

Intracerebral Whipple disease: unusual location and bone destruction

Case report

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✓ Whipple disease is a rare systemic bacterial infection characterized by migratory polyarthralgia and chronic diarrhea. In 5 to 20% of patients with Whipple disease, the infection may present initially with or eventually develop symptoms related to the central nervous system (CNS). Although CNS involvement is a known feature of systemic Whipple disease, intracerebral mass lesions are uncommon. Mass lesions in these cases are typically deep seated and multifocal. Cortico-subcortical regions are unusual sites of CNS involvement in cases of Whipple disease. In the present paper, the authors describe the first case of Whipple disease to feature a single corticosubcortical solid frontoparietal mass lesion that displayed homogeneous contrast enhancement on neuroimaging and was associated with bone destruction of the calvaria. Although CNS involvement has been observed in the form of deep-seated mass lesions in cases of systemic Whipple disease, unusual manifestations should be kept in mind during diagnosis and follow-up review in these patients.

KEY WORDS • Whipple disease • bone necrosis • brain biopsy • central nervous system

THE first description of Whipple disease was published in 1907 as a case report about a medical missionary living in Istanbul.²⁴ In the first 85 years after this discovery, little was added to our knowledge of this condition. In the past decade, however, researchers have identified the bacterial species involved, and valuable information has been gained regarding the diagnosis and management of Whipple disease.²¹

Whipple disease is a systemic infection caused by the bacterium *Tropheryma whipplei*. Fewer than 1000 cases have been reported in the literature since the disease was first described.³ Reviews in the literature report rates of CNS involvement ranging from 5 to 20%.^{7,9,12,13,20} The most common clinical CNS manifestations are dementia, disturbances of ocular movement, abnormal involuntary movements (particularly myoclonus), and hypothalamic disturbances.^{11,23}

In cases of Whipple disease with CNS involvement, intracranial computerized tomography and MR studies have demonstrated atrophic changes, mass lesions with contrast enhancement, non-space-occupying high-signal lesions in the white matter, ring-enhancing lesions, and hydrocephalus.^{4,10,17,18,25}

Mass lesions in these cases are typically deep seated and have been observed in the hypothalamus, cingulate gyrus, basal ganglia, insular cortex, and cerebellum.¹⁶ In this report, we describe the first case of Whipple disease in which there was a single corticosubcortical frontoparietal mass lesion. Neuroimaging examination in this patient revealed an area of homogeneous contrast enhancement; a mass effect, indicated by shifting of midline structures; and bone destruction of the calvaria.

Case Report

History. This 18-year-old man had experienced diarrhea and a progressively worsening headache for 3 months. After he suffered two simple partial epileptic seizures with motor signs localized to the left side of his face and left arm, he was admitted to our department.

Examination. On admission, the patient was afebrile and all vital signs were normal. A neurological examination showed that the second and third cranial nerves were intact. He exhibited hemiparesis with motor deficits in his left arm and leg (muscle strength 4/5), but there was no sensory disturbance. The deep tendon reflexes in the patient's left upper and lower extremities were increased. His gait was steady and he was able to ambulate independently. Cerebellar examination yielded normal findings.

Abbreviations used in this paper: CNS = central nervous system; MR = magnetic resonance; PAS = periodic acid-Schiff; TMP-SMZ = trimethoprim sulfamethoxazole.

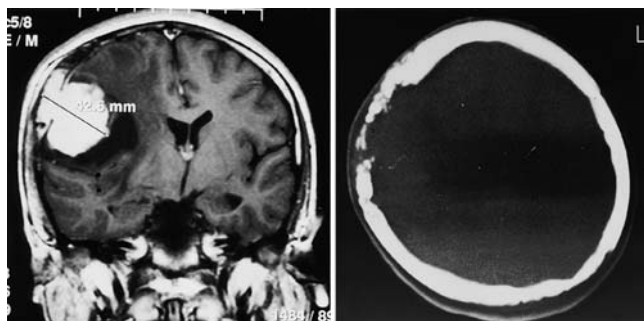


FIG. 1. *Left*: Contrast-enhanced coronal T₁-weighted MR image revealing a homogeneously enhancing, solid mass lesion with a cystic component in the right frontoparietal region. Marked edema and a midline shift are evident. The mass is protruding through the expanded diploë in the calvaria. *Right*: Preoperative computerized tomography scan demonstrating the bone destruction caused by the mass, which is indicated by the erosion of the tabula interna.

