Brain involvement by leprosy presenting as a frontal cystic lesion

Case report

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Leprosy has a predilection for peripheral nerves and is not considered to involve the CNS. The idea that the CNS is exempt from Mycobacterium leprae bacilli has been suspected from a clinical perspective or CSF study in leprosy patients. However, there has been no direct evidence for CNS involvement by leprosy in a living patient. To the best of the authors’ knowledge, the present case is the first report providing histopathological and molecular evidence for CNS involvement by leprosy in a living patient. Brain MRI revealed a 2-cm cystic lesion in the right frontal lobe of the patient. The medical history revealed that the patient had been receiving multidrug therapy for borderline lepromatous leprosy. Neuronavigation-guided craniotomy and lesion removal were performed due to a presumptive diagnosis of low-grade glioma. The brain specimen demonstrated variably thickened blood vessels and densely scattered foamy macrophages in the perivascular spaces and parenchymal stroma. Fite acid-fast stain displayed red granular inclusions that were suggestive for fragmented M. leprae. M. leprae-specific nested polymerase chain reaction amplification showed positive bands, and DNA sequencing also demonstrated homology with the M. leprae genome. This case supports the notion that M. leprae can involve the cerebral cortex regardless of cranial nerve engagement.

Abbreviations used in this paper: BBB = blood-brain barrier; PCR = polymerase chain reaction.

Case Report

History and Examination. A 69-year-old man presented with a 1-month history of dizziness and general weakness. The patient was neurologically intact except for mild facial palsy on the left side. The complete blood count showed mild anemia with a hemoglobin value of 9.6 g/dl. Other laboratory findings were unremarkable. Brain MRI obtained at another hospital demonstrated a 2-cm nonenhancing cystic lesion with perilesional edema in the right frontal lobe (Fig. 1A and B). Three years prior to this visit, the patient initially presented to the dermatology department with stinging erythematous annular indurated plaques and nodules on the body and deep perforating ulcers on the hands and feet (Fig. 2). Based on clinical presentations and skin biopsy samples, borderline lepromatous leprosy was diagnosed. Neuronavigation-guided craniotomy and lesion removal were performed due to a presumptive diagnosis of low-grade glioma. The brain specimen demonstrated variably thickened blood vessels and densely scattered foamy macrophages in the perivascular spaces and parenchymal stroma. Fite acid-fast stain displayed red granular inclusions that were suggestive for fragmented M. leprae. M. leprae-specific nested polymerase chain reaction amplification showed positive bands, and DNA sequencing also demonstrated homology with the M. leprae genome. This case supports the notion that M. leprae can involve the cerebral cortex regardless of cranial nerve engagement.
lepromatous leprosy was diagnosed, which is one of the definitive leprosy types. The patient had a 3-year history of medication with dapsone 100 mg/day, rifampin 600 mg/day, and clofazimine 50 mg/day.

**Operation and Postoperative Course.** A neuronavigation-guided right frontal craniotomy and tumor resection was performed based on a presumptive diagnosis of low-grade glioma for the brain lesion. A meticulous dissection of the surrounding structures revealed a cystic lesion containing yellow cystic fluid. The cystic wall comprised numerous small vessels and the cystic capsule was poorly delineated. The postoperative clinical course was uneventful. Follow-up MRI at 6 months demonstrated a near-complete collapse of the lesion without recurrence or development of a new lesion (Fig. 1C and D). The plan was to maintain the patient’s lifelong daily dapsone treatment with regular follow-up. The patient has attended regular checkups for 12 months and has no neurological symptoms or signs. Currently, the skin lesions have resolved with mild hyperpigmentation.

**Histopathological Analysis.** Skin biopsies from the erythematous papule on the left forearm and plaque on the right upper arm showed a grenz zone in the upper dermis, and dense variably sized granulomas in the dermis. The granulomas were composed of many foamy histiocytes and lymphocytes. Smaller-sized granulomas were concentrated around hair follicles, eccrine glands, and nerves in the dermis (Fig. 3A). Fite acid-fast stain revealed red scattered bacilli and globi in the cytoplasm of foamy histiocytes (Fig. 3A inset). Histopathological examination of the brain specimen demonstrated a number of thickly hyalinized vessels, mainly in the superficial capsular areas, but sometimes in the parenchyma (Fig. 3B). Strikingly, there was a dense population of foamy histiocytes with abundant clear cytoplasm both in the stroma and in the perivascular spaces (Fig. 3C). Those foamy histiocytes were intermingled with hemosiderin-laden macrophages and reactive astrocytes. Rosenthal fibers and eosinophilic granular bodies were also frequently identified (Fig. 3D). Immunohistochemistry showed strong positivity of CD68 in the histiocytes. Glial fibrillary acidic protein stain highlighted reactive astrocytes. Congo-red stain was positive in the hyalinized vessels, indicating amyloidosis in the vessels. Fite acid-fast stain, a modified acid-fast stain to protect the acid-fastness of *M. leprae*, demonstrated some fragmented granular inclusions in the cytoplasm of the histiocytes (Fig. 3C inset). Fragmented acid-fast bacilli were strongly suspected on repeated Fite stains.

