

Langerhans cell histiocytosis of skull: a retrospective study of 18 cases

Xiang-Heng Zhang, Ji Zhang, Zheng-He Chen, Ke Sai, Yin-Sheng Chen, Jian Wang, Chao Ke, Chen-Chen Guo, Zhong-Ping Chen, Yong-Gao Mou

Department of Neurosurgery, Sun Yat-sen University Cancer Center, Guangzhou 510060, China

Contributions: (I) Conception and design: XH Zhang, YG Mu; (II) Administrative support: None; (III) Provision of study materials or patients: CC Guo, ZP Chen; (IV) Collection and assembly of data: XH Zhang, J Zhang, YS Chen, J Wang, C Ke; (V) Data analysis and interpretation: ZH Chen, K Sai; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yong-Gao Mou. State Key Laboratory of Oncology in South China, Department of Neurosurgery, Sun Yat-sen University Cancer Center, Guangzhou 510060, China. Email: mouyg@sysucc.org.cn.

Background: The present study presents 18 cases of Chinese patients harboring a Langerhans cell histiocytosis (LCH) of the skull.

Methods: Eighteen consecutive patients were diagnosed as LCH of the skull and confirmed pathologically between March 2002 and February 2014. In the present study, the patients of LCH without skull involvement were excluded. According to disease extent at diagnosis, the 18 LCH patients with skull involvement were divided into three groups: (I) unifocal-monosystem group, including ten cases with solitary skull lesion; (II) multifocal-monosystem group, including two cases with multiple bone lesions and no extra-skeletal involvement; (III) multisystem group, including six cases with LCH lesions involving both skeletal and extra-skeletal system. In unifocal-monosystem group, excision of the skull lesion was performed in eight of ten cases, a low dosage of local radiotherapy and a purposeful observation was accepted by the remaining two cases of this group after biopsy respectively. In multifocal-monosystem group, both of the two cases were received chemotherapy. In multi-system group, all the six cases were managed with systemic chemotherapy, after their diagnoses of LCH were confirmed.

Results: The mean age at the time of diagnosis was 9.4 years. There was a male predominance in this disease male/female ratio was 3.5:1. In our cases, a skull mass with or without tenderness was the most common chief complaint (13 cases, 72.2%), and frontal bone was the most frequent affected locations of skull (6 cases, 33.3%). In unifocal-monosystem group, nine of ten remained free from LCH, the remain one lesion recurred 22 months after his surgical excision. In multifocal-monosystem group, a complete response (CR) was obtained in one of them, and a stable disease (SD) of multiple osseous lesions was obtained in another one. In the multi-system group, a CR in four cases and a partial response (PR) in one case were obtained, and a progressive disease (PD) was observed in the remaining one.

Conclusions: The unifocal-monosystem of LCH of the skull is a clinicopathological entity with a good outcome, and resection, irradiation or purposeful observation are also can be been utilized as the choice of treatment. For the multifocal bone lesions and multisystem lesions of LCH, chemotherapy is an effective treatment as a systemic therapy. There is no enough publication literature to determine guidelines or indications for managing this disease.

Keywords: Langerhans cell histiocytosis (LCH); skull; treatment

Submitted Sep 05, 2016. Accepted for publication Oct 11, 2016.

doi: 10.21037/apm.2016.11.04

View this article at: <http://dx.doi.org/10.21037/apm.2016.11.04>

Introduction

Langerhans cell histiocytosis (LCH) is a rare histiocytic disorder which affects all age groups with mostly unexplained etiology and unusual histology. Practically every organ can be involved by this disease, and the skull is a favored location. The clinical spectrum and prognosis of LCH are extremely diverse. Up to now, there is still no consensus exists for the optimal therapy for LCH, since this disorder was first described by Dr. Smith in 1865 (1). Meanwhile, there is also no generally accepted prognostic factor. The aims of this study were to evaluate our experience of LCH in Chinese patients with skull involvement, and also to investigate the related factors influencing the prognosis.

Methods

Patient selection and characteristics

We conducted a retrospective chart review of 18 consecutive patients treated at Sun Yat-sen University Cancer Center for LCH with the skull involvement between March 2002 and February 2014. The pathological diagnosis of LCH in each case was confirmed at the pathologists of the Sun Yat-sen University Cancer Center according to the World Health Organization classification of tumors (2). Clinical parameters of each case were checked, including patient demographics, location and amount of lesions, pathological profiles, and therapeutic modalities. Age, gender, extent of disease, type of therapy, reactivation, and long-term outcome were analyzed.

