmed CNS Whipple disease in a patient with AIDS.

**Conclusions**

Involvement of the CNS in both Whipple disease and AIDS is common. However, Whipple disease of the CNS in a patient with AIDS has only been documented once previously. We present the case of CNS Whipple disease in a patient with newly diagnosed AIDS. The use of stereotactic biopsy allowed us to establish a histological diagnosis of Whipple disease. Appropriate antimicrobial therapy resulted in resolution of neurological symptoms.
Our case raises questions about whether Whipple disease may be an opportunistic infection and certainly supports an immune-mediated pathogenesis. Whipple disease should be added to the differential diagnosis of intracranial mass lesions in patients with AIDS.

Disclosure

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References


Whipple disease of the CNS in AIDS


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