Cranial MR imaging performed on the day of admission revealed a solid mass lesion containing a cystic component in the right frontoparietal region of the brain (Fig. 1 *left*). The lesion was isointense on T₁-weighted and hypointense on T₂-weighted images. The mass was protruding through the expanded diploë in the calvaria and eroding the tabula interna (Fig. 1 *right*). Injection of contrast agent revealed that the intradiploic–intradural solid portion of the mass measured 42 × 43 mm in diameter, and the lesion displayed intense, homogeneous contrast enhancement. The medial cystic portion of the lesion exhibited only minimal contrast enhancement. There was a significant mass effect, with marked supratentorial edema in the right cerebral hemisphere. The midline structures were noticeably shifted to the left side, with resultant compression of the right lateral ventricle.

Operation. The patient underwent surgery on the first available day for elective procedures. Directly following the skin incision we could observe the mass, which was causing bone destruction of the calvaria and invading the dura mater. Gross-total excision of the lesion was performed via a right frontoparietal craniectomy, followed by duraplasty (Fig. 2).

Pathological Findings. Pathological examination of the lesion showed reactive gliosis and infiltration of the leptomeninges and brain parenchyma by perivascular lymphocytes and macrophages. There was no evidence of a neoplastic process. Histiocytic and lymphoplasmacytic inflammatory infiltration was noted, and the observed histiocytes contained foamy cytoplasm (Fig. 3). Periodic acid–Schiff preparation revealed intense staining in macrophages and histiocytes, and both cell types contained Gram-positive bacilli in their cytoplasm (Fig. 4). Marked fibrosis accompanied the inflammatory infiltration. Special staining for acid-fast bacilli and fungi was nondiagnostic.

Diagnosis and Postoperative Course. The diagnosis of intracerebral Whipple disease was made on the basis of the patient's clinical status and the pathological characteristics of the cellular infiltration. During the early postoperative period, the patient's motor deficits remained unchanged. When the pathology results were available, the patient was placed on a regimen of oral TMP-SMZ. The young man

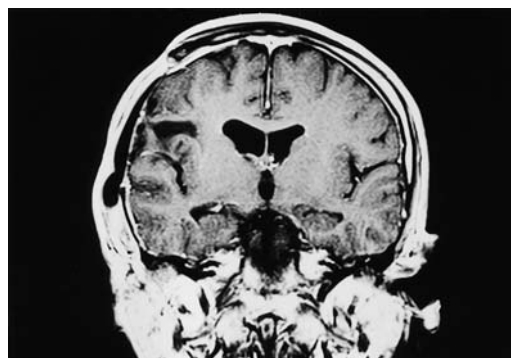


FIG. 2. Postoperative contrast-enhanced coronal T₁-weighted MR image demonstrating total removal of the mass lesion with disappearance of the midline shift.

was discharged without complications after 7 days, and an extended course of oral TMP-SMZ was prescribed. Five months after the operation MR imaging confirmed that there was no recurrence at the original site of the lesion. Currently, the patient is seizure free with no headaches, and his left hemiparesis has improved; he remains on a regimen of oral TMP-SMZ.

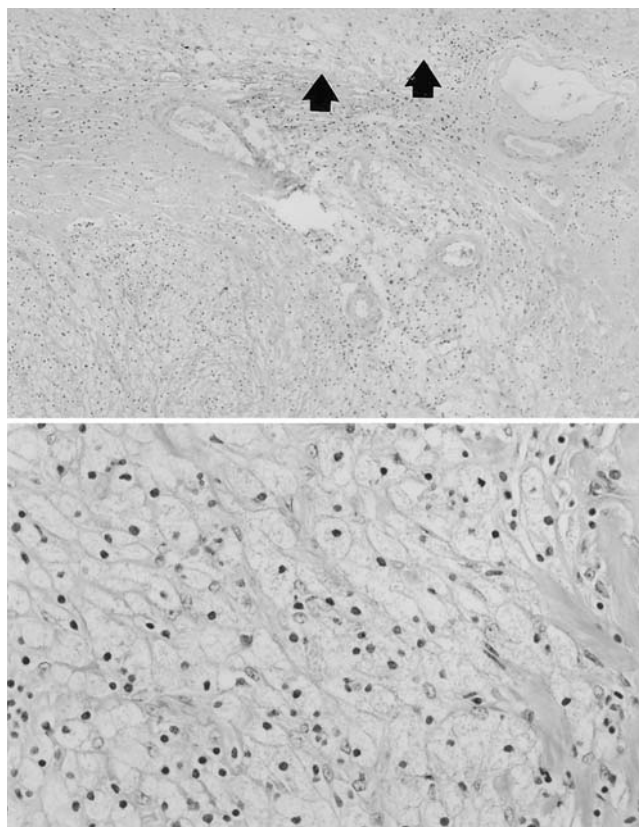


FIG. 3. *Upper*: Photomicrograph of excised tissue showing infiltration of the leptomeninges, subarachnoid space, and brain parenchyma by perivascular lymphocytes and macrophages (*arrows*). H & E, original magnification × 200. *Lower*: Photomicrograph showing histiocytic and lymphoplasmacytic inflammatory infiltration and histiocytes with foamy cytoplasm. H & E, original magnification × 400.