A complete work-up was performed for each case to determine the affected extent by LCH disease, including skull X-ray, head computed tomography (CT), chest X-ray, ultrasound of abdomen and pelvis regions. A magnetic resonance imaging (MRI) of brain was performed in 13 patients underwent to delineate the size and borders of the lesion in detail. Additionally, after the histopathologic diagnosis of LCH was confirmed, a skeletal survey had been performed using radionuclide bone scan.

In the present study, the patients of LCH without skull involvement were excluded. According to disease extent at diagnosis, the 18 LCH patients with skull involvement were divided into three groups: (I) unifocal-monosystem group, including ten cases with solitary skull lesion; (II) multifocal-monosystem group, including two cases with multiple bone lesions and no extra-skeletal involvement; (III) multisystem group, including six cases with LCH lesions involving both

skeletal and extra-skeletal system. This study was approved by the ethics committee of Sun Yat-sen University Cancer Center.

Treatment

In unifocal-monosystem group, excision of the skull lesion was performed in eight of ten cases, a low dosage of local radiotherapy (20 Gy) and a purposeful observation was accepted by the remaining two cases of this group after biopsy respectively. In multifocal-monosystem group, both of the two cases were received chemotherapy to control the multiple bone lesions, after their pathological diagnoses of LCH were confirmed by biopsy. In multi-system group, all the six cases were managed with systemic chemotherapy, after their diagnoses of LCH were confirmed by biopsy.

Results

A total of 18 patients, including 14 males and 4 females, with skull involvement of LCH were enrolled in the study. The mean age at the time of diagnosis was 9.4 years, ranged from 0.9 to 64 years. Follow-up duration ranged from 14 to 139 months, with a mean of 43.6 months. There was a male predominance in this disease, since the male/female ratio was 3.5:1. The patient's age, sex, presentation, lesions location, treatment modalities and follow-up were summarized in *Table 1*.

In our series, a skull mass with or without tenderness was the most common chief complaint (13 cases, 72.2%), followed by an exophthalmos (3 cases, 16.7%), diplopia (1 case, 5.6%), and epistaxis (1 case, 5.6%). Frontal bone was the most frequent affected locations of skull (6 cases, 33.3%), followed by occipital bone (5 cases, 27.8%), orbit bone (5 cases, 27.8%), temporal bone (4 cases, 22.2%), and parietal bone (3 cases, 16.7%). The involvement of basilar skull bone was observed in three cases, and the affected locations included sphenoid, clival and petrosal bone. The involvements of rib bone, scapula bone, femur bone, and sacral vertebrae were observed in our cases, but much less frequently than the skull bone. In the cases classified as multisystem LCH, the involvement of the tissues in zygomatic fossae, pituitary mediastinum and nasopharynx were recorded.

In our series, the clinical effect was evaluated with Macdonald standard. The classification of 18 patients and the efficacy of various treatments were summarized in *Table 2*. In unifocal-monosystem group, eight of ten were

Table 1 Summary of 18 patients with LCH in the skull

Case	Sex	Age (years)	Presentation	Location of skeletal system	Other findings of extraskeletal system	Treatment	Follow-up (months)	Effication
1	F	64.0	Painful mass	Parietal	–	Res	49	CR
2	M	6.0	Scalp swelling	Temporal	–	Res	52	CR
3	F	3.0	Facial mass	Zygoma	–	Res	36	CR
4	M	4.0	Exophthalmos	Orbit	–	Res	24	CR
5	M	15.0	Scalp swelling	Occipital	–	Bio + RT	24	CR
6	M	2.0	Exophthalmos	Orbit	–	Res	28	Rec
7	M	4.0	Scalp swelling	Parietal, temporal, frontal, petrosal	–	Bio + Chem	Bio + Chem	CR
8	M	5.0	Exophthalmos	Orbit	–	Res	18	CR
9	M	2.0	Facial mass	Occipital, temporal	Zygomatic fossa	Bio + Chem	78	CR
10	M	2.0	Epistaxis	Sphenoid, clival	Nasopharynx	Bio + Chem	72	CR
11	M	11.0	Scalp swelling	Occipital, scapula	Mediastinum	Bio + Chem	36	PD
12	M	13.0	Diplopia	Sphenoid	Nasopharynx	Bio + Chem	36	PR
13	M	0.9	Scalp swelling	Frontal, orbit, rib	–	Bio + Chem	47	SD
14	M	6.0	Scalp swelling	Frontal	–	Bio + Ob	51	CR
15	M	4.0	Scalp swelling	Frontal, temporal, occipital, parietal orbit, rib and femur	Zygomatic fossae, pituitary	Bio + Chem	30	PD
16	F	17.0	Scalp swelling	Frontal	–	Res	36	CR
17	M	2.8	Scalp swelling	Occipital	Neck	Bio + Chem	14	CR
18	F	7.0	Painful mass	Frontal	–	Res	15	CR

Res, resection; Bio, biopsy; Chem, chemotherapy; RT, radiotherapy; Ob, observation; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; Rec, recurrence; LCH, Langerhans cell histiocytosis.

Table 2 Classification of 18 patients and the efficacy of various treatments

Group	Case	CR	PR	SD	PD	Rec
Unifocal-monosystem	10	9	–	–	–	1
Multifocal-monosystem	2	1	–	1	–	–
Multisystem	6	4	–	–	2	–

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; Rec, recurrence.

received surgical excision without other postoperative treatment, and seven of eight lesions remained free from LCH during the follow-up duration (ranged from 15 to 52 months, with a mean of 32.9 months). The remaining

one lesion recurred 22 months after his surgical excision, and radiotherapy was performed to control the recurrent lesion. A complete response (CR) of lesion was also observed in the other two patients of this group, although they accept very different therapeutic regimen after biopsy, ranged from a junior dosage of radiotherapy (20 Gy) to a conservative observation. In multifocal-monosystem group, both of the two cases were received chemotherapy to control the multiple osseous lesions. A CR was obtained in one of them, after a chemotherapy protocol consisted of 12 cycles of vincalokoblastine + 6-mercaptopurine + prednisone, and 6 cycles of vincristine + etoposide + prednisone, with a 139 months of follow-up. A stable disease (SD) of multiple osseous lesions was obtained in another case, after a chemotherapy protocol consisted

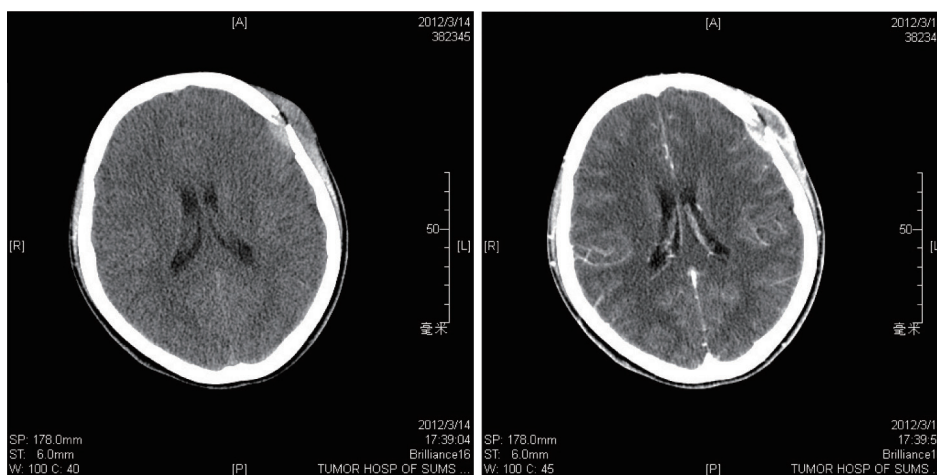


Figure 1 CT scan of one patient demonstrating an osteolytic lesion in the left frontal cranium. CT, computed tomography.

of 15 cycles of vincalukoblastine + 6-mercaptopurine + prednisone, and 9 cycles of vincalukoblastine + 6-mercaptopurine + prednisone. In the six cases of multi-system group, the following chemotherapy regimens were applied, prednisone + etoposide + vincalukoblastine, vincalukoblastine + 6-mercaptopurine + prednisone, vincalukoblastine + prednisone, and methotrexate + imuran + ornithine aspartate. After multi-cycles of chemotherapy, a CR in four cases and a partial response (PR) in one case were obtained, and a progressive disease (PD) was observed in the remaining one.

Discussion

Reclassification

Until the current reclassification of the disease by the Writing Group of the Histiocyte Society (3), LCH was formerly referