EOSINOPHILIC GRANULOMA OF THE ORBIT: A PARADOX OF AGGRESSIVE DESTRUCTION RESPONSIVE TO MINIMAL INTERVENTION

BY Gerald J. Harris MD FACS,* AND Kyung In Woo MD

ABSTRACT

Purpose: To describe the findings and outcomes in eosinophilic granuloma (unifocal Langerhans cell histiocytosis [LCH]) of the orbit, and to explain the paradox of aggressive bone destruction responsive to minimal intervention.

Methods: Retrospective, consecutive, interventional case series of patients treated from 1985 through 2001. Minimum inclusion criteria were demonstration of CD1a positivity or Birbeck granules, treatment by a single surgeon, systemic evaluation by a pediatric oncologist, and follow-up of 12 months. A pathogenetic construct was assembled from general LCH concepts and the specific orbital findings.

Results: Seven patients met study criteria. All were male, 2 to 16 years of age. All had eyelid or forehead swelling and osteolytic defects, with symptoms of 2 to 6 weeks' duration. All underwent incisional biopsy, with frozen-section examination suggestive of LCH in 6 of 7 cases. The 2 earliest patients received low-dose irradiation after simple biopsy. The 5 most recent patients had subtotal curettage at the time of biopsy; 4 of 5 received simultaneous intraleisional corticosteroid injection. In all cases, systemic evaluation showed no other focus of LCH, reossification was timely, and no local recurrence or additional focus was noted in follow-up of 1 to 17 years.

Conclusions: Transient immune dysfunction may provoke the cytokine-mediated proliferation of pathologic Langerhans cells within the hematopoietic marrow of the anterolateral frontal bone. These cells cause osteolysis through elaboration of interleukin-1 and prostaglandin E2. Corticosteroids can inhibit the mediators. We recommend incisional biopsy, frozen-section provisional diagnosis, subtotal curettage, intraleisional corticosteroid instillation, postoperative systemic evaluation, and long-term follow-up.


INTRODUCTION

In 1987, the disorders previously grouped under the rubric of histiocytosis X were reclassified as Langerhans cell histiocytosis (LCH). These terms embrace a broad clinical spectrum, including acute disseminated LCH (eg, Letterer-Siwe disease), multifocal LCH (eg, Hand-Schüller-Christian syndrome), and unifocal LCH (eg, eosinophilic granuloma). Orbital involvement by LCH most often represents unifocal disease. The condition is uncommon, and descriptions of isolated eosinophilic granuloma of the orbit generally have been limited to single case reports, small case series, or minor subsets of full-spectrum LCH series. The process usually involves the superior temporal quadrant, associated with an osteolytic defect of the orbital roof. There is a male predominance, with onset in the first or second decade. Symptoms include rapidly progressive upper eyelid edema and erythema, bone pain, and tenderness. Computed tomography (CT) shows extensive frontal bone destruction, and other conditions in the clinical differential diagnosis include metastatic tumors and lacrimal gland neoplasms. The lesion's cellular components include pathologic Langerhans cells (histiocytes similar to the Langerhans cells of the epidermis), chronic inflammatory cells, and eosinophils. Eosinophilic granuloma of the orbit has been reported to resolve after low-dose irradiation, intraleisional corticosteroid injection, and simple biopsy or subtotal curettage.
between the magnitude of tissue destruction and the minimal intervention needed for complete resolution, as described in sporadic case reports of unifocal orbital LCH. We analyzed our own experience with the disease and reviewed the recent laboratory and clinical research on extraorbital LCH in an effort to explain this paradox and develop a rational basis for therapy.

METHODS

We performed a retrospective review of patients with clinical and pathological diagnoses of eosinophilic granuloma, histiocytosis X, or LCH treated at the Eye Institute of the Medical College of Wisconsin between December 1985 and December 2001. Clinical, operative, pathology, and laboratory records were reviewed, and orbital CT scans were examined. Among the inclusion criteria were those for “definitive diagnosis” of LCH proposed by the Writing Group of the Histiocyte Society: the immunohistochemical demonstration of characteristic surface antigens (ie, CD1a) and/or the electron microscopic demonstration of Birbeck (Langerhans) granules. Other requirements were as follows: treatment by a single surgeon (G.J.H.); systemic evaluation by a pediatric oncologist, including a complete medical history and physical examination, laboratory studies, and a skeletal survey or bone scan; and minimum follow-up of 12 months. If any patient had been last examined less than 12 months following presentation, the authors obtained additional follow-up information by direct telephone contact with a parent.

Initial management involved incisional biopsy, usually within 48 hours of presentation to the authors. This generally was accomplished through an upper eyelid-crease incision, with dissection between orbicularis muscle and orbital septum to the superior orbital rim, and posterior subperiosteal dissection to the lesion. Tissue was submitted for frozen-section, permanent-section, and electron microscopic evaluation. Additional intraoperative intervention was dictated by the frozen-section interpretation and the extent of orbital and intracranial involvement. Postoperative treatment was influenced, in part, by when patients were encountered during the 16-year time frame of the study.

RESULTS

Seven patients met the inclusion criteria for this study (Table). Ages ranged from 2 to 16 years, with a median and a mean of 8 years. All patients were male, and none had a previous history of serious illness. Involvement was unilateral in all cases, with the right side affected in four cases and the left in three. Symptom duration ranged from 2 to 6 weeks, with a median and a mean of 4 weeks. Eyelid or forehead swelling was the most common complaint (Figures 1 and 2); three of seven patients reported pain or tenderness. Vision was mildly decreased in three patients, with the largest relative disparity (20/40 OD, 20/15 OS) in a patient with macular striae. Two patients had palpable enlargement of ipsilateral preauricular lymph nodes. The CT findings are shown in Figures 3 through 9.

All patients underwent incisional biopsy (Figure 10). Frozen-section examination of specimens was suggestive of LCH in 6 of 7 cases, with some variation in the confidence level among these 6. In the remaining case (case 2), the initial frozen-section evaluation was inconclusive. In cases 1 and 2, the earliest in the series, there was no additional operative intervention (Table). Following definitive permanent-section and electron microscopic diagnosis, these 2 patients were treated with fractionated external beam radiation to total doses of 400 and 800 cGy, respectively. In the remaining 5 cases (cases 3 through 7), a strongly presumptive frozen-section diagnosis of LCH prompted curettage of grossly abnormal tissue. These

![Figure 1](image1.png)

Case 5. Nine-year-old boy with right eyebrow and eyelid edema, erythema, and tenderness of 6 weeks’ duration.

![Figure 2](image2.png)

Case 6. Two-year-old boy with 4-week history of right forehead and eyebrow swelling.
efforts were limited to the orbital and clearly intraosseous components, and abnormal tissue was not pursued into the epidural space, temporal fossa, or forehead. For example, the prominent forehead masses that had erupted through the anterior table of the frontal bone in cases 4 and 6 (Figure 8) were not disturbed at surgery. Intralesional corticosteroids were instilled into the osteolytic cavity in cases 3, 5, 6, and 7. This maneuver was not performed in case 4 because the orbital aspect of the tumor was separated from the intracranial compartment by only a thin-edged orbital roof defect (Figure 6). There was no postoperative therapeutic intervention in cases 3 through 7.

Light microscopic examination of formalin-fixed specimens showed fairly uniform findings. Infiltrates comprised pathologic Langerhans cells, eosinophils, scat-

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**TABLE: CLINICAL DATA IN 7 CASES OF EOSINOPHILIC GRANULOMA OF THE ORBIT**

<table>
<thead>
<tr>
<th>CASE/AGE(YR)/SEX/SIDE</th>
<th>SYMPTOMS/DURATION (WK)</th>
<th>PHYSICAL FINDINGS</th>
<th>YEAR</th>
<th>INTERVENTION</th>
<th>FOLLOW-UP VISIT/PHONE CONTACT (MOS)</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/5/M/L</td>
<td>Eyelid swelling/6</td>
<td>Upper eyelid edema, proptosis, palpable spongy mass, preauricular adenopathy, 20/20 OD, 20/30 OS</td>
<td>1985</td>
<td>Incisional biopsy; 400 cGy</td>
<td>20/204</td>
<td>No other foci; no recurrence; normal vision</td>
</tr>
<tr>
<td>2/16/M/R</td>
<td>Eyelid swelling; pain, blurred vision/4</td>
<td>Upper eyelid edema, proptosis, inferior globe displacement, preauricular adenopathy, macular striae; 20/40 OD, 20/15 OS</td>
<td>1987</td>
<td>Incisional biopsy; 800 cGy</td>
<td>4/180</td>
<td>No other foci; no recurrence; normal vision</td>
</tr>
<tr>
<td>3/8/M/L</td>
<td>Eyelid, forehead swelling/3</td>
<td>Upper eyelid edema, forehead mass, proptosis; 20/25 OU</td>
<td>1999</td>
<td>Incisional biopsy, subtotal curettage</td>
<td>4/36</td>
<td>No other foci; no recurrence; normal vision</td>
</tr>
<tr>
<td>7/14/M/L</td>
<td>Eyelid swelling, headache/4</td>
<td>Upper eyelid edema, proptosis, limited upgaze; 20/20 OU</td>
<td>2001</td>
<td>Incisional biopsy; subtotal curettage; intralesional methylprednisolone, 125 mg</td>
<td>12</td>
<td>No other foci; no recurrence; normal vision</td>
</tr>
</tbody>
</table>

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**FIGURE 3**

Case 1. Full-thickness defect of orbital roof; soft tissue mass causing proptosis and inferior globe displacement in a 5-year-old boy. An ipsilateral preauricular lymph node was enlarged.
tered lymphocytes, plasma cells, and multinucleated giant cells (Figure 11). Immunohistochemical staining for CD1a was performed in the 4 most recent cases, and all were strongly positive (Figure 12). Among the 5 cases in which staining for S-100 was performed, 4 were positive and 1 was equivocal. Electron microscopic examination was performed in the 5 earliest cases, and all were positive for Birbeck granules (Figure 13). Every case was positive for CD1a, Birbeck granules, or both.

Following definitive diagnosis, all patients were evaluated by pediatric oncologists for systemic involvement. Every patient underwent a complete physical examination, routine laboratory testing, and radiographic skeletal survey. Other evaluation varied and included radionuclide bone scanning, abdominal and pelvic CT scanning, blood chemistry, blood and urine osmolarity, water deprivation testing, and bone marrow aspiration. There was no evidence for multifocal LCH in any case. Ipsilateral preauricular adenopathy in cases 1 and 2 was thought to be secondary to unifocal anterior orbital disease with eyelid extension.

Follow-up by the authors, oncologists, and pediatricians included periodic physical examination, orbital CT scanning, skeletal survey, and, in some cases, bone scanning. Follow-up for the 3 most recent patients continues 12 to 24 months after initial presentation (Table). The 4 earliest patients were last examined by the authors 4 to 20 months after their initial presentation, and information was updated to the time of this report by direct telephone contact with parents. The total follow-up intervals in cases 1, 2, 3, and 4 were 17, 15, 10, and 3 years, respectively. None of the 7 patients has had local recurrence, other foci of LCH, or other serious illness. All patients regained normal vision. Patient 5, with substantial anterior orbital and eyelid involvement (Figures 1 and 7), had mild ptosis and eyelid fold asymmetry in late follow-up. Of interest was the rapid resolution of soft tissue involvement, including areas that were not surgically exposed,
curetted, injected with corticosteroids, or subsequently irradiated. For example, the prominent forehead masses of patients 4 and 6 resolved within 1 week of intervention that had been limited to the orbital masses. Throughout the series, follow-up CT scanning showed progressive, timely reossification (Figures 4 through 9).

