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CT and MR of Lymphomatoid Granulomatosis of the CNS: Report of Four Cases and Review of the Literature

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Lymphomatoid granulomatosis is an uncommon disease characterized by a perivascular pleomorphic cellular infiltration and necrosis. CNS involvement occurs in 20% of the cases. CT findings have been described in five of the previously reported cases of CNS lymphomatoid granulomatosis, and include unifocal, multifocal, and diffuse contrast-enhancing supratentorial lesions. We reviewed the CT scans of three patients and the MR image of a fourth patient with histologically confirmed CNS lymphomatoid granulomatosis. The lesions were in the posterior fossa in three of the four cases. Hemorrhage, which was present in three of the four cases, was detected by imaging studies in two and at autopsy in the third. Systemic involvement was present at autopsy in three cases and was clinically suspected in the fourth. A diagnosis of CNS lymphomatoid granulomatosis should be considered when hemorrhagic or posterior fossa lesions occur in patients with constitutional symptoms.

Lymphomatoid granulomatosis (LG), first described as a specific disease by Liebow et al. in 1972 [1], is a necrotizing pseudogranulomatous process characterized by a multifocal "angiocentric and angiodestructive" pleomorphic cellular infiltrate. While LG primarily involves the lungs, kidneys, and skin, the CNS is ultimately affected in about 20% of the cases. Occasionally, CNS lesions may be the initial or the only manifestation of the disease. Because of the infrequent occurrence of this disease, reports of cases illustrating radiologic features of CNS LG are scarce. The purpose of this article is to illustrate the CT (three patients) and MR (one patient) findings in four patients who had brain involvement by LG, analyze their pertinent clinical and autopsy data, and review CT findings previously described in the literature. The pathologic findings in case 1 were the subject of a previous case report, but the CT findings were only mentioned briefly and the scan was not included in the publication [2].

Case Reports

Case 1

A 54-year-old man was admitted with a 6-month history of generalized malaise; intermittent fever and weight loss; and a few weeks of blurred vision, difficulty in hearing, and heaviness in his head. On admission, he had slurred speech, right gaze-evoked nystagmus, a staggering gait, bilateral hearing loss, and a perforated left tympanic membrane. Subsequently, he developed a peripheral left seventh nerve palsy and became lethargic. A chest X-ray showed bilateral nodular infiltrates. Head CT showed an approximately 3-cm contrast-enhancing mass in the left middle cerebellar peduncle (Fig. 1). An open lung biopsy revealed LG. He was treated with cyclophosphamide, cytarabine, intrathecal methotrexate, and whole-body irradiation. An enhanced CT scan 4 weeks later was normal. He died 2 months after admission from recurrent aspiration pneumonia. At autopsy, a soft, discrete 2-cm tumor was present in the left flocculus, filling the cerebellopontine angle. The sixth through tenth cranial nerves were not identified and were either destroyed or engulfed by the mass. A cavitary lesion was found in the lungs and a mass similar to the intracranial lesion was present in the kidney. Histology of these lesions was consistent with LG.

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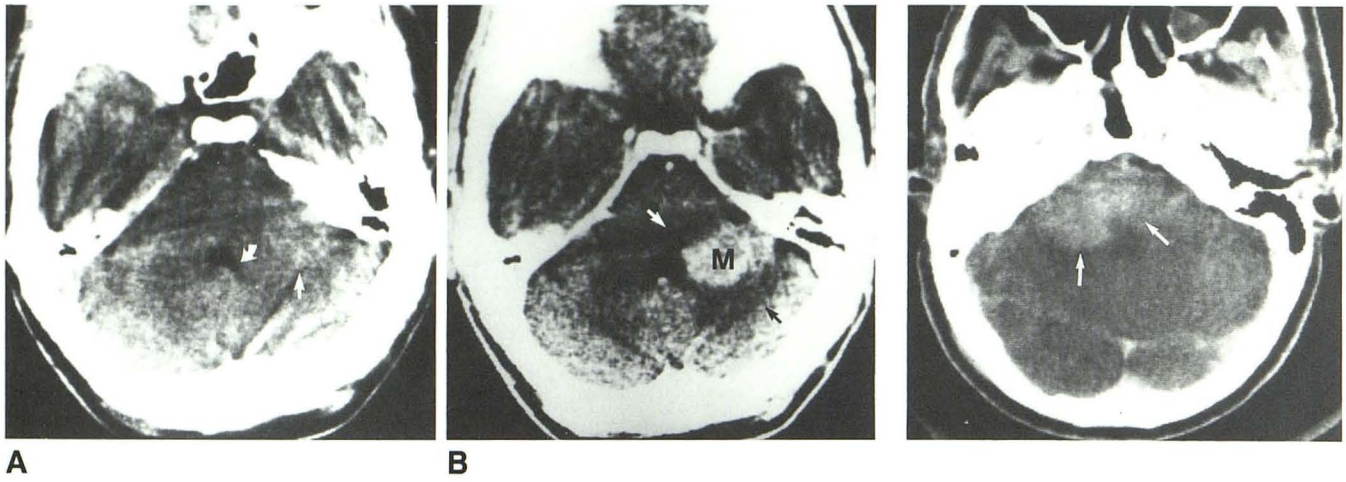

Fig. 1.—Case 1.

