Lymphomatoid granulomatosis (LG) is an uncommon multisystem disease characterized by multifocal “angiocentric angiodestructive lymphoreticular proliferative and granulomatous lesions” (1). LG involves the lungs most frequently, followed by the skin and brain (2). Neurologic symptoms may be the initial or only manifestation of the disease, but they are nonspecific. Laboratory findings usually are unremarkable (2). The reported radiologic appearance of LG of the brain, mostly using CT, has varied and has been nonspecific. Thus, the diagnosis of LG of the brain, without lung or skin involvement, usually is delayed or made only at autopsy. In this report, we characterize the MR appearance of the LG of the brain through review of imaging data from four local cases and those in the literature.

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Methods

We retrospectively reviewed four cases of LG in the brain from our case records. The patients were three men and one woman, ranging in age from 35 to 72 years (mean, 60 years). At diagnosis, three of the patients had presented with spastic gait, and one had presented with polyradiculoneuritis, skin eruptions, and spastic gait (Table). This latter patient (case 3) also had pulmonary lesions. The other three patients had no evidence of LG lesions outside the central nervous system. LG was confirmed histologically in all cases by means of either open or stereotactic brain biopsy.

All tissues were fixed in 10% neutral formalin and embedded in paraffin. Five-micrometer sections were stained with hematoxilin-eosin and lymphocyte surface markers. We followed the avidin-biotin-peroxidase complex procedure, using antibodies to CD20 (a cytoplasmic antigen in B-lymphocytes) and to CD3 (a marker for T-lymphocytes).

MR imaging data were collected from three institutions. The interval between initial presentation and MR imaging ranged from 1 week to 7 years (Table). MR images were obtained with 1.5-T scanners. We obtained axial images of 4- to 6-mm thickness in the following pulse sequences: pre- and postcontrast T1-weighted spin-echo sequences with imaging parameters of 540–600/14–20/1–2 (TR/TE/excitations) and T2-weighted fast spin-echo sequences with imaging parameters of 3500–4500/93–96/1–2 (TR/TE_{eff}/excitations) with a field of view of 23 × 23 cm and an image matrix of 256 × 256. Each patient also underwent MR imaging after intravenous administration of 0.1 mmol/kg of gadopentetate dimeglumine or gadoteridol. The images were evaluated by two neuroradiologists.

On T2-weighted images, we described the location of abnormalities in signal intensity and categorized them as patchy or diffuse hyperintense areas, infarctlike, suggestive of a mass lesion, perifocal edema; or suggestive of hemorrhage. Enhancement was divided into parenchymal and meningeal. Pa-
Summary of MR findings in patients with LG of the brain

<table>
<thead>
<tr>
<th>Case (No.)</th>
<th>Age (y)/Sex</th>
<th>Symptoms at Onset</th>
<th>Symptoms at Presentation</th>
<th>Interval between MR Examination and Onset</th>
<th>MR Findings</th>
<th>Peritumoral Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patchy</td>
<td>Diffuse</td>
</tr>
<tr>
<td>1</td>
<td>72/M</td>
<td>Spastic gait</td>
<td>Paraparesis</td>
<td>1 week</td>
<td>(−)</td>
<td>(−)</td>
</tr>
<tr>
<td>2</td>
<td>58/M</td>
<td>Spastic gait</td>
<td>Paraparesis</td>
<td>7 years</td>
<td>(−)</td>
<td>Bilateral cerebral and cerebellar WM, brain stem</td>
</tr>
<tr>
<td>3</td>
<td>56/F</td>
<td>Polyradiculoneuritis, skin lesions, spastic gait</td>
<td>Left facial nerve palsy, nystagmus, dysarthria</td>
<td>4 years</td>
<td>(−)</td>
<td>Bilateral cerebral WM (−)</td>
</tr>
<tr>
<td>4</td>
<td>35/M</td>
<td>Spastic gait</td>
<td>Chorea-athetosis, dementia, anosmia, apraxia, rigidity, spasticity</td>
<td>10 months</td>
<td>Brain stem</td>
<td>Bilateral cerebral WM (−)</td>
</tr>
</tbody>
</table>

Note.—WM indicates white matter; NA, not applicable; PR, partial regression; RT, radiation therapy; Rec, recurrence.

enchymal enhancement was categorized as no enhancement, solid, ringlike, nodular, punctate, or linear. Nodular enhancements were defined as round enhancements 3–9 mm in diameter, and this abnormality was observed in the brain stem (n = 2) and cerebellar white matter bilaterally (n = 1). One patient also showed patchy hyperintense areas in the brain stem (case 1 [Fig 1]). On postcontrast T1-weighted images, two patients showed multiple punctate and linear enhancements (cases 2 and 4 [Figs 2 and 3]), one showed multiple punctate enhancement (case 1), and one showed multiple linear enhancements (case 3). The punctate and linear enhancements seemed to reside along the intramedullary vessels. Nodular enhancement was not present.

Microscopic examination revealed LG in all four cases. All patients showed perivascular polyclonal lymphoid cell infiltrates and angiodestructive features. The infiltrate was composed of mononuclear cells admixed with histiocytes and plasma cells. Lymphoid cells with atypical nuclei were seen in two patients (cases 2 and 3 [Figs 2E and 4G]). The lymphoid infiltrates were composed predominantly of the T-cell phenotype in two patients (cases 1 and 3) and were composed of both T- and B-cell phenotypes in two patients (cases 2 and 4).

All patients received pulsed and maintenance corticosteroid treatment. The steroid therapy was followed by cyclophosphamide in one patient (case 2) and by radiation therapy in the other three patients (cases 1–3). In all patients, the lesions became smaller or disappeared with treatment. One patient with acute onset (case 1) died from recurrence 15 months after radiation therapy. Another patient (case 3) showed a relapsing-remitting clinical course.

Discussion

Lymphomatoid granulomatosis was first described in 1972 as an angiocentric, angiodestructive lymphoproliferative, and granulomatous disease that predominantly affects the lung (1). The most commonly involved extrapulmonary sites are the skin and the nervous system; however, any organ system may contain the lesions typical of LG (1). The clinical manifestations of LG generally consist of chest symptoms such as cough and shortness of breath, systemic complaints such as fever, weight loss, or malaise. Frequently, skin lesions (a raised erythematous rash or nodules) appear si-
mass simultaneously with the lung lesions. Neurologic symptoms also are common, present in 30% of cases, and usually are seen with chest or systemic complaints (2). Neurologic symptoms may be the initial or only manifestation of the disease, however. Such symptoms frequently are nonspecific and may consist of headache, seizures, hemiparesis, ataxia, blindness, deafness, cranial-nerve palsies, altered consciousness, or dementia (2–4). All of our cases had an initial manifestation of the disease in the central nervous system, it was localized in the brain in all but one patient (case 3), and all patients had spastic gait. In case 3, multiple pulmonary nodular lesions were seen on chest radiography, but this patient had no respiratory symptoms.

Histologically, LG is characterized by a polymorphic lymphoid infiltrate of atypical mononuclear cells, small lymphocytes, plasma cells, and histiocytes. Most lymphocytes exhibit the T-cell phenotypic pattern. Granulomas may form and infiltrate the meninges, vessels, and parenchyma (11). Neurologic involvement may reflect direct infiltration of cranial and peripheral nerves by the perivascular lymphoid infiltrates or thrombosis and infarction from vasculitis (13).

The pathogenesis of LG remains to be elucidated. Some investigators consider LG to be a reactive or “preneoplastic” process, possibly in reaction to antigen stimulation, such as that induced by the Epstein-Barr virus (16, 17). Others consider LG an angiocentric variant of T-cell lymphoma (14), because a certain proportion of patients with LG develop non-Hodgkin’s lymphoma (1, 2). Lipford et al (18) showed that LG represents a spectrum of T-cell proliferation from lack of atypia to frank angiocentric lymphoma. Histologic subclasses have been proposed by Jaffe et al (19).