**DISCUSSION**

The treatment responses in our series paralleled those in isolated case reports and smaller clinical series. All of our 7 patients underwent open, diagnostic biopsy. Five also had some degree of subtotal curettage at the time of biopsy. Four of these 5 received a single intralcal corticosteroid injection during the same procedure, and 1 had no additional treatment. The 2 earliest patients in the series were not treated with curettage or corticosteroids but received very low-dose radiation after simple biopsy. In every case, despite extensive and rapidly progressive bone destruction at first presentation, prompt reversal with-out local recurrence followed relatively minor intervention. By assembling a pathogenetic construct, built on current general concepts of LCH and the specific findings in the orbital disease, we can attempt to explain the response of this aggressive process to conservative treatment.

**PATHOGENESIS**

Normal Langerhans cells begin as pluripotential stem
cells in active bone marrow. Under the influence of multiple cytokines (e.g., granulocyte-macrophage colony-stimulating factor, tumor necrosis factor α, interleukin [IL]-3, and IL-4), these stem cells differentiate into two major classes of histiocyte: antigen-processing macrophages and antigen-presenting dendritic cells. Cytokines further induce dendritic cells to diverge along multiple phenotypic paths, with one leading to the

FIGURE 8
Case 6. Top, Erosion of soft tissue mass through anterior and posterior cortex of frontal bone, with forehead prominence (see Figure 2). Middle and bottom, Progressive reossification 1 and 10 months after biopsy, curettage, and corticosteroid injection, all limited to small orbital component. Forehead mass resolved within 1 week of treatment.

FIGURE 9
Case 7. A, Large lytic defect of orbital roof, and intracranial and orbital mass with dural and periorbital enhancement in a 14-year-old boy. B, C, and D, Reossification 2, 4, and 10 months after biopsy, curettage, and corticosteroid injection limited to orbit and osteolytic cavity.
Langerhans cell. These cells characteristically express the CD1a antigen, the S-100 protein, and Birbeck granules. The normal bone marrow does not retain a large, permanent population of Langerhans cells. Following migration to the epidermis, oral mucosa, lungs, and other sites, the cells participate in immunosurveillance by engaging extrinsic antigens. Langerhans cell–antigen complexes then travel via lymphatic channels to regional lymph nodes, where the antigens are presented to paracortical T cells.

The primary agent or event that impacts this orderly process and causes an accumulation of pathologic Langerhans cells is unknown. A number of infectious, genetic, and neoplastic disorders have been associated with LCH, but the findings have not been consistent. There is evidence that aberrant or uncontrolled cytokine production may play a key role in the pathogenesis of LCH. In a unifying concept, Zelger proposed that several different events can trigger an immune dysregula-
tion that leads to the common phenotype—but diverse clinical spectrum—of LCH. In some cases, the transient immunodeficiency of a viral infection might provoke a “dysregulated cytokine concert” that transforms precursor cells into pathologic Langerhans cells. The transience of the inciting event could contribute to the generally favorable outcome of unifocal LCH. In other cases, a persistent immunodeficiency caused by a genetic defect or by an acquired lymphoma, leukemia, or myelodysplasia might sustain a “cytokine storm” that leads to acute disseminated LCH with a lethal outcome, or to multifocal LCH with a chronic course of intermediate severity.

The morbidity of LCH results from the mass effect of proliferating pathologic Langerhans cells within multiple organs, and involved sites can include bone, skin, lymph nodes, spleen, lung, liver, brain, and gastrointestinal tract. The severity of the disease may depend on the “upstream” immune dysfunction or other factors, but not on the histopathology of the “downstream” lesions, which are fairly uniform throughout the clinical spectrum. The pathologic Langerhans cell, the basic unit in all forms of LCH, differs from the normal cell in lacking dendritic morphology, but is similar in its expression of CD1a, S-100, and Birbeck granules. (Histiocytoses caused by non-Langerhans-cell histiocytes, including Rosai-Dorfman disease, juvenile xanthogranuloma, xanthogranuloma, Erdheim-Chester disease, xanthelasma, and xanthoma, do not share this exact phenotypic signature.)

Pathologic Langerhans cells are cytologically benign and diploid in DNA profiles. The cells are also monoclonal in all forms of LCH, including rapidly resolving unifocal cases. Therefore, clonality is not thought to be indicative of either neoplasia or prognosis in this group of diseases. There are, however, some differences in phenotypic cytochemistry: cells in the disseminated infantile form of LCH release prostaglandin D2 and thromboxane;18 cells from eosinophilic granuloma of bone produce IL-1 and prostaglandin E2 (PGE2) in culture.19 Explanations for the specific clinical findings and response to treatment of eosinophilic granuloma of the orbit can be sought within this general context.

The LCH disorders have a predilection for hematopoietically active bone marrow (the residence of Langerhans cell precursors), and osseous lesions are present in the majority of isolated and multisystem cases. The typical orbital locus might be explained by the age-related distribution of active marrow within normal orbital bones. (This distribution can be demonstrated in magnetic resonance images: red hematopoietic marrow has low signal intensity in T1-weighted images; yellow, fatty inactive marrow has high signal intensity.)21 The marrow of the maxillary and zygomatic bones loses its hematopoietic ability in infancy, converting from red to yellow, while the frontal bone retains active marrow function into adulthood. However, the marrow space of the frontal bone progressively contracts into the bone’s anterolateral portion, as the anteromedial portion yields to the expanding frontal sinus.23 In our series, as in others,4,24 the site predilection of eosinophilic granuloma was the anterolateral aspect of the superior orbit. In the age range for the disease, with a mean of 8 years in our series, this region may be the only periorbital site containing hematopoietic marrow. Of interest, 2 of our 7 patients had somewhat more central or medial involvement of the anterior orbital roof (Figures 3 and 5). These patients were 3 and 5 years of age, at an early stage of frontal sinus development. The greater sphenoid wing may also contain active marrow in the first two decades and is an occasional site of unifocal orbital LCH.

The major and most dramatic form of tissue destruction in eosinophilic granuloma of the orbit is osteolysis, while pressure erosion through soft tissue planes and inflammatory sequelae seem to have lesser roles. The disproportionate bone destruction might be explained by...
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the cytochemistry of Langerhans cells, which, in addition to responding to cytokines in their differentiation, also produce cytokines as a normal functional activity. Cytokine elaboration by pathologic Langerhans cells is an amplification of that normal activity.14 As noted, purified cells from eosinophilic bone granuloma produce IL-1 and PGE2 in culture.19 IL-1 is the major osteoclast-activating factor and is a potent inhibitor of bone formation, interfering with collagen synthesis.20-27 PGE2 induces bone resorption in vitro.26 It would appear that pathologic Langerhans cells are capable of significant osteolysis through the elaboration of these two mediators.

RESPONSE TO TREATMENT
How is this highly destructive process so easily reversed? While a transient, rather than sustained, trigger event (eg, viral infection) might support a favorable long-term outcome, termination of the local osteolysis—once set in motion—requires explanation.

One possibility is that eosinophilic granuloma is entirely self-limited, and even minimalistic intervention is unnecessary. To our knowledge, truly spontaneous recovery (without biopsy) has not been reported in orbital cases and would be presumptive without diagnostic confirmation. In a retrospective series of 30 patients with localized LCH involving various bones and treated with different methods, one patient did not undergo a biopsy; the radiographically diagnosed parietal bone lesion resolved with observation alone.20

Resolution of orbital eosinophilic granuloma after biopsy alone, or after biopsy with subtotal curettage, has been reported by others6,10,11 and occurred in our case 4. Whether this intervention altered the natural history is unknown, but the rapid disappearance of soft tissue signs and the timely reossification that followed suggest a possible therapeutic impact. The mechanism is uncertain. We could speculate that simple operative changes in the physical microenvironment (eg, PO2, PCO2, pH) might have interrupted a complex, but fragile, pathological cascade. However, simple biopsy or partial resection of unifocal LCH does not guarantee a sustained favorable outcome.20,21 Song and colleagues21 reported a patient with orbital eosinophilic granuloma that recurred 6 weeks following biopsy and curettage; the patient then received chemotherapy.

Response of LCH bone lesions to low-dose radiation is well documented,22 and this approach was used for unifocal orbital disease by other investigators2 and in our two earliest cases. While the anti-inflammatory effects of low-dose radiotherapy are not completely understood, a possible mechanism pertinent to LCH is the diminished release by activated macrophages of nitric oxide, which plays a central, multifunctional role in inflammation.33

Treatment of orbital eosinophilic granuloma with intralesional corticosteroids has been reported by others7,8 and was used in 4 of our 7 cases. The experience in nonorbital LCH of bone is extensive.34-36 Yasko and associates21 reported complete resolution of symptoms and radiographic evidence of healing in 31 of 35 lesions (89%) after a single intralesional injection of methylprednisolone. Of the remaining 4 lesions, 3 resolved after two or more injections. In vitro studies have demonstrated that corticosteroids inhibit IL-1-induced bone resorption and PGE2 production.29 Therefore, corticosteroids may directly forestall cytokine-mediated osteolysis, the major destructive mechanism of pathologic Langerhans cells in eosinophilic granuloma.

MANAGEMENT RECOMMENDATIONS
We recommend diagnostic biopsy in suspected cases of eosinophilic granuloma. Although the clinical presentation and CT findings are fairly uniform, they are not pathognomonic, and other serious conditions in the same age-group can have similar manifestations. Neuroblastoma, Ewing’s sarcoma, and Wilms’ tumor can each metastasize to the pediatric orbit.28 Tumor cells have a general tendency for adhesion to vascular endothelium, and the rich, sinusoidal channels of hematopoietic marrow are favored sites of metastasis.21 Therefore, metastatic malignancies and eosinophilic granuloma share the same predilection for the superolateral orbit in this population. Granulomatous bone diseases also have a preference for marrow spaces, presenting as local osteolytic lesions,7 and the superolateral orbit can be the locus of giant cell reparative granuloma,38,39 aneurysmal bone cyst,40 resorptive giant cell granuloma (brown tumor),41 or hematocystic.42 A ruptured dermoid cyst can produce eyelid erythema by eliciting a lipogranulomatous response.15 The associated bone defect is generally better margined, but may not always be distinguishable from the osteolytic lesion of eosinophilic granuloma.

We favor open, incisional biopsy over percutaneous, fine-needle aspiration biopsy. The disease can be nodular with pathologic Langerhans cells occurring in aggregates, and aspiration cytology may miss the diagnostic cells.43 Extensively necrotic or healing lesions may have sparse pathologic Langerhans cells and can be mistaken for osteomyelitis or xanthomatous fibrous dysplasia.12,24 Adequate samples allow definitive immunohistochemistry and electron microscopy. Percutaneous fine-needle aspiration, with or without core-needle biopsy, has been used for eosinophilic granuloma of the extremities in cooperative patients.44 For periorbital lesions, however, the need for general anesthesia in children, the risk of hemorrhage within a closed orbit, and the frequent extension of the process to dura all weigh toward open biopsy. An inci-
sional approach also allows simultaneous, intraoperative therapy based on a presumptive frozen-section diagnosis.

While some cases of unifocal LCH may be self-limited, early treatment can truncate disease activity and minimize morbidity. Our preference is for limited curettage and intralesional corticosteroids, avoiding postoperative irradiation and chemotherapy as primary treatment. Curettage is restricted to soft tissue components and bony cavities that are accessible without risk to dura or functional structures of the orbit. Because recurrence may follow simple curettage, and because corticosteroids have an inhibitory effect on osteolysis, we recommend instillation of methylprednisolone, 125 mg, into the residual-tumor-lined cavity.

Most patients with orbital eosinophilic granuloma will prove to have unifocal disease. However, concurrent or consecutive multifocal LCH has been reported with prove to have unifocal disease. However, concurrent or consecutive multifocal LCH has been reported with concurrent or recurrent nonorbital bone lesions treated by various modalities (intralesional corticosteroids were administered in only 5% of unifocal lesions). Eighteen percent of pediatricians and oncologists, using serial CT scans to confirm timely reossification. A guideline for adequate follow-up might be derived from a series of 155 unifocal and multifocal nonorbital bone lesions treated by various systemic corticosteroids, vinca alkaloids, and antimetabolites.

In our experience, most patients will not have a local recurrence after the recommended treatment. However, we advise follow-up by orbital surgeons in concert with pediatricians and oncologists, using serial CT scans to confirm timely reossification. A guideline for adequate follow-up might be derived from a series of 155 unifocal and multifocal nonorbital bone lesions treated by various systemic corticosteroids, vinca alkaloids, and antimetabolites.

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**DISCUSSION**

Dr Barrett G, Haik. Harris and Woo present seven cases of isolated Langerhans cell histiocytosis (LCH) of the orbit, all of which responded to minimal intervention, and summarize the current understanding in the pathogenesis and treatment of LCH. The paper is very well written; the information provided is current, which results in a great overview of LCH. In particular, the description of the pathogenesis of the bone lesions and of the particularities of the lesions with orbital involvement is one of the best in the literature.

As the authors point out, LCH is a proliferative disorder of activated Langerhans cells characterized by a variable biological behavior and a spectrum of distinct clinical presentations. Patients with localized disease in bone like eosinophilic granuloma, in skin such as Hashimoto-Pritzker disease or in lymph nodes have an excellent prognosis with minimal or no therapy, whereas patients with multi-system disease like Letterer-Siwe require intensive therapy and yet do not survive.1

The pathogenesis of LCH is poorly understood. Because LCH has been demonstrated to be a monoclonal condition, it has been considered a neoplastic disorder. However, the benign histopathological appearance of the lesions, the occurrence of spontaneous remissions, and the ability to respond to immunomodulation suggest at least in some cases a reactive clonal disorder rather than a malignant process.

These difficulties in understanding the pathogenesis of LCH have contributed to a lack of effective staging systems and delayed development of more rational thera-
pies. In the current stratification proposed by the International Histiocyte Society, patients are stratified into different risk categories based on extent of disease, and degree of organ dysfunction. Patients with single-system disease confined to a single site usually require only local therapy or observation. Patients with somewhat more extensive disease (multiple bone lesions or multiple lymph nodes) usually require systemic therapy. The best therapeutic option in these cases has not been defined, and responses have been observed with short courses of steroids with or without the addition of chemotherapeutic agents. The prognosis for this group of patients is usually excellent. Treatment of patients with high-risk disease refractory to conventional multi-agent chemotherapy ranges from the use of immunosuppressive therapies to bone marrow transplantation, but has often been unsatisfactory.

It is well known that isolated bone lesions can be treated with minimal therapy or observation alone. The rate of response to observation alone is not clear, since most patients undergo biopsy for diagnostic procedures, and some type of curettage is performed. The response of these lesions to curettage (with or without intralesional instillation of steroids) is well described. Even lesions with significant bone destruction and soft tissue involvement respond to this minimal intervention. As the authors point out, the reasons for this behavior are not well understood. However, Titgemeyer et al. found no evidence that orbital lesions behave differently from other bone lesions. As this is a small series, major conclusions regarding outcome cannot be made. Further, patients with larger lesions, or with multifocal bone (involving orbit) may not be referred for a diagnostic procedure, or may be referred to other surgical specialists, which would introduce selection or referral bias.

The outcome for patients without multi-system involvement or organ dysfunction is usually very good. For those with single bone lesions, the vast majority are cured with focal therapy alone. The small proportion of patients who have multiple bone lesions, an indication of systemic involvement, or experience recurrence usually require systemic therapy typically with two drugs (prednisone and vinblastine). The outcome for these patients is usually excellent, although there is still a risk of subsequent recurrences.

Although cure is achieved in the majority of patients with single or multiple bone lesions, approximately 20-25% of patients with LCH develop CNS involvement that appears to be based on two determinants. The first is multiple recurrences that may increase the risk of CNS by requiring additional therapies. The second determinant is when lesions are located in the facial bones or anterior or medial cranial fossa with intra cranial tumor extension. A retrospective analysis of 1524 patients in multi-institutional studies found that lesions in those locations carry about a 3-fold risk for the development of diabetes insipidus, which is the hallmark of CNS involvement in LCH.

Although the exact incidence of CNS involvement in patients with LCH is unknown, three major clinical syndromes, in addition to long-term neuropsychological sequelae characterized by varying degrees of global cognitive deficits, memory loss, concentration and attention deficits, have been described. The first is hypothalamic-pituitary involvement typically manifested by diabetes insipidus, with multiple neuroendocrine deficits present. The second syndrome is extraparenchymal-space-occupying lesions, usually derived from the meninges or the choroids plexus, or with enlargement of the pineal gland. The third is neurodegenerative syndrome, characterized by intellectual impairment, behavioral changes, tremor, ataxia, or even progressive CNS degeneration. The incidence of diabetes insipidus is about 15-20%; the incidence of the other conditions is less than 10%.

Of note, CNS manifestations may develop as long as 10-15 years after LCH was diagnosed and treated. The significance is unclear of MR imaging studies in asymptomatic patients who show different degrees of CNS changes.

The pathogenesis of the CNS-LCH is not known, but may be related to the direct neuronal damage by cytokines released by Langerhans cells and the chronic inflammatory reaction that may ensue. This may explain why orbital disease with intra-crani extension is thought to be risk factor.

For this reason, the International Histiocyte Society, in its current protocol (LCH-III), recommends that patients with the so-called CNS-risk lesions be treated with systemic prednisone and vinblastine for six months. The role of chemotherapy is to prevent the development of the devastating CNS complications, not to treat the lesion itself (which may respond to minimal intervention). However, we must remember that this treatment is being administered within a research study and has not been proven to be effective against the CNS complications.

REFERENCES

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DR VICTOR M. ELNER. I have three such patients that we’ve also treated with minimal therapy. These lesions appear currant jelly-like and they have very little fibroblastic response. Did you see any involvement through the dura or invasion of the orbital tissues? In the cases that I’ve seen, it seems like a “pushing” lesion without real invasion of the surrounding structures.

Are you comfortable with doing the minimal treatment in a younger patient who may have multicentric disease? Do you think that these resolved because they don’t have a good stromal response and then the surrounding tissues overtake the lesion once it’s been curetted and treated minimally and that the bed actually fills in with connective tissue?

DR GERALD J. HARRIS. Dr Elner, I agree that this is primarily an expansile lesion, rather than an invasive lesion, once it’s outside of bone. Our experience has been similar regarding the lack of invasion of orbital soft tissue. As to multicentric disease, our recommendations relate only to unifocal orbital disease. If multicentric involvement were determined by initial systemic evaluation or in long-term follow-up, pediatric oncologists would administer systemic therapy.

This leads into Dr Haik’s concern, which appears to stem from the designation of orbital foci as “CNS-Risk” lesions in the LCH-III study’s internal protocol. A statistical analysis of the 1524 patients that comprise the combined cohorts of the DAL-HX 83/90 and LCH I and II studies has not been published (Nicole Grois, MD, Study Coordinator, LCH III; electronic communication, 2003). However, the basis for this thinking might be gleaned from the DAL-HX 83 study, which evaluated 199 patients with LCH (106 with disseminated disease; 93 with localized disease). Nineteen of the 199 patients developed diabetes insipidus (DI), and because 7 of the 19 had skull or orbital lesions with intracranial extension, orbital involvement was interpreted as a risk factor for DI. However, 16 of the 19 patients with DI had disseminated LCH at initial diagnosis. The three patients with localized disease at diagnosis included one with congenital skin disease; one with a solitary pelvic lesion, but with DI and bilateral exophthalmos 15 months earlier; and one with a solitary rib lesion, but with DI and other pituitary signs 4 months earlier. Fewer details about patients with DI are available in the combined DAL-HX 83/90 report. We are not certain that data published thus far has established that unifocal orbital LCH, treated and followed in the manner we’ve recommended, leads to DI with a frequency or morbidity that warrants a 6-month course of prophylactic chemotherapy for all such children. Perhaps the more recent, not-as-yet published data will show otherwise.

REFERENCES