***A*, CT scan without IV contrast. Slight mass effect is present in left middle cerebellar peduncle with some flattening of the posterosuperior recess of fourth ventricle (*curved arrow*). There is suggestion of a mass of slightly greater attenuation than surrounding white matter in the left cerebellopontine angle (*straight arrow*).**

***B*, CT scan with IV contrast. Enhancing mass (M) is identified in left middle cerebellar peduncle and flocculus with surrounding rim of edema (*arrows*).**

Fig. 2.—Case 2. CT scan with IV contrast. Contrast-enhancing lesion is present in pons and in right brachium pontis (*arrows*). The lesion was isodense before contrast (not shown).

Case 2

A 54-year-old man was admitted with a 6-month history of intermittent nose bleeds on the right, 3 months of right frontal molar problems, 1 month of generalized weakness and speech difficulty, and a few weeks history of inability to close the right eye, drooling from the right side of his mouth, and inability to walk without support. On examination, the patient had a right peripheral seventh nerve palsy, decreased sensation in the left foot, and a positive Romberg sign. The mucosa of the right nares was hemorrhagic. Chest X-ray showed numerous pulmonary nodules measuring up to 1 cm in diameter. Head CT showed an enhancing 4-cm mass in the right middle cerebellar peduncle (Fig. 2). CSF cytology was negative. Multiple nasopharyngeal biopsies and a transbronchial biopsy were negative for malignancy. The patient developed pneumothorax and, subsequently, respiratory distress, and then died.

At autopsy there were numerous nodular infiltrates of LG in the lungs, liver, pancreas, kidneys, and thyroid gland. A 2.5-cm hemorrhagic lesion was identified in the right brachium pontis, and fresh subarachnoid hemorrhage was present. The fifth, sixth, and seventh cranial nerves were incorporated in this hemorrhagic mass. Small hemorrhages were present in the right thalamus and adjacent to the left temporal horn. Sections from the medulla, lower pons, and upper cervical spinal cord contained tumor nodules composed of plasma cells, macrophages, monocytes, lymphocytes, and occasional eosinophils, usually arranged circumferentially to blood vessels of medium caliber. Coagulation necrosis of the brain parenchyma and atypical nuclear forms were common in these nodules. Some of the cellular infiltrates were present within the vascular walls.

Case 3

A 62-year-old man with a long history of chronic obstructive pulmonary disease had a 20-pound weight loss over 3 months. Three days before admission he developed an increasingly productive cough, respiratory difficulty, fever, and a diffuse erythematous macular rash with scattered purpura. He was placed on a respirator on admission. Sputum cultures were positive for pseudomonas, and the patient was treated with antibiotics. While in the hospital, he had an episode of gastrointestinal bleeding. Three weeks after admission he had a seizure that started in the face, with deviation of the eyes to the left, that developed into epilepsy. Between spells of generalized seizure activity he had focal seizures of the right side of the face and right arm. Brain CT showed a 5-cm hemorrhage in the left temporoparietal region and small hemorrhages in the left frontal and right temporal lobes (Fig. 3). At autopsy no evidence of LG infiltrates in the lungs, liver, skin, or kidneys could be found. The lesions in the brain consisted of fresh hemorrhages that seemingly had occurred simultaneously. Multiple sections taken at the periphery of these hemorrhages showed angiodestructive infiltrates consisting of plasma cells, lymphocytes, macrophages, and occasional cells with atypical nuclei. Plasmacytoid cell infiltration, typical for LG, was present in several large subarachnoid arterial branches.