In our series, perivascular granulomatous infiltrates of lymphoid cells in the biopsy specimens correlated with enhanced lesions on MR images. Because the biopsy specimens were small, we could not completely correlate the MR imaging and histopathologic findings. We speculate, however, that multiple punctate and linear enhancements, which appear to reside along the medullary vessels on MR imaging, represent abnormal perivascular tissue and affected walls of small vessels, and nodular enhancements represent granuloma formation. We also speculate that the hyperintense areas on T2-weighted images, other than peritumoral edema, represents reactive or ischemic changes including vacuolization, reactive and ischemic gliosis, and ischemic demyelination caused by vascular stenosis and thrombosis (20, 21).

The appearance of LG of the brain on CT varies but most often shows intraparenchymal lesions, which may be unifocal or multifocal and supra- or infratentorial in location. These lesions may appear as solid or ringlike, enhanced masses with or without edema, or nonconfluent, low-density areas of white matter without enhancement. They may have associated leptomeningeal thickening or enhancement. Occasionally, they appear as intraparenchymal hemorrhage, cerebral infarction, extraparenchymal mass lesions, or aneurysm (3–11). Cerebral
Case 1.

A. Contrast-enhanced T1-weighted axial image (spin-echo sequence with parameters 600/14 [TR/TE]) shows an enhanced lesion from the splenium of the corpus callosum extending to the right parietal white matter. There is a small area of necrosis within the mass (arrow). Nodular and multiple punctate enhancements are seen in the white matter (arrowhead).

B. T2-weighted image (fast spin-echo sequence with parameters of 4000/96 [TR/TE]) shows a hyperintense mass (arrow) and surrounding edema.

C and D. Contrast-enhanced T1-weighted images show multiple punctate enhancements in the pons and cerebral white matter bilaterally.

E and F. T2-weighted axial image shows patchy hyperintense areas in the pons and cerebral white matter bilaterally (arrows).

G. Stereotactic biopsy specimen from the right parietal lobe shows small lymphoid cells, microglia, and macrophages, which were prominent in the perivascular space (arrow).

H. Contrast-enhanced T-weighted image 6 months after radiation therapy shows that the mass has almost disappeared.
FIG 2. Case 2. A and B, T2-weighted images (fast spin-echo sequence with parameters of 4500/96 [TR/TE]) show diffuse hyperintense lesions in the white matter bilaterally, as well as in the pons, middle cerebellar peduncle, and cerebellar hemispheres (arrows). C and D, Contrast-enhanced T1-weighted images (spin-echo sequence with parameters 600/14 [TR/TE]) show multiple punctate and linear enhancements scattered both in the white matter bilaterally (that appear to reside along the intramedullary vessels) and in the pons and cerebellar hemispheres (arrows indicate linear enhancements). Nodular enhancement also is shown (curved arrows). E, Brain stereotactic biopsy specimen from the right occipital lobe shows inflammatory destruction of the cerebral cortex with mononuclear cell infiltration. The infiltrating cells consist of polyclonal small lymphoid cells that include nuclear atypia predominantly in the perivascular space (arrow).

angiography may show findings consistent with vasculitis (12).

We found 15 case reports in the English-language literature that describe findings on MR imaging for LG of the central nervous system (3, 4, 6, 10, 13, 21–27). Thirteen of these cases had intracranial lesions, two had intraorbital lesions, and two had intraspinal lesions. Of the 13 patients with intracranial lesions, 11 had intraparenchymal lesions (3–7, 9, 10, 13, 21, 24, 26), one had supratentorial extraaxial masses (27), and one had a cavernous sinus mass and meningeal thickening (22). The intraparenchymal lesions often were multifocal but unifocal lesions were observed in two cases. These lesions were found in supratentorial or infratentorial locations; the affected areas were the cerebral white matter with or without extension into the adjacent cortical gray matter, basal ganglia, cerebellum, or brain stem. The white matter lesions were located in the periventricular, deep, or sub-
cortical regions. On T2-weighted images, these lesions were most frequently hyperintense relative to the brain parenchyma, with small foci, round, globular, infarctlike, or masslike lesions with or without associated edema or mass effect. In two cases the lesion showed low signal intensity centrally (necrosis with hemorrhage) with peripheral hyperintense edema, and in one case the lesion showed mixed intensity. On T1-weighted images, these lesions were hypointense relative to the brain parenchyma. As for the intraparenchymal lesions, contrast-enhanced T1-weighted images showed ringlike enhancements in three patients and multiple punctate and linear enhancements in one patient (6, 9, 21). Serial MR imaging findings were described for four patients (4, 21, 22, 26); the lesions increased in size or number after variable follow-up periods.