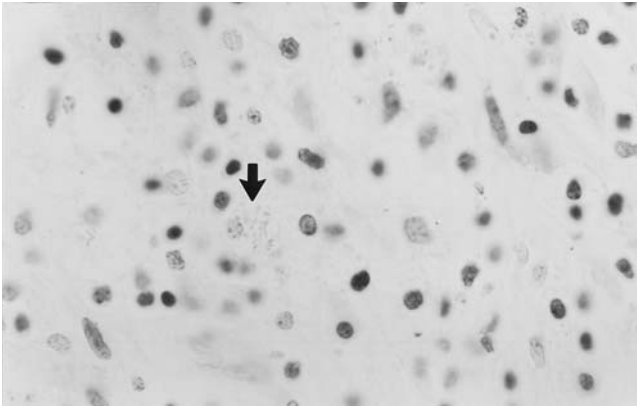


FIG. 4. Photomicrograph demonstrating intracytoplasmic Gram-positive bacilli (arrow) in histiocytes. PAS, original magnification $\times 1000$.

Discussion

Whipple disease is a rare condition characterized by migratory polyarthralgia and chronic diarrhea. In some patients this disease may present initially with or eventually develop signs of CNS involvement.¹⁵ Up to 15% of patients with Whipple disease do not exhibit typical gastrointestinal symptoms or arthralgia during the initial period of the illness.³ In this subset of individuals, the diagnosis may not be made for some time, and is generally only established when symptoms associated with other organ systems predominate during the course of the disease. This was the scenario with our patient, in whom a diagnosis was made only after he started to display neurological manifestations of Whipple disease.

The gross pathological features of Whipple disease in the CNS are mainly seen in the subependymal gray matter surrounding the ventricles and the aqueduct, and in the gray matter surrounding other deep-seated structures.^{3,16} Investigators have noted a predilection for the hypothalamus, cingulate gyrus, basal ganglia, and insular cortex.^{1,10,14,16,17,25}

The morphological characteristics of the causative organism, *T. whipplei*, have been described elsewhere.¹⁹ This pathogen is a rod-shaped bacillus that appears to be weakly Gram positive, stains with PAS dyes, and has no acid-fast properties. This is diagnostically important because the use of staining techniques allowed us to rule out other acid-fast bacilli in our case. Microscopically, the hallmark of Whipple disease in the CNS is the finding of granulomas containing foamy macrophages that react strongly positively to PAS staining and are surrounded by large reactive astrocytes.^{6,16,25}

In our case, the pathological examination of the lesion tissue revealed reactive gliosis and infiltration of the leptomeninges and brain parenchyma by perivascular lymphocytes and foamy macrophages. The macrophages and histiocytes that stained intensely positively for PAS contained Gram-positive bacilli. The specimen also contained free bacilli infiltrating the glial tissue surrounding the abnormal macrophages. These findings are all consistent with intracerebral Whipple disease, in accordance with other reports in the literature.

To date, very few cases of Whipple disease with CNS involvement have been documented sufficiently with MR

images,^{1,2,4,5,8,16,18,22,25} and only three cases of intracerebral Whipple disease have been diagnosed during craniotomy.^{4,22,25} In only one of these cases was the lesion excised through a craniotomy, similar to our case. In that particular patient, however, there were multifocal lesions, a typical feature of CNS involvement in Whipple disease,²⁵ whereas in our patient there was a solitary mass.

This is the first reported case of Whipple disease featuring a single solid mass in the CNS with homogeneous contrast enhancement on neuroimaging and bone destruction of the calvaria. Another unique aspect of this case is that the mass was not deeply seated, which is atypical for cases of cerebral Whipple disease.

Conclusions

Although CNS involvement is a known feature of systemic Whipple disease, intracerebral mass lesions are uncommon. When they do arise, these tend to appear as deep-seated multifocal lesions. The case we have described is important in that it demonstrates that a single solitary intracerebral mass lesion associated with bone destruction may occur in cases of systemic Whipple disease. This unusual manifestation should be kept in mind during follow-up review in these patients.

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