Case 4

A 69-year-old man was admitted to a community hospital with a several-week history of severe dizziness followed by an acute onset of nausea, vomiting, nystagmus, and bilateral lower extremity weakness. Brain CT and a vertebral angiogram were reported as normal. CSF from lumbar puncture showed 39 white blood cells (84% lymphocytes), a protein of 280 mg/100 ml, and was negative for bacterial cultures. The patient improved initially, but subsequently became hypotensive and required ventilatory assistance. Repeat CT reportedly showed increased ventricular size and compression of the aqueduct and fourth ventricle. When seen at University Hospital he was awake and confused, could move his extremities to verbal command, and had a decreased left corneal reflex and left peripheral facial weakness. Tone was increased in all extremities, there was generalized hyperreflexia, and mild left upper extremity dysmetria was present. MR (0.5 T) showed low-intensity abnormalities on the T2-weighted image in the brainstem around the fourth ventricle and in the right cerebellar hemisphere, with surrounding high intensity (Fig. 4). Autopsy demonstrated the characteristic lesions of LG in the lungs. In the brain, the parenchyma around the fourth ventricle showed coagulation necrosis and was partly replaced by fresh hemorrhages, which extended into the subarachnoid space near the right flocculus (Figs. 4E and 4F). The periphery of these necrotic areas showed multiple sites of angiocentric, angiodestructive infiltrates of

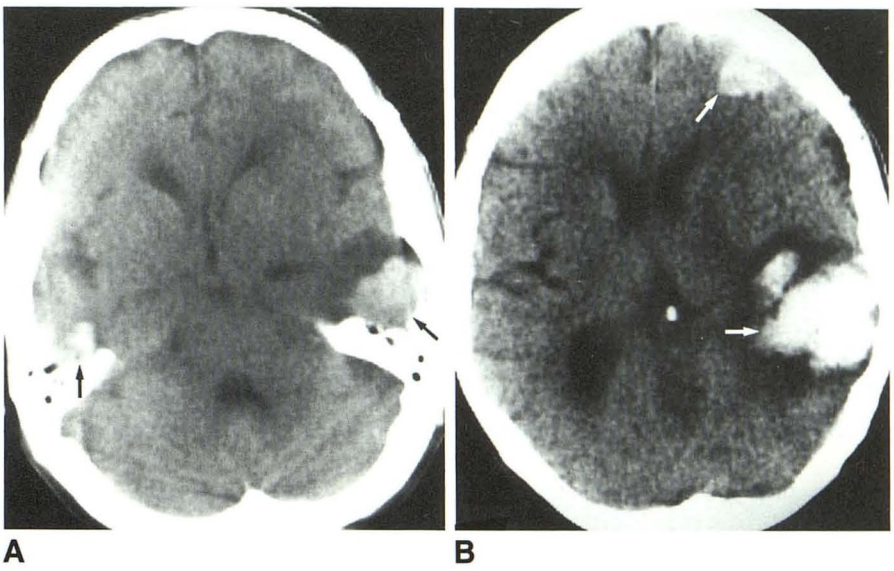

Fig. 3.—Case 3.
***A* and *B*, CT scan without contrast. Hemorrhages with surrounding edema are present in both temporal lobes and in left frontal lobe (*arrows*).**

plasma cells, macrophages, lymphocytes, and cells with atypical nuclear patterns. Many of these cells infiltrated through the vascular walls and were intimately associated with either focal hemorrhages or necrosis. Most hemorrhages were fresh; older hemorrhages were suggested by abundant hemosiderin-laden macrophages.

Discussion

Lymphomatoid granulomatosis is a relatively rare disorder that involves the lungs, kidneys, skin, and nervous system. The lungs are almost always involved by this disease [3]. Histologically, LG has been described as a proliferative and "granulomatous angiitis" associated with an infiltration of small lymphocytes, plasma cells, histiocytes, and atypical lymphoreticular cells [1–5]. Mitoses are commonly seen, and intense cellular proliferation often suggests a malignant process [4]. The diagnosis of LG is based on the demonstration of the typical histologic lesions existing in proximity to medium-caliber blood vessels. The vascular changes in LG may lead to the occlusion of the vessel lumen and result in large areas of infarction, which have commonly been described in the lung. Massive hemorrhages into cavitary lesions, superficially resembling tuberculous caverns, have also been described in the lung and probably represent a further expression of parenchymal necrosis caused by either vascular occlusion or neoplastic infiltration.

Many investigators believe that virtually all cases of LG of the lung are primary lymphoproliferative disorders, with most being malignant lymphomas [6]. Progression to immunoblastic lymphoma occurs in 12–30% of all cases of LG [3, 5]. The prognosis is poor, with the mortality ranging from 60–90% [7]. Neurologic manifestations represent a grave prognostic sign. The pathogenesis of the disease is uncertain, although an association has been made between LG and diseases in which immunity is impaired, such as in patients with renal transplantation, viral hepatitis, Sjogren syndrome, and rheumatoid arthritis [4, 8]. None of these risk factors was present in any of our patients. Typically, LG spares the bone marrow, spleen, and lymph nodes [8]. Various therapeutic agents have been used, including corticosteroids, immunosuppressive and cytotoxic agents, and irradiation, with variable results.

