Langerhans Cell Histiocytosis in the Pediatric Population: Treatment of Isolated Craniofacial Lesions

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Abstract: Langerhans cell histiocytosis (LCH) commonly affects the craniofacial skeleton and prognosis depends on location, extension, and recurrence of the disease. The aim of our study is to better define the treatment of single craniofacial lesions, as to date different treatment modalities have been suggested and recurrence rates for both unifocal and multifocal bony lesion range between 10% and 70%. Between 2000 and 2014, we retrospectively reviewed clinical findings, anatomic location, extent of the disease, therapy, and outcomes in 24 pediatric patients with histologically confirmed LCH. Seventeen patients (67%) had craniofacial involvement, of which 13 had single system involvement and 4 had multisystem involvement. Eight patients (33%) had no craniofacial involvement. Eleven patients affected by unifocal cranial lesions were treated with resection and reconstruction. One patient with a unifocal mastoid lesion was treated with chemotherapy alone (vinblastine and prednisone). Four patients with mandible lesions were treated with curettage alone.

There were no recurrences in patients treated with excision alone. One patient (25%) treated with curettage recurred. Two patients with diffuse disease manifested organ dysfunction and diabetes insipidus. Chemotherapy was tolerated in 12 patients treated.

Our findings suggest that resection of isolated LCH lesions of the cranium is safe and chemotherapy is effective and well tolerated for nonsurgical cases.

Key Words: Langerhans cell histiocytosis, pediatric craniofacial tumors, treatment algorithm of craniofacial masses

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Langerhans cell histiocytosis (LCH) has an incidence ranging between 0.2 and 0.5 cases per 100,000 children per year in the United States.[1] The disease mainly affects children, with 50% of cases occurring in individuals younger than 15 years, and a peak incidence between 1 and 4 years of age.[2] LCH has a variable clinical presentation from a solitary bony lesion to multisystemic disease.[3] The tumor arises from the mononuclear phagocytic system and its pathogenesis remains unknown.[4] Historically, LCH was first known as histiocytosis X,[5] and later classified into 3 distinct syndromes that showed identical histology with S-100 and CD1a positivity, and the pathognomonic presence of Birbeck granules in the cytoplasm of the dendritic cells.[6] The term eosinophilic granuloma was used to describe solitary bony lesions. Hand-Schuller-Christian disease was characterized by multifocal bony lesions and extraskeletal involvement of the reticuloendothelial system (RES) and pituitary gland. Letterer-Siwe disease described disseminated involvement of the RES with a fulminant course. Fifty to 80% of LCH cases manifest in the head and neck, most commonly in the calvarium (45%). These lesions often present as a tender, palpable scalp soft-tissue mass with seborrheic appearance in the skin.[7] Other possible craniofacial signs and symptoms include swelling, vertigo, deafness, middle ear polyps, otorrhea resistant to medical treatment, and proptosis. The characteristic radiologic findings[8] include bony destructive, lytic "punched out" bony lesions or MRI findings in the CNS. Gadolinium enhanced images show dural enhancement adjacent to the bone destruction.[9] Central nervous system involvement in LCH, which occurs in approximately 16% of cases, most commonly is localized to the hypothalamic-pituitary axis and can cause diabetes insipidus and growth hormone deficiency (GHD).[9] Definitive diagnosis of LCH requires tissue biopsy and positivity to S-100, CD1a, and CD207 (langerin).[10]

Prognosis in LCH depends on location and extent of disease. Prognosis is worse in cases of multisystem involvement and recurrence. The Histiocyte Society recently defined a therapy orientated classification of LCH into single-system LCH (SS-LCH) and multisystem LCH (MS-LCH) with or without "Risk organs" (hematopoietic, spleen, liver, lung) and "special sites" (vertebra) involvement.[11,12] Indications for systemic therapy include multifocal, multisystem, and craniofacial single-system LCH with "CNS risk lesions" (ear, eye, oral) [13] or "special sites" (vertebra) (Appendix 1, Supplemental Digital Content, http://links.lww.com/SCS/A412).

Multifocal disease is typically responsive to chemotherapy,[14] but the treatment of single craniofacial lesions is not well delineated, and has varied dramatically from center to center. Historically, some centers have approached these with curettage, and low-dosage radiotherapy if the bony tumor recurrs.[15,16] For both unifocal and multifocal bony lesions, one series suggests recurrence rates after curettage of almost 70%.[15] The aim of our study is to review our institution's experience with pediatric LCH with a particular focus on those children with isolated craniofacial lesions.

MATERIALS AN METHODS

After IRB approval, we performed a database search on our pediatric patients from 2000 to 2014 with *ICD-9* codes 170.0

and 170.1 (malignant neoplasm of skull, face and mandible), 213.0, 213.1 (benign neoplasms of skull, face and mandible) and 277.89 (metabolic disorder NEC). A total of 535 patients were identified with the above *ICD-9* codes. Langerhans cell histiocytosis was clinically suspected in 28 patients and confirmed histologically in 25 patients. We collected data on age at diagnosis, clinical findings, anatomic location, extent of the disease, therapy, and outcomes. Operative time, transfusion rates, and perioperative complications were recorded for those patients who underwent surgery. Response to treatment was defined according the Histiocyte Society guidelines as Non-Active disease or Active disease and defined into 3 categories (better, intermediate, worse).[11,12]

RESULTS

Two pediatric patients were diagnosed with LCH confirmed by histology. The mean age at diagnosis was 5.5 years (range 2 days–18 years). Mean follow-up to date was 4.5 years (range 3 months–19 years). Seventeen patients (68%) had craniofacial involvement, of which 13 had single-system disease and 4 had multisystem disease. Eleven of the 13 with single-system disease and craniofacial involvement had solitary lesions, and 2 had multiple lesions. Eight patients (32%) had noncraniofacial disease, 7 of which were unifocal (Supplemental Table 1, Supplemental Digital Content, http://links.lww.com/SCS/A412).

Two patients presented with multifocal disease, both with multiple cranial lesions. Seven patients with isolated calvarial lesions were treated with resection (limited craniectomy) and autologous reconstruction (cranioplasty). Skull defects were reconstructed with mesh cranioplasty for smaller defects <2 cm in diameter or split calvarial bone grafts larger defects (Fig. 1A-F).

Three patients with unifocal mandibular lesions were treated with curettage or biopsy alone. One patient with a unifocal mastoid lesion was treated with chemotherapy alone (vinblastine and prednisone). Two patients had multifocal disease treated with chemotherapy (Fig. 2).

Noncraniofacial lesions located at long bones were treated with curettage. These patients had no recurrences, no need for chemotherapy and no organ dysfunction. Two patients, one with and one without craniofacial involvement, presented with diffuse disease and manifested organ dysfunction and diabetes insipidus. Patients with multifocal LCH, cranial base location, and multisystem disease were treated with chemotherapy alone (vinblastine and prednisone) or in conjunction with surgery (Supplemental Table 2, Supplemental Digital Content, http://links.lww.com/SCS/A412).

DISCUSSION

Historically, a variety of treatments have been advocated for LCH of the craniofacial skeleton including prednisone, curettage, biopsy, resection, radiotherapy, and chemotherapy.[2,12,14–17] Advances in medical treatment of LCH have been achieved with international clinical trials initiated by the Histiocyte Society.[18] The first trial LCH-I in 1991 showed the superiority of combination chemotherapy over monotherapy. LCH-II trial started in 1996, but did not achieve its goal of discriminating which drugs are more effective in combination therapy. The LCH III trial standardized the use of prednisone, vinblastine in association to methotrexate for more severe cases. Based on the above-mentioned clinical trials, the Histiocyte Society published treatment guidelines based on location and extent of disease (Appendix 2, Supplemental Digital Content, http://links.lww.com/SCS/A412).

Indications for systemic therapy include multifocal, multisystem, and craniofacial single-system LCH with "CNS risk lesions" (ear, orbital, oral cavities)[13] or "special sites"(vertebra).[11,12] New protocols of combined chemotherapy have shown to be both

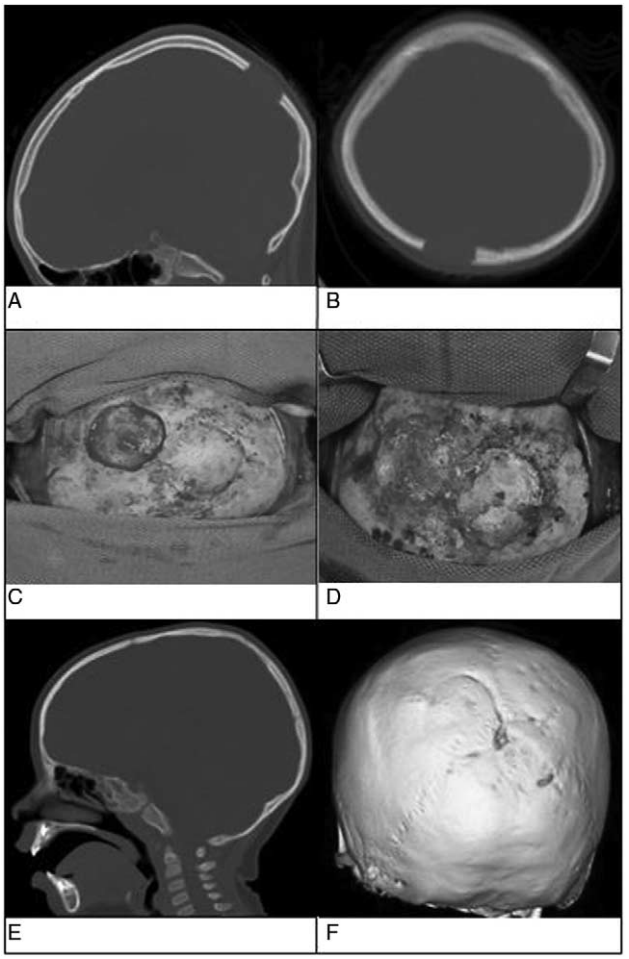

FIGURE 1. A parietal lesion with full-thickness destruction of the bone ([A] sagittal preop view, [B] axial preop view). 5-cm defect created by resection of a single parietal cranial lesions (C) and reconstruction using a split autologous cranioplasty from adjacent bone, secured with absorbable hardware (D). Postoperative computed tomography after reconstruction ([E] sagittal view, [F] 3D reconstruction).

effective and safe.[14] Surgical treatment of single-site LCH (SS-LCH) remains controversial and no guidelines have been suggested to date to determine the optimal treatment.

Previous authors[2,10,15,16,19] have treated single-site unifocal or multifocal disease with curettage or wide biopsy adding

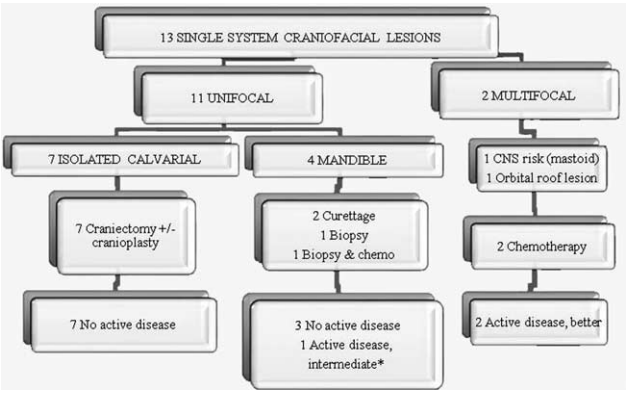

FIGURE 2. Distribution of craniofacial single-system lesions, treatments, and outcomes.

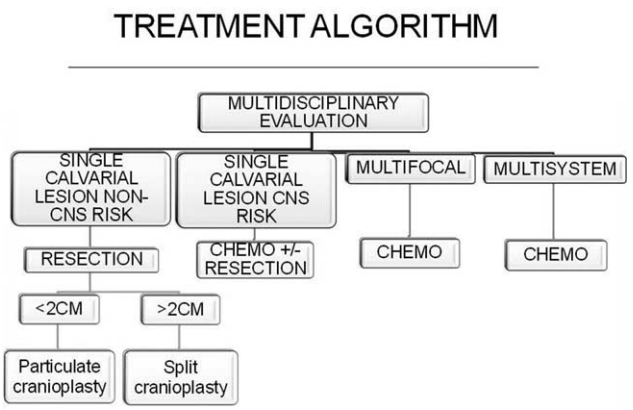

FIGURE 3. Treatment algorithm.

radiotherapy in case of recurrences. Published recurrence rates range from 10% to 76%.[15–17] At our institution, single cranial lesions have been treated with conservative excision and reconstruction at the time of biopsy. As tissue is required for diagnosis, we feel the added morbidity of excision is minimal, and justified if it reduces recurrence or the need for chemotherapy. Our protocol includes resection of single cranial lesions and immediate reconstruction with autologous cranioplasty. For small defects (<2 cm in diameter), we typically perform a mesh cranioplasty which does not require a craniotomy for harvest of donor bone. For larger defects, a split cranioplasty is harvested from the adjacent bone. None of the patients treated with excision had recurrence, required adjuvant therapy, or had morbidity associated with this technique. No patients required transfusion or had surgical complications, and the average length of stay was 2 days, not significantly longer than it would have been for biopsy alone.

Our data show similar demographics and anatomic distribution of LCH as compared to previously published series in the literature.[1] One older series published recurrence rates of 70% for cranial lesions treated with curretage.[15] In our series, the 7 patients with calvarial lesions that were excised and reconstructed, none have so far recurred with a mean follow-up of 25 months.

Based on our findings, we propose a treatment algorithm based on a multidisciplinary evaluation (Fig. 3).

For those children with craniofacial involvement, patients are evaluated by an oncologist, a neurosurgeon, and a plastic surgeon. Evaluation includes a complete history and physical, and a skeletal survey. Single calvarial, "non-CNS risk" lesions are treated with resection and reconstruction with autologous cranioplasty. In our protocol, the choice of the cranioplasty procedure depends on size of the defect: mush cranioplasty for defect < 2 cm and split cranioplasty for lesions >2 cm. Multifocal, multisystem, and unifocal LCH with "CNS risk lesions" (ear, eye, oral) or "special sites" (vertebra) are treated with chemotherapy.

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