In this study, ringlike enhancement was observed in one patient, and multiple linear or punctate enhancements were observed in all four patients. Although the literature has described the findings of contrast-enhanced T1-weighted images for only three patients with brain lesions, these enhancement patterns were in accord with those of the previous reports. In case 1, a large, enhanced, solid mass lesion was observed in the splenium to the deep white matter of the right parietal lobe. The stereotactic biopsy specimen was not obtained from this lesion but from a nodular, enhanced lesion at the subcortical white matter of the right parietal lobe. We speculated that the mass was lymphoma associated with or evolved from LG. We consider the multiple punctate and linear enhancements on MR imaging to be characteristic of LG because they most likely represent perivascular tissue and walls of small vessels affected by the disease. The punctate or linear enhancements are not diagnostic for the disease, however, because these can occur in other diseases, including sarcoidosis, primary angitis of the central nervous system, other granulomatous angiitis (such as Churg-Strauss syndrome), and intravascular lymphomatosis (8, 28). Nonetheless, the possibility of LG should be considered if these findings are observed. Ringlike enhancement was seen in one patient in our series and in three cases in the literature (two patients with brain lesions and one patient with a spinal cord lesion) (6, 10, 25). It is known that ringlike enhancement can be seen in various diseases, such as metastatic tumors, glioblastomas, abscesses, and acute demyelinating plaques in multiple sclerosis. Among these diseases, ringlike, enhanced brain lesions in LG may especially mimic metastatic tumors, and differentiation may be quite difficult without histologic examination.

On T2-weighted images, we noted patchy or diffuse hyperintense areas other than peritumoral edema in the cerebral white matter in all patients in our study. Two patients also showed hyperintense areas in the brain stem and cerebellar hemisphere. We speculate that the hyperintense areas represent reactive or ischemic change caused by the disease; however, this finding is nonspecific, and it is difficult to suggest LG on the basis of T2-weighted images alone.

The prognosis of LG is poor, especially in LG of the brain, and its treatment is controversial. Treatment with various cytotoxic agents, corticosteroids, and radiotherapy have been described (14). Among these, the combination chemotherapy of cyclophosphamide and corticosteroid has been reported as a strategy for long-term remission (15). All of our cases received pulsed and maintenance steroid therapy; three patients also received radiation therapy, and one received the combination of steroid and cyclophosphamide therapy. All patients showed partial remission immediately after treatment, but two patients later had recurrence of disease. Although the number of patients is limited, our data suggest that acute onset of the disease predicts poor prognosis, whereas gradual onset or progression predicts a better prognosis after therapy.

Conclusion

The clinical diagnosis of LG is difficult when the lesion is confined to the brain. Although radiologic findings in LG of the brain are quite variable, the
Fig 4. Case 3.

A and B, Contrast-enhanced T1-weighted images (spin-echo sequence with parameters of 600/14 [TR/TE]) show ringlike enhancements in the left middle cerebral peduncle and pons and in the right cingulate gyrus (arrowheads).

C, The slices of 4-mm thickness show linear enhancements in the pons (arrows).

D and E, T2-weighted MR images (fast spin-echo sequence with parameters of 4500/96 [TR/TE]) show that the ringlike, enhanced lesions are hypointense to isointense with gray matter (arrowheads). There are hyperintense areas surrounding these lesions, suggesting perifocal edema (arrow).

F, Chest radiograph shows multiple nodular shadows in both lung fields (arrows).

G, Open brain biopsy specimen from the left middle cerebellar peduncle shows perivascular lymphoid-cell infiltration with partial nuclear atypia (arrows).
presence of multiple punctate or linear enhancements that reside along the perivascular space on MR imaging suggests LG or other diseases affecting the vascular wall or perivascular space, such as sarcoidosis, primary angitis of the central nervous system, and other granulomatous angiitis. Although less specific for LG, when ringlike enhancement or meningeal thickening and enhancement is observed on MR images, the possibility of LG should be considered in an appropriate clinical setting.

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