In the original description of 40 patients by Liebow et al. [1], clinical evidence of CNS involvement was present in 23% and peripheral neuritits in 15%. In a subsequent review of 152 patients by Katzenstein et al. [3], there was clinical evidence of CNS involvement in 30% of the subjects. This number included brain involvement in 19%, cranial nerve neuropathy in 11%, and peripheral neuropathy in 7%. In this same series, there was involvement of the brain in 26% of the 72 autopsied cases. CNS involvement in LG usually occurs after the disease is well established in the lungs and other organs [8]. Rarely, LG of the CNS may be the first or only manifestation of the disease [7]. There was no evidence of systemic LG in our case 3 at autopsy, although the clinical features suggested systemic involvement. The CNS lesions may be similar to LG elsewhere in the body, or they may have one or more foci of malignant transformation (immunoblastic sarcoma) [1, 9]. CNS lesions may take many forms, including solid tumor masses, necrotic cavitary masses, and leptomeningeal and parenchymal infiltrates [10–12]. The frequent meningeal infiltration together with adjacent parenchymal involvement suggest a primary invasion of the leptomeninges with infiltration of brain along the Virchow-Robin spaces. Brain infarctions, brain hemorrhages (ascribed to the vascular infiltrates), and aneurysms have also been described as prominent complications of LG [8, 12, 13]. Brain hemorrhage was a prominent feature in three of our four cases.

We reviewed the CT appearance of five previously reported cases. Sackett et al. [13] reported a case of LG with bilateral enhancing lesions adjacent to the sylvian fissures in the insular and medial temporal lobes. These were poorly visualized before contrast. The case reported by Schmidt et al. [7] showed a similar but unilateral enhancing perisylvian lesion. Ironside et al. [14] described a case of solidly enhancing intracerebral masses that decreased in size with radiotherapy. Sunderrajan and Passamonte [15] demonstrated diffuse parenchymal enhancement, which was maximal in the frontal

