Primary Langerhans’ cell histiocytosis of the central nervous system with fatal outcome

Case report

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An unusual case of primary parenchymal Langerhans’ cell histiocytosis of the central nervous system is reported. The definitive diagnosis was obtained by ultrastructural detection of Birbeck granules and by immunohistochemical evidence of CD1a expression. Despite complete surgical resection, there was an early recurrence with multiple central nervous system metastases leading to a fatal outcome.

KEY WORDS • Langerhans’ cell histiocytosis • central nervous system • electron microscopic study • immunohistochemistry

Langerhans’ cell histiocytosis (LCH) corresponds to a wide clinicopathological spectrum of disorders ranging from benign to extremely aggressive systemic forms. Involvement of the central nervous system (CNS) is frequently observed by contiguous spreading from osseous loci.23,24 In contrast, isolated LCH of a cerebral hemisphere, without evidence of systemic disease, is rare, with only a few cases previously reported.8,12,17,19,21,33,34,37,44 The prognosis appeared to be good in these cases, and surgical resection alone has been recommended as the first line of treatment.33 We describe a patient with isolated LCH of the CNS who had multifocal recurrence and a rapid fatal outcome, despite complete surgical resection, radiotherapy, and chemotherapy.

Case Report

This 32-year-old woman without a significant history of disease was admitted in October 1994 with intracranial hypertension of 3 weeks’ duration.

Examination. The examination was normal and no cutaneous or genital lesions, lymphadenopathy or hepatosplenomegaly, fever, or weight loss were noted.

Laboratory Investigations. Laboratory studies showed only a mild leukocytosis (10.28 × 10^9/L) without eosinophilia. Erythrocyte sedimentation rate, liver enzymes, natremia, blood osmolality, and C-reactive protein plasma level were normal and human immunodeficiency virus 1 and 2 serologies negative.

Radiological Examinations. Postinfused computerized tomography (CT) scanning revealed a well-delineated, homogeneous intracranial mass with a cystic portion within the right insula. It was surrounded by a large hypodensity with a mass effect. Magnetic resonance (MR) imaging showed a large hyperintensity on T2-weighted sequences (Fig. 1 right) and a well-delineated hyperdensity on postgadolinium T1-weighted sequences (Fig. 1 left). Skull and chest x-ray films were normal.

Operation. The patient was placed on a course of clonazepam and methylprednisolone (2 mg/kg/day) and a stereotactic biopsy was obtained on October 17, 1994. Pathological examination of the formalin-fixed specimens was inconclusive, and, 9 days later, direct surgical removal of the tumor was attempted via a right transsylvian approach. A smooth grayish-white mass was found at surgery. Dissection of the tumor from the adjacent brain was easily accomplished because of its firm consistency and the presence of a capsule. Removal was almost macroscopically complete.

Pathological Examination. The biopsy specimens were fixed in 10% formalin and the surgically resected specimens were fixed in 2.5% glutaraldehyde for electron microscopy examination; one specimen was frozen. Hematoxylin and eosin–stained paraffin sections of the biopsy specimens showed a cellular lesion that was relatively well demarcated from the surrounding brain parenchyma. This lesion was composed of large cells, with pale cytoplasm and vesicular oval, reniform, or indented nuclei.
with inconspicuous nucleoli. Few mitoses were present. Multinucleated giant cells with foamy cytoplasm were occasionally seen. The same cellular population was found on the surgically resected specimens, in which mild foci of necrosis and scattered eosinophils and lymphocytes were also observed (Fig. 2).

Immunohistochemical analysis of the paraffin-embedded sections showed strong S-100 protein and vimentin immunoreactivity in the large cells, which were negative for glial fibrillary acidic protein (GFAP), cytokeratin, epithelial membrane antigen, and HMB45. Positive staining was variable for CD68 and moderate for CD45. Some of these large cells expressed CD1a on cryostat sections (Fig. 3 left).

Electron microscopic study disclosed trilaminar rod-shaped structures characteristic of Birbeck granules in a few large cells (Fig. 3 right). The large cells presented interdigitating cellular processes but no cell junctions.

Postoperative Course. The patient’s initial postoperative period was uneventful. Abdominal ultrasonography was normal and a bone scan isotope showed a single hyperfixation, which was located in the flap area. Steroid medication was discontinued in November of that year. Four weeks postoperatively, clinical examination was normal; however, CT and MR imaging disclosed a tumor relapse at the operative site. Steroid medication was resumed. Localized brain radiation therapy was instituted (total dose 60 Gy, daily administration 2 Gy). The patient tolerated the radiotherapy well and MR imaging on December 28, 1994 showed a reduction in mass volume. Chemotherapy (vinblastine 10 mg/kg/week) was initiated.

In March 1995, the patient suffered cervical pain with a Lhermitte’s sign. Magnetic resonance infused T1-weighted sequences showed multiple lesions located in the right frontal lobe, postoperative bed, and cervicomedullary junction (Fig. 4). A second radiation therapy limited to the cervicomedullary junction was instituted.

The patient was referred to a general hospital in May 1995 for chronic abdominal pain. On May 8, she suffered sudden headaches. A CT scan showed a hemorrhagic expanding lesion within the right frontal lobe. The patient became drowsy and then comatose. She died on May 9, 1995. No autopsy was permitted.

Discussion

Histiocytosis can be subdivided into LCH and non-LCH.47 The initial name for LCH was histiocytosis X, in which X indicated the unknown origin of the disease.29 Because the original cell is the Langerhans’ cell, the entity is now called LCH.3,39 According to international criteria, the Langerhans’ cell lineage is demonstrated either by ultrastructural detection of Birbeck granules in the cytoplasm or by immunohistochemical evidence of CD1a expression.3,11

![Fig. 1. Preoperative horizontal magnetic resonance images. Left: After administration of gadolinium diethyleneetriamine pentaacetic acid, T1-weighted views (TR 680 msec; TE 22 msec) showing homogeneous hyperintensity with a small cystic anterior part. Right: Two T2-weighted (TR 2200 msec; TE 80 msec) showing heterogeneous signal within a huge hyperintensity.](image1)

![Fig. 2. Photomicrograph of a paraffin section showing a lesion composed of large cells with pale cytoplasm and vesicular nuclei. There are foci of necrosis and scattered eosinophils and lymphocytes. H & E, original magnification × 158.](image2)
Our case fulfills the histological criteria for LCH. The CD1a positivity of some large cells and the ultrastructural evidence of Birbeck granules in a few of them constitute specific findings. These immunohistochemical and ultrastructural criteria help to differentiate foci of LCH from other histiocyte-derived lesions. In tuberculosis or sarcoid granulomatous histiocytic inflammations, nodular masses of epithelioid histiocytes are characteristic. Some lesions of cerebral LCH may exhibit a marked xanthomatous reaction and must be distinguished from other pseudo-tumoral or tumoral xanthomatous lesions. Presumably reactive processes should be considered, including xanthogranulomas of the choroid plexus, and those associated with hyperlipidemia, systemic xanthogranulomatosis, or Weber–Christian disease. These diseases rarely affect the CNS without conspicuous systemic lesions.

Brain localizations of Rosai–Dorfman disease (extranodular sinus histiocytosis with massive lymphadenopathy) are rare and always dura based, mimicking meningiomas. Fewer than 10 cases without adenopathy have been published and were recently reviewed. Histologically, the lesions are somewhat similar to LCH. The large histiocytes are S-100 protein positive, but Birbeck granules are not found on electron microscopy. In pleomorphic xanthoastrocytomas, xanthomatous tumor cells are prominent but usually express GFAP.

The majority of primary histiocytic tumors encountered within the CNS are malignant fibrous histiocytomas of the storiform pleomorphic type, and they often arise within the meninges or are connected with them. Only a few cases are located intracerebrally without any relationship to the overlying meninges.

Isolated involvement of the CNS by LCH without evidence of systemic disease is rare. Hypothalamic involvement suggests disease; however, isolated involvement of the spinal cord or cerebral cortex, as in our case, constitutes a diagnostic challenge. To our knowledge, only nine cases of isolated cerebral LCH have previously been reported in the literature. There are two additional cases but the details are
Langerhans’ cell histiocytosis of the central nervous system