**Polymerase Chain Reaction.** For a more confirmative diagnosis, *M. leprae*-specific nested polymerase chain reaction (PCR) was designed as previously described. Genomic DNA was extracted from microdissected tissue according to the manufacturer’s instruction (Boehringer Mannheim). A nested PCR for *M. leprae* genomic DNA was performed by modification of the method of Donoghue et al. Polymerase chain reaction amplification was performed in a GeneAmp PCR System 9700 thermocycler (Perkin Elmer) with primers targeted to the *M. leprae*-specific repetitive element sequence, yielding a 129-bp outer product and a 99-bp nested product. The following primers were used: forward-1, 5’-TGAGGTCGGCTGGGCTTCCTTTGAGG-3’; reverse-1, 5’-CAGCGATACCGCGCCAGGACAA-3’; forward-2, 5’-TGAGGTCGGCCTGTCCTTC-3’; and reverse-2, 5’-CAGAAATGGTGCCAGGAAGGGA-3’. These primers were purchased from Macrogen. The PCR conditions were an initial cycle at 95°C for 15 minutes, followed by 35 cycles at 95°C for 40 seconds, 58°C for 1 minute,
and 72°C for 30 seconds, and 72°C for 1 minute in the first PCR. The product of the first PCR (1 μl) was used as a template for a second PCR, in which 30 cycles of the same PCR conditions were used. *M. leprae* DNA (provided by Dr. Y. H. Won) was used as a positive control, and a tube of sterile water mixed with PCR mixture was included as a negative control. The amplified DNA band was purified using a QIAquick PCR purification kit (Qiagen) according to the manufacturer’s instruction. Nucleotide sequencing was performed by Macrogen.

The surgical specimen was positive with outer band primers and inner band primers (Fig. 4A and B). The DNA sequencing result demonstrated more than 99% homology with *M. leprae*-specific genomic sequences obtained from a Basic Local Alignment Search Tool (BLAST) search of the gene database of the National Center for Biotechnology Information (Fig. 4C). The final pathological diagnosis was CNS involvement by leprosy.

**Discussion**

The only histopathological descriptions to date on CNS involvement by leprosy have been provided by Aung et al. in autopsy cases. The majority of the leprosy cases displayed vacuolar changes of motor neurons in the medulla oblongata or the spinal cord. Polymerase chain reaction revealed *M. leprae*-specific genomic DNA in the cases with vacuolated changes. The current case provides histopathological and molecular evidence for CNS involvement by leprosy in a living patient. The brain lesion was exclusively composed of foamy histiocytes, which was dissimilar to the skin lesion that was composed of numerous granulomas. Foamy histiocytes were densely scattered in the parenchymal stroma and perivascular spaces. Although Fite acid-fast stain in the current case showed fragmented granular bacilli, it was successfully proven using PCR analysis and nucleotide sequencing that the acid-fast inclusions were fragmented bacilli containing intact *M. leprae* genome DNA. In addition, those reactive changes, including Rosenthal fibers and eosinophilic granular bodies, have not been previously described in the literature.

It does not appear to be plausible to prove whether *M. leprae* can reach the brain through a broken blood-brain barrier (BBB) or through the brainstem peripheral nerves. The latter hypothesis on CNS involvement via brainstem peripheral nerves is less likely. Vaidya et al. reported that the route of entry of bacilli into dorsal root ganglion cells was from the bloodstream and not via the axon, which was inferred from the presence of bacilli in the lumen of vessels. Scollard et al. also suggested the possibility of hematogenous spread evidenced by localization of *M. leprae* to endothelial cells.

Vaidya et al. also proved that *M. leprae* was capable of crossing the BBB and present in both the gray and white matter of the brain and spinal cord in thymectomized, irradiated mice. Nonetheless, there has been no direct evidence of penetration of bacilli through
the BBB in human CNS leprosy. In fact, CNS does not appear to be the suitable site of growth, given that *M. leprae* tends to grow in low-temperature organs such as the skin, nasal cavity, testes, and anterior part of the eye. However, in advanced cases *M. leprae* frequently involves visceral organs, including the bone marrow, liver, and spleen. The involvement of deep-seated organs appears to be a result of direct hematogenous spread of *M. leprae* and may be related to the duration of the disease and/or to the number of circulating organisms in the blood. Additionally, leprosy is a common cause of secondary systemic amyloidosis in some parts of the world, and the reported incidence of amyloidosis in multibacillary leprosy patients ranges from 5.9% to 55%. A clue to the possible role of an impaired BBB as a pathway for CNS leprosy is the observation of amyloid angiopathy in the current case, because blood vessels involved by amyloidosis would not have junctions as tight as those in the normal BBB. The damaged BBB from amyloidosis may have prompted the passage of bacilli through the vessels toward the brain parenchyma. Possible preceding microhemorrhage, supported by hemosiderin-laden macrophages and reactive gliosis, also appeared to stem from amyloid angiopathy.

The PCR primers used in the present case were optimally designed to target small-sized DNA fragments specific for the *M. leprae*-specific repetitive element sequence, because *M. leprae* DNA in long-term treated cases is likely to be degraded or fragmented. The sequence is repeated 37 times in the *M. leprae* chromosome, and PCR using primers amplifying the repetitive element sequence are 1000-fold more sensitive than previously used primers targeting the 36-kD antigen. Kang et al. also confirmed the *M. leprae* specificity of LP1/LP2. Amako et al. emphasized the notion that the nucleic acid fragments remain intact within the peptidoglycan layer despite mycobacterial degradation (either naturally or due to multidrug therapy regimen) that occurs in the bacterial cytoplasm.

Leprosy is one of the oldest infectious diseases in humans, but CNS involvement by leprosy has remained enigmatic mainly due to the lack of histological evidence. Given that leprosy is more prevalent in underprivileged areas, other CNS cases may have been overlooked due to restricted available resources. Central nervous system manifestations with regard to leprosy that have been reported so far can be evidenced by the current case. We believe that our case provides a firm basis for better understanding the pathophysiology of leprosy.

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**Disclosure**

The authors report no conflict of interest concerning the mate-
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