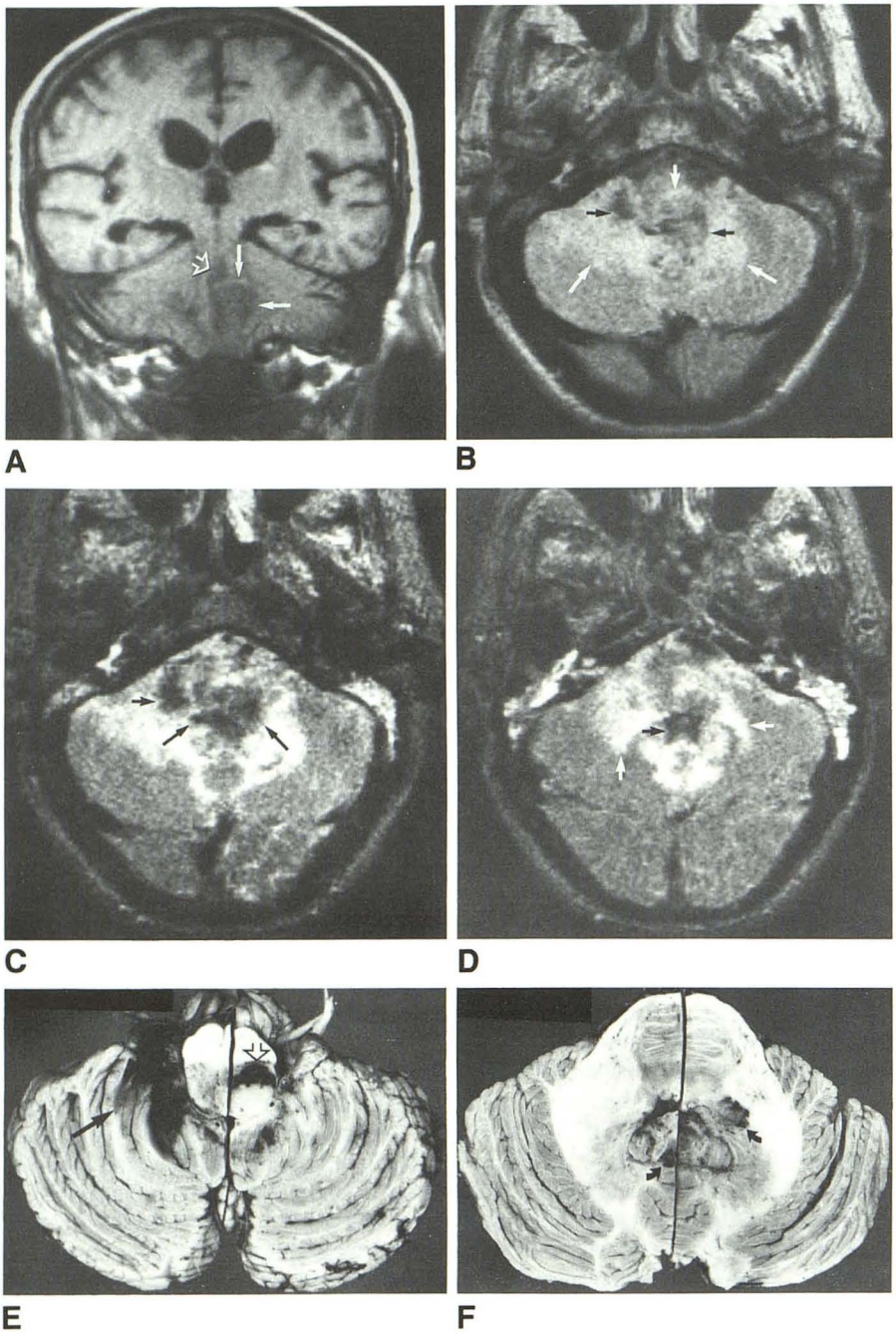

Fig. 4.—Case 4.

***A*, Coronal MR image (500/30) shows slightly hypointense abnormality in pons (*arrows*) indenting fourth ventricle (*open arrowhead*).**

***B*, Axial MR image (2500/30). Abnormal high signal is present in medulla and in deep white matter of cerebellar hemispheres (*white arrows*). There is low signal in right cerebellar hemisphere and around caudal fourth ventricle (*black arrows*).**

***C*, Axial MR image (2500/100) at level of Fig. 4B. Areas of low signal seen in Fig. 4B demonstrate very low signal on this second echo (*arrows*).**

***D*, Axial MR image (2500/100), 5.0 mm above Fig. 4C. Abnormal high intensity is present in brainstem and cerebellum (*white arrows*). Low signal surrounds fourth ventricle (*black arrow*).**

***E* and *F*, Gross specimen of brain. Transverse cuts through cerebellum and brainstem, at levels roughly corresponding to and in similar orientation to transverse MR images, show dark areas representing hemorrhage in right flocculus and adjoining cerebellum (*arrow* in *E*), around fourth ventricle (*curved arrows* in *F*), and in left side of medulla (*open arrowhead* in *E*).**

lobes, and Simon et al. [16] reported a case in which CT showed multiple, thin, ring-enhancing lesions. It is significant that the LG lesions in all of these cases were located above the tentorium.

The CT findings in our case 3 consist of several parenchymal hemorrhages in the absence of coagulopathy, head trauma, or hypertension. This expression of LG has not been reported previously. The hemorrhages were most likely caused by the underlying vascular necrosis, although transient elevation in blood pressure may have had a precipitating role in the simultaneous occurrence of hemorrhages at different sites. In case 4, low signal on the T2-weighted sequence around the fourth ventricle and in the dorsal pons was most suggestive of the magnetic susceptibility effect of hemosiderin, especially in view of the absence of significant changes in this region on CT [17]. Hemorrhages of different ages were documented in this region at autopsy, and it is possible that some of the low signal changes on the T2-weighted image were due to deoxyhemoglobin. Cases 1 and 2 had solidly enhancing cerebellar lesions, which were isodense to gray matter prior to contrast administration, but a large amount of fresh blood within the lesion in case 2 suggests that this was a contributing factor in the patient's death. Systemic LG was demonstrated at autopsy in three of our patients, and al-

though autopsy was reportedly negative for systemic LG in one patient, the clinical features of that case strongly suggest such involvement.

After reviewing the cases previously reported as well as our own, it is apparent that LG of the CNS has a varied radiologic expression. Our cases suggest a propensity for posterior fossa involvement, although all five of the CT scans of previously reported cases show only supratentorial involvement. Hemorrhage, apparently caused by involvement of brain parenchymal vessels, appears to be a common feature of this disease not reported previously. It occurred in three of our four cases. Whether or not LG is finally classified as a type of lymphoma, certain features set it apart from both primary and secondary CNS lymphomas. Primary CNS lymphoma usually does not have coexisting systemic involvement. Brain parenchymal involvement is very uncommon in secondary CNS involvement by lymphoma. Gross or even microscopic hemorrhage is not a feature of primary or secondary brain lymphoma [18–20].

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