Craniospinal Langerhans cell histiocytosis in children: 30 years’ experience at a single institution

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Object. The goal of this study was to review a large series of patients with Langerhans cell histiocytosis (LCH) who had craniospinal lesions to assess the long-term course, outcome, and efficacy of treatment of the disease.

Methods. Forty-four patients with LCH who presented to a single pediatric neurosurgical department between 1976 and 2006 were retrospectively reviewed.

Results. This series included 29 boys and 15 girls, ranging in age from 2 months to 13 years, with a mean follow-up duration of 4.5 years. Twenty-seven patients (61%) had unifocal bone lesions, 12 (27%) had multifocal bone disease, 2 (5%) had solitary hypothalamic-pituitary axis lesions, and 3 (7%) had multiple organ involvement at presentation. Five (19%) of the 27 patients with unifocal bone disease and 4 (33%) of the 12 patients with multifocal bone disease had delayed development of new bone lesions during the follow-up period. The time to development of new bone lesions ranged from 1 month to 1 year. Two of the 3 patients with multiple-organ LCH died. Patient age ≤ 2 years at the time of initial presentation was a risk factor for both initial multifocality and eventual dissemination. In all patients with initial multifocal bone involvement or late dissemination of unifocal bone disease, LCH was controlled by chemotherapy, except for 2 who were treated by surgery alone. Three patients had histological evidence of spontaneous resolution of their lesions.

Conclusions. Patients with unifocal LCH can be effectively treated with surgery alone. Very young patients are more likely to have multifocal disease and disseminations, and will usually require chemotherapy to control their disease. Spontaneously regressing lesions need not be resected; however, a biopsy procedure can be performed for diagnostic purposes. (DOI: 10.3171/PED/2008/1/3/187)

KEY WORDS • eosinophilic granuloma • Hand-Schüller-Christian disease • histiocytosis X • Langerhans cell histiocytosis • Letterer-Siwe disease

Langerhans cell histiocytosis is a rare disease of unknown origin that is characterized by an abnormal proliferation of Langerhans cells. Langerhans cells are part of the reticuloendothelial system and participate in the cutaneous immune response as antigen-presenting cells. The presentation and course of LCH is highly variable, ranging from a spontaneously resolving unifocal lesion to a fulminant multisystem disease. Historically, the various manifestations of LCH have been grouped as eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease. Eosinophilic granuloma is a unifocal or multifocal lytic disease of bone; Hand-Schüller-Christian disease classically is the triad of diabetes insipidus, exophthalmos, and bone lesions; whereas Letterer-Siwe is a fulminant multisystem disease occurring in infants. In 1953 Lichtenstein noted the histopathological similarity among these various manifestations and placed them under the heading of histiocytosis X. The name was changed from histiocytosis X to LCH in 1973 when Nezelof et al. reported that the abnormally proliferating cell in histiocytosis X is the Langerhans cell. In 1987 the Writing Group of the Histiocyte Society officially categorized LCH as a Class I histiocytosis.

Langerhans cell histiocytosis has a varied presentation and an unpredictable course whose optimal management is evolving. In this study we reviewed our series of patients with LCH who had craniospinal lesions to better define the optimal neurosurgical treatment and long-term outcome.

Clinical Materials and Methods

The complete records of all patients with LCH who presented to the neurosurgical service of Childrens Hospital Los Angeles between 1976 and 2006 were retrospectively reviewed with institutional review board approval. Forty-seven patients were identified and their charts were reviewed. Of the 47 patients, the 44 in whom the follow-up duration was at least 6 months form the study group for this paper. A histopathological confirmation of the diagnosis was obtained in all patients (Fig. 1). The information ob-
tained for this study included demographic data, diagnostic methods, location of disease, disease course, treatment, and outcome. The patients ranged in age from 2 months to 13 years, with a mean age of 5 years. There was a male preponderance; the male/female ratio was 1.9:1. The mean follow-up duration was 4.5 years.

Plain x-ray films or CT scans were obtained in all patients as part of their initial workup. Those with more complicated lesions, including those involving the brain parenchyma and spine, also received MR imaging studies later in the series when this diagnostic modality became available. As part of the initial workup, all patients were also evaluated with at least 1 x-ray skeletal survey or radionucleotide bone scan to assess the extent of disease. Further CT scans and MR imaging studies were used during follow-up as needed based on lesion location. For patients with multifocal disease, surveillance imaging using either an x-ray skeletal series or a radionucleotide bone scan was performed annually for those with stable LCH, whereas patients with active LCH underwent more frequent imaging.

Patients were classified at the time of diagnosis as having involvement of a single bone, multiple bones, the hypothalamic–pituitary axis, or multiple organ systems. Their outcome was analyzed in terms of progression of the treated lesion(s), dissemination resulting in new lesions, and death.

### Results

Twenty-seven patients (61%) presented with single bone lesions, 12 (27%) with multiple bone lesions, 2 (5%) with involvement of the hypothalamic–pituitary axis only, and 3 (7%) with involvement of multiple organs. Patients with multiple organ involvement tended to be the youngest, with a mean age of 6 months (range 2 months–1 year), whereas those presenting with multiple bone lesions had a mean age of 2.5 years (range 6 months–9 years). Patients with single bone lesions were the oldest, with a mean age of 7 years (range 6 months–13 years), and in the 2 patients with hypothalamic involvement, one was 3 and the other was 4 years of age (Table 1).

Patients most commonly presented with a localized skull mass, most of which were tender to palpation. Less common signs and symptoms included rash, proptosis, polyuria and polydipsia, chronic otitis media, and ptosis. All patients presenting with spine lesions had associated weakness from either nerve root or spinal cord compression (Table 2). The mean time from symptom onset to presentation was 2 months. Eight patients had a recent history of trauma to the affected area.

Bone lesions ranged in size from 1 to 5 cm in diameter and had the typical lytic appearance on plain x-ray films and CT scans. Some lesions had large associated epidural or extracranial soft-tissue components. None of the skull lesions showed dural penetration on imaging. Regarding the 2 patients with lesions involving the hypothalamic–pituitary axis, 1 lesion was 1 cm and the other was 2 cm in greatest dimension; both showed enhancement with contrast administration.

At the time of surgery, no bone lesion penetrated the dura mater. The tumor color ranged from white to brown, and some were hemorrhagic. A cranioplasty was performed in 9 cases by using wire mesh, hydroxyapatite, or both.

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**Fig. 1.** Photomicrographs showing histological findings in sections of LCH tumors prepared with H & E staining (A), CD1a immunostaining (B) viewed with light microscopy, and with electron microscopy (C). On standard H & E staining one can see loosely arranged histiocytes with large invovled nuclei (large arrows) and interspersed eosinophils (small arrows). To make a definitive diagnosis of LCH the specimen must have either CD1a positivity (tan colored cell membrane staining) or show Birbeck granules on electron microscopy (arrowheads). Original magnifications × 40 (A and B) and × 100,000 (C).

**Unifocal Skeletal LCH**

Most of our patients presented with unifocal skeletal LCH; of these, 24 had skull involvement and 3 had vertebral lesions. The frontal bone was the one most frequently affected (Figs. 2 and 3). Twenty-two patients (81%) were treated...
with surgery alone. Two patients with subtotally resected frontal bone lesions received postoperative low-dose radiation (1000 cGy in 1 and 1080 cGy in the other). Two patients received postoperative chemotherapy but not radiation for subtotally resected lesions; 1 of them had progression of his medial sphenoid wing lesion following biopsy and chemotherapy, which was ultimately treated successfully with a complete resection. One patient underwent surgery, radiation, and chemotherapy for a medial sphenoid wing mass involving the cavernous sinus (Table 3).

Of the 27 patients who presented with unifocal skeletal LCH, 5 (19%) had subsequent dissemination of their disease. The mean time from initial diagnosis to the appearance of new lesions was 6 months (range 1 month–1 year). Patients in this group ranged in age from 1.5 to 10 years at the time of dissemination. The locations of dissemination were the skull, clavicle, and sternum. Four of the 5 patients ultimately received chemotherapy for their disseminated lesion (Table 4). Patients given chemotherapy usually received vincristine along with prednisone; however, in some cases methotrexate or cyclophosphamide was also used.