TABLE 1
Characteristics and clinical course of nine patients with Langerhans’ cell histiocytosis reported in the literature*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Clinical Signs</th>
<th>Location</th>
<th>CT Scan (infused)</th>
<th>MR Imaging</th>
<th>Radiation Therapy</th>
<th>Follow-Up Duration</th>
<th>Pathological Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sivilingam, et al., 1977</td>
<td>9, M</td>
<td>intracranial hypertension, seizures</td>
<td>lt temporal</td>
<td>normal</td>
<td>ND</td>
<td>20 Gy</td>
<td>18 mos, 17 yrs†</td>
<td>US:ND; IHC:ND</td>
</tr>
<tr>
<td>Cerda-Nicolas, et al., 1980</td>
<td>35, M</td>
<td>seizures</td>
<td>lt frontal</td>
<td>NA</td>
<td>ND</td>
<td>ND</td>
<td>2 yrs</td>
<td>Birbeck granules; IHC:ND</td>
</tr>
<tr>
<td>Greenwood, et al., 1982</td>
<td>14, M</td>
<td>seizures, intracranial hypertension</td>
<td>lt temporal</td>
<td>ring-shaped</td>
<td>ND</td>
<td>ND</td>
<td>2 yrs</td>
<td>no Birbeck granules; IHC:ND</td>
</tr>
<tr>
<td>Mosinski &amp; Kleinschmidt-DeMasters, 1985</td>
<td>30, M</td>
<td>seizures</td>
<td>rt frontal-temporal</td>
<td>hyperdense</td>
<td>ND</td>
<td>ND</td>
<td>13 yrs†</td>
<td>9 mos US:ND; S-100</td>
</tr>
<tr>
<td>Hammar, et al., 1986</td>
<td>19, M</td>
<td>seizures, headaches</td>
<td>lt temporal</td>
<td>hypodense</td>
<td>hyper T₂</td>
<td>16 mos</td>
<td>Birbeck granules; S-100</td>
<td></td>
</tr>
<tr>
<td>Penar, et al., 1987</td>
<td>26, M</td>
<td>seizures, headaches</td>
<td>lt frontal</td>
<td>hyper T₂</td>
<td>hyper T₂</td>
<td>5 mos</td>
<td>US:ND; S-100</td>
<td></td>
</tr>
<tr>
<td>Eriksen, et al., 1988</td>
<td>31, F</td>
<td>seizures</td>
<td>rt parieto-occipital</td>
<td>hyperdense</td>
<td>hyper T₂</td>
<td>6 mos</td>
<td>Birbeck granules; S-100</td>
<td></td>
</tr>
<tr>
<td>Itoh, et al., 1992</td>
<td>7, M</td>
<td>seizures</td>
<td>rt frontal</td>
<td>hyper T₁G</td>
<td>20 Gy</td>
<td>2 yrs</td>
<td>Birbeck granules; S-100</td>
<td></td>
</tr>
<tr>
<td>Montine, et al., 1994</td>
<td>37, M</td>
<td>headaches, seizures</td>
<td>rt temporal</td>
<td>hyperdense</td>
<td>NA</td>
<td>6 mos</td>
<td>Birbeck granules; S-100</td>
<td></td>
</tr>
</tbody>
</table>

* CT = computerized tomography; hyper T₁G = hyperintense on T₁-weighted gadolinium-enhanced image; hyper T₂ = hyperintense on T₂-weighted image; IHC = immunohistochemistry; MR = magnetic resonance; NA = not available; ND = not done; US = ultrastructural study.

Isolated cerebral LCH typically occurs in young (age range 7–37 years) male patients (sex ratio 8:1), and is heralded by seizures and/or headaches. Radiological examination shows various features on CT or MR imaging (Table 1). Such images are comparable to those observed in disseminated forms of LCH. Most of the previously reported cases of localized forms of LCH appeared to respond well to surgery alone, and only a few had additional radiotherapy. Early local recurrence was observed in only one case. All patients were alive at presentation, but the longest initial follow-up period was 2 years. A recent paper reported long-term follow ups of 13 and 17 years, respectively, in two previously documented cases. Prognosis appeared to be generally good in these localized forms and no systemic disease was noted. In this respect, our case is very unusual, with early recurrence, then multifocal disseminating lesions, and a fatal outcome. A quite similar case was termed “primary intracranial histiocytic lymphoma with Langerhans’ granules,” which is not a satisfactory term.

The etiology and pathogenesis of LCH remain mysterious; it has been suggested that it is an immunological disorder. It is conceivable that the different clinicopathoanatomical patterns are all reactive disorders of variable severity, corresponding to unknown triggering agents, possibly viruses. Several attempts have been made to correlate the clinical and morphological features observed in LCH with prognosis. Age was considered to be correlated or not with prognosis. Other parameters (fever, weight loss, organ dysfunction) strongly suggesting a malignant clinical course were absent or normal as in our case. Isolated cerebral LCH cannot be considered one of the clinical prognostic factors defined in systemic LCH. Histologically, a background relatively devoid of eosinophils has been considered to suggest a poor prognosis, but atypical Langerhans’ cells and mitotic rate did not prove to be significant predictors of survival. In our case with a fatal outcome, eosinophils were not numerous and a few mitoses were observed. The lack of correlation between prognosis and atypical Langerhans’ cells was confirmed by authors who identified a malignant LCH distinct from Letterer–Siwe disease.

There is no clearly identified clinical or pathological prognostic factor in localized CNS LCH because of the small number of reported cases. As in diffuse LCH, the main factor is probably the clinical course. However, a single surgical resection appears to be the first line of treatment.

Acknowledgments

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References


A. Vital, et al.