**Multifocal Skeletal LCH**

Twelve patients presented with multifocal skeletal LCH. Seven of them were referred for neurosurgical treatment of a single lesion and were found to have multifocal involvement on the initial radiographic skeletal survey or radionuclide bone scan. One patient had 3 skull lesions treated with surgery alone and had no recurrence. All other patients were treated with chemotherapy once the diagnosis had been made. Readily accessible lesions were completely removed during the initial surgery; however, those that could not be completely resected underwent biopsy sampling because chemotherapy would be given to treat the unresected lesions anyway. Four patients also received local radiation for subtotally resected lesions. No patient had progression of a resected lesion. Four patients (33%) had dissemination of their LCH resulting in new lesions. Those with dissemination often developed numerous new lesions. No patient presenting with multifocal skeletal LCH died.

**Hypothalamic–Pituitary Axis LCH**

Two patients had lesions in the hypothalamic–pituitary axis. In 1 patient, a frontotemporal craniotomy was performed and the lesion, which was adjacent to and safely separable from the infundibulum, was completely resected (Fig. 4). A subfrontal approach was undertaken in the other patient whose lesion was within the hypothalamus; however, because the lesion was adherent to the hypothalamus the procedure was limited to biopsy sampling of the mass, which was followed by low-dose radiotherapy and chemotherapy.

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**TABLE 1**

*Characteristics at diagnosis in 44 patients with LCH*

<table>
<thead>
<tr>
<th>Lesion Location</th>
<th>M/F</th>
<th>Mean Age (range)</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>all patients</td>
<td>29:15</td>
<td>5 yrs (2 mos–13 yrs)</td>
<td>44 (100)</td>
</tr>
<tr>
<td>single bone</td>
<td>19:8</td>
<td>7 yrs (6 mos–13 yrs)</td>
<td>27 (61)</td>
</tr>
<tr>
<td>multiple bone</td>
<td>7:5</td>
<td>2.5 yrs (6 mos–9 yrs)</td>
<td>12 (27)</td>
</tr>
<tr>
<td>hypothalamic–pituitary</td>
<td>2:0</td>
<td>3.5 yrs (3–4 yrs)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>axis only</td>
<td>1:2</td>
<td>6 mos (2 mos–1 yr)</td>
<td>3 (7)</td>
</tr>
</tbody>
</table>

**TABLE 2**

*Presenting symptoms and signs in 44 patients with LCH*

<table>
<thead>
<tr>
<th>Symptom or Sign</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>skull mass</td>
<td>33</td>
</tr>
<tr>
<td>tenderness</td>
<td>22</td>
</tr>
<tr>
<td>weakness</td>
<td>4</td>
</tr>
<tr>
<td>rash</td>
<td>4</td>
</tr>
<tr>
<td>proptosis</td>
<td>3</td>
</tr>
<tr>
<td>polyuria &amp; polydipsia</td>
<td>3</td>
</tr>
<tr>
<td>chronic otitis media</td>
<td>2</td>
</tr>
<tr>
<td>ptosis</td>
<td>1</td>
</tr>
</tbody>
</table>

**Fig. 2.** Admission CT head scans without (left) and with (right) addition of contrast agent, revealing an LCH lesion eroding the left frontal bone with a prominent extracranial soft-tissue component. There was enhancement with contrast administration.

**Fig. 3.** Plain skull x-ray film showing a right calvarial radiolucency (arrow) resulting from LCH.
One patient received follow-up care for 2.5 years and the other for 9 years, during which time neither had progression or dissemination of their disease.

**Multiple-Organ LCH**

Three patients presented with multiple-organ LCH. Two underwent a complete resection of their skull lesions followed by chemotherapy. In a third patient a large temporal lobe mass developed 7 years after diagnosis of multiple-organ LCH and treatment with chemotherapy; a biopsy sample of the mass was obtained for diagnostic purposes and the lesion was treated with chemotherapy and radiation. One patient in this group had progression of her initial disease and the other 2 had dissemination. Two patients (66%) in this group died of respiratory failure (Table 5).

**Central Diabetes Insipidus**

Three patients in our study presented with CDI. Two had lesions involving the hypothalamic–pituitary axis, and a third patient presented with polyostotic bone disease that included a lytic lesion of her dorsum sellae. All 3 of these patients had complete resolution of their lesions after treatment. Three other patients had subsequent development of CDI; none of them had identifiable lesions of the hypothalamic–pituitary axis. None of the patients in our series experienced an improvement in their CDI.

**Spinal LCH**

Four patients presented with weakness secondary to LCH of the spine. One patient had spinal cord compression from a C-7 vertebra plana resulting in quadriplegia, and a second patient had a T-4 body lesion with spinal cord compression and bilateral lower-extremity weakness. The other 2 had unilateral weakness from nerve root compression. Surgery was performed to prevent further neurological injury. Four patients with multifocal bone or organ LCH, for which they were being treated with chemotherapy, experienced delayed development of spinal lesions without neurological deficit and were followed conservatively; no neurological sequelae occurred (Fig. 5).

**Spontaneous Resolution**

In our series, 1 patient had complete resolution of his lesion following biopsy sampling alone, and 2 others had spontaneously resolving lesions at the time of surgery. A 13-year-old boy underwent biopsy sampling of an isolated orbital roof LCH lesion. Following the biopsy procedure, chemotherapy was recommended; this was refused, and 3 months later complete curettage of the affected area re-
Langerhans cell histiocytosis

Table 5
Outcomes in 44 patients with LCH

<table>
<thead>
<tr>
<th>Lesion Location</th>
<th>No. of Patients</th>
<th>No. Cured</th>
<th>No. w/ Progression</th>
<th>No. w/ Dissemination</th>
<th>No. Who Died</th>
</tr>
</thead>
<tbody>
<tr>
<td>single bone</td>
<td>27</td>
<td>21</td>
<td>1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>multiple bone</td>
<td>12</td>
<td>8</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>hypothalamic–pituitary</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1*</td>
</tr>
<tr>
<td>axis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>multiple organs</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

* Cause of death unrelated to LCH.

revealed fibrosis, chronic inflammation, and reparative bone changes without residual LCH. An MR imaging study obtained 1 year later showed no residual tumor or recurrence. Two patients in our series had skull lesions that had begun to regress prior to surgery. In both cases the histological studies revealed a late-stage healing LCH lesion. One patient was a 5-year-old boy with a 6-month history of a raised 4-cm frontal lesion that became progressively depressed over the month prior to surgery. Histological studies revealed a dense inflammatory infiltrate with foam cells, lymphoid cells, and Touton-like giant cells. The other patient had a 2-month history of a 4-cm parietal mass that had begun to regress and was concave at the time of surgery. His lesion consisted mostly of fibrosis.

Discussion

Langerhans cell histiocytosis is a rare disease primarily found in children. The incidence is estimated at 1 to 5 children per million per year. To our knowledge this is the largest pediatric neurosurgical series presenting the long-term follow-up results of comprehensive surgical management of craniospinal LCH.

Prognosis in Children With LCH

When all patients with LCH are considered, including those without craniospinal lesions, very young patients, especially those with multiple organ involvement, have the worst prognosis. In this study, patients who were younger were more likely to have multiple bone or organ involvement and to have dissemination or progression of their disease. Ten (83%) of the 12 patients with multiple bone involvement and all 3 patients with multiple-organ LCH were ≤ 2 years of age. Ten (77%) of the 13 patients who had dissemination or progression of their disease were also ≤ 2 years of age. Furthermore, of the 17 children ≤ 2 years of age in this study, all except 1 (94%) had multifocality, progression, or dissemination. Patients at that age should receive prolonged follow-up care with surveillance imaging regardless of the extent of their disease at presentation.

In our series, 19% of the 27 patients presenting with unifocal bone LCH had dissemination. Other authors have reviewed smaller numbers of pediatric patients with solitary skull or spine LCH and have reported variable rates of dissemination. For solitary skull LCH, Rawlings and Wilkins found a dissemination rate of 31% based on the 26 adult and pediatric patients in their study, 18 of whom were < 21 years of age. Arseni et al. reviewed 27 cases of adult and pediatric cranial LCH, 8 of whom were < 21 years old, and found a dissemination rate of 15%. Martinez-Lage et al. presented a series of 9 pediatric patients with single lesions of the skull and spine in whom there were no disseminations. No comparison was made with patients presenting with hypothalamic–pituitary axis, multiple bone, and multiple-organ LCH in these 3 studies.

Cerebral Parenchymal LCH

Cerebral parenchymal involvement in LCH is usually localized to the hypothalamic–pituitary axis (Gagel granuloma). Due to the predilection of LCH to involve the hypothalamic–pituitary axis, it is the most common systemic disease to cause CDI. Risk factors include multiple organ involvement and skull lesions. In cases of CDI due to LCH, the pituitary stalk may be normal or thickened. Because the MR imaging findings are nonspecific and primary brain tumors, most notably germinoma, cannot be ruled out by MR imaging findings alone, a histological diagnosis is ultimately needed. Most patients with LCH who present with CDI will be found to have extracranial lesions within the 1st year of diagnosis, making a pituitary stalk biopsy unnecessary for diagnosis. Nevertheless, because patients who present with a thickened pituitary stalk and central diabetes insipidus are more likely to have a germinoma than LCH, the initial workup should include serum and CSF β–human chorionic gonadotropin and α fetoprotein.
and CSF cytology. In stable patients with a negative systemic workup, nonsurgical management may be undertaken, with follow-up MR images obtained every 3–6 months for 5 years.\textsuperscript{38,44} When indicated, the risk of a diagnostic pituitary stalk biopsy is low.\textsuperscript{7}

Three patients in our study presented with CDI, and developed it during the course of their disease. Two of the patients presenting with CDI were found to have unifocal LCH involving the hypothalamic–pituitary axis, neither of whom had progression or dissemination. Unifocal hypothalamic LCH is very rare: only a handful of cases have been diagnosed in living patients.\textsuperscript{20,21,41,56} In those cases, patients were treated successfully with complete resection,\textsuperscript{20,21} biopsy sampling followed by low-dose radiation,\textsuperscript{41} and with biopsy sampling followed by low-dose radiation and steroids.\textsuperscript{56} Although some cases of hypothalamic–pituitary axis LCH are amenable to complete resection,\textsuperscript{20,21,40,52} attempts at aggressive removal of adherent lesions may expose patients to unnecessary risk, given the effectiveness of chemotherapy and low-dose radiotherapy.\textsuperscript{41,56}

There is considerable controversy surrounding the optimal treatment of CDI caused by LCH. Several groups found no improvement in CDI in children treated with chemotherapy alone.\textsuperscript{13,16,28} However, chemotherapy may prevent the onset of CDI, as indicated by the lower frequency of this disease in the so-called DAL-HX 83 study.\textsuperscript{28} Regarding radiation to the hypothalamic–pituitary axis, the results have been mixed, with some centers finding no improvement in CDI and others documenting benefit.\textsuperscript{13,37,40} Rosenzweig et al.\textsuperscript{49} reviewed 14 patients treated with hypothalamic–pituitary axis radiation therapy for CDI and reported a complete response in 2 patients, both of whom had “early” disease. In a study conducted at the Mayo Clinic, 5 of 28 patients treated with radiotherapy had a complete clinical response; 4 of the 5 received treatment within 2 weeks of the diagnosis of CDI.\textsuperscript{37} Interestingly, none of the 4 patients in that study who had a radiographic response had a clinical response. If radiation is to be given, it should be started soon after the diagnosis of CDI has been made. Resection can also lead to improvement in CDI. D’Avella and colleagues\textsuperscript{21} completely resected a hypothalamic LCH lesion in a patient presenting with CDI and panhypopituitarism, who postoperatively attained resolution of the CDI but not the hypopituitarism. Nishio et al.\textsuperscript{40} completely resected a pituitary LCH lesion, resulting in a partial resolution of the preoperative CDI. Although the possibility of improvement in CDI after complete resection is intriguing, the rarity of such cases and the lack of improvement in CDI in the patient we present, who underwent complete resection of a lesion adjacent to the infundibulum, makes it difficult to draw any conclusions.

Langerhans cell histiocytosis rarely involves the brain parenchyma outside of the hypothalamic–pituitary axis.\textsuperscript{30} Cerebral LCH can present as a single lesion, but is much more common in patients with multiple organ involvement.\textsuperscript{30,31,53,55} Rarely, CSF cytology will reveal Langerhans cells.\textsuperscript{27} As is the case in extracranial LCH, cerebral parenchymal lesions usually respond well to surgical excision, conventional radiation, radiosurgery, and chemotherapy.\textsuperscript{15,21,30,31,40,48,53} One patient in our series, who was diagnosed when she was 1 year old with multisystem LCH, developed a large frontotemporal mass 7 years later, which was proven based on biopsy findings to be LCH. The patient later died of respiratory failure. Although the prognosis for intraaxial LCH is generally good, it can be refractory to multimodality treatment, and ultimately can be fatal.\textsuperscript{58}

**Spinal LCH**

The frequency of spinal involvement in patients with LCH is 6–25%.\textsuperscript{10,24,26,55} Lesions predominantly involve the vertebral body, with only 5% of spine lesions involving the posterior elements.\textsuperscript{28} Patients most often present with pain or torticollis; however, neurological deficits are uncommon.\textsuperscript{10,24,26,45} Spinal cord or nerve root compression with subsequent weakness and numbness occurred in 4 patients in our series, 2 of whom required decompression for spinal cord compression and another 2 for unilateral weakness due to nerve root compression. Radiographically, lytic lesions are the most common, followed by partial or complete vertebral body collapse.\textsuperscript{10} Complete collapse, known as vertebra plana, is usually seen in children because the lytic lesions involve more of the vertebral body in this age group. Long-term follow-up has shown that most patients have some reconstitution of vertebral body height.\textsuperscript{30,34} The prognosis for isolated spine lesions is good, and they can resolve without treatment.\textsuperscript{10} We only operated on patients with neurological deficits and just observed the 4 patients with multifocal bone or organ LCH in whom spinal LCH had developed from dissemination without associated neurological deficit, and were already being treated with chemotherapy. Each of those patients ultimately developed multiple collapsed vertebrae. After a follow-up period of 4.5–24.5 years there were no neurological sequelae; however, we observed only little return of vertebral body height during that time period. In neurologically intact patients with stable spine lesions, nonsurgical follow-up is appropriate once the diagnosis has been made (Fig. 6).\textsuperscript{10,26}

**Cranioplasty for Large Lesions in the Cranial Vault**

Nine patients in our series underwent a cranioplasty after gross-total resection of lesions involving the cranial vault. These patients had lesions of at least 3 cm in diameter, and most involved the frontal bone. Wire mesh, hydroxyapatite, or a combination of both, were used for the cranioplasties. Belen et al.\textsuperscript{5} used autologous bone grafts for cranioplasty in all patients with completely resected cranial vault lesions. Martinez-Lage and colleagues\textsuperscript{14} used autologous bone grafts in 3 of their 5 craniec tomy patients. Rawlings and Wilkins\textsuperscript{10} performed cranioplasty in 5 of 15 craniectomy patients by using methyl methacrylate. Small cranietomies, especially those in inconspicuous locations, generally do not require a cranioplasty, and in young children the defects are likely to fill in. Patients who are older, have lesions in exposed locations, or have large postoperative defects, are often best treated with a cranioplasty during their initial procedure. A good cosmetic result can also be achieved in patients who heal after biopsy alone.\textsuperscript{4} As illustrated in our case of spontaneous resolution in a 13-year-old boy with LCH of the orbital roof, reparative bone changes have been seen during the healing process.

**Nonsurgical Management**

Although the mainstay of treatment for isolated cranial LCH is primarily surgical, in some settings isolated lesions can be observed (watchful waiting) for spontaneous resolution if the lesion has begun to decrease in size and is readi-
ly followed by clinical examination. In some cases a lesion may completely regress following biopsy procedures alone. Furthermore, even without biopsy sampling, lesions can undergo spontaneous resolution. The 13-year-old boy in our series who underwent biopsy sampling of an isolated orbital roof LCH lesion followed 3 months later by curettage and showing no residual LCH is only the second reported case of orbital LCH with histological evidence proving resolution following biopsy sampling. In addition, the 2 patients in our study whose skull lesions had begun to regress prior to surgery and in whom pathological studies showed late-stage healing LCH lesions, lends important histological documentation of the spontaneously resolving nature of this disease in some patients. We recommend observation or biopsy sampling alone in patients with small asymptomatic or resolving unifocal lesions consistent with LCH.

Bone lesions are usually best treated with resection alone; however, those that are inaccessible, recurrent, or subtotally resected can be effectively treated with radiotherapy. In a metaanalysis by Olschewski and Seegenschmiedt, patients given radiotherapy for unifocal and multifocal bone disease had a local control rate of 96%, with a complete remission in 93%. Bone lesions treated with radiotherapy in patients with multiple-organ LCH had a local control rate of 92% and a complete remission in 76%. Nonetheless, patients with multifocal bone and multiple-organ LCH often need to be treated with chemotherapy. Corticosteroids alone, or in combination with 1 or more chemotherapeutic agents, have been shown to be effective. Agents with proven efficacy include cyclophosphamide, etoposide, methotrexate, vincristine, and vinblastine, and vincristine, which can control the disease in 50–60% of cases. These drugs may only be effective temporarily, and LCH can become resistant to conventional chemotherapy. Refractory LCH can be treated with other agents such as cytosine arabinoside and 2-chlorodeoxyadenosine or, in extreme cases, hematopoietic stem cell transplantation (Fig. 7).

We successfully used surgery alone to treat 1 patient who had a dissemination to the sternum after being treated for a unifocal skull lesion, and another who presented with multifocal LCH of the skull; however, we believe that all patients who have multifocal disease or a dissemination should still be considered for systemic therapy. Nonetheless, if the location of the dissemination is easily accessible, a second surgery may be undertaken with systemic therapy reserved for further dissemination, as was done in one of our patients.

**Surveillance Imaging**

Whole-body surveillance imaging can be done using either x-ray skeletal surveys or radionucleotide bone scans. Dogan et al. found x-ray skeletal surveys and radionu-

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**Fig. 6.** General treatment algorithm for spinal LCH.

**Fig. 7.** General treatment algorithm for cranial LCH.
cleft bone scans to be complementary, in that x-ray skeletal surveys were more sensitive in the detection of skull lesions and radionucleotide bone scans were more sensitive for detecting spine lesions. These authors recommended that both x-ray skeletal surveys and radionucleotide bone scans be used initially and that radionucleotide bone scans be used for follow-up. Van Nieuwenhuyse et al.\textsuperscript{57} found that x-ray skeletal surveys and radionucleotide bone scans alone should be used for follow-up. The basis for the debate over which modality to use is that both modalities tend to miss some lesions. Patients receiving chemotherapy or those whose lesions are not growing are more likely to have their lesions detected by an x-ray skeletal series and may have a normal bone scan. Conversely, actively growing bone lesions, and those in the soft tissue, are best detected by radionucleotide bone scans.\textsuperscript{3,51} It is reasonable to use either modality for follow-up evaluations, with the other being used to reveal suspected lesions not visualized with one technique. Due to the limitations of these imaging techniques, missed lesions may have resulted in the misclassification of some patients in this study who had multifocal disease as having unifocal disease; however, it is not possible to determine the extent to which that may have occurred.

Future Directions

Over the last few decades great advances have been made in the diagnosis and treatment of LCH. From a diagnostic perspective, high-resolution CT and MR imaging has made the precise localization of complex and deep-seated lesions possible. From a surgical perspective, the advancement of the operating microscope and the refinement of microsurgical techniques has allowed surgeons to address intraxial lesions more safely, including those involving the hypothalamic–pituitary axis. Continued innovation in the operative theater in the areas of intraoperative guidance systems and imaging, spinal instrumentation, and minimal invasive techniques will serve to increase even further the scope and safety of neurosurgical disease treatment. Gamma Knife radiosurgery has also recently been shown to be effective for select lesions involving the brain and skull base.\textsuperscript{15,22}

Despite advances in the understanding of the biology of LCH, it remains an enigmatic disease. It is still unclear whether it is a clonal neoplastic disorder or due to dysregulation of the immune system.\textsuperscript{1,3,30,60,61} To that end, many treatments are based less on an understanding of the disease than on its presentation and course.\textsuperscript{12} Greater insight into the pathophysiological features of LCH will enable better targeting of future therapies.\textsuperscript{1}

Conclusions

This series of patients with craniospinal LCH demonstrates the need to discern the extent of disease both at presentation and at follow-up, especially in children ≤ 2 years of age, because this subgroup is more likely to have multiple-bone or multiple-organ LCH and dissemination. Patients with unifocal bone and hypothalamic LCH can be effectively treated with surgery alone, although low-dose radiation or chemotherapy is effective for subtotally resected lesions. Spontaneously regressing lesions need not be resected; however, a biopsy procedure can be done for diagnostic purposes. Chemotherapy should be considered for dissemination of the disease. Very young patients with multiple-bone or multiple-organ LCH will usually require systemic therapy to control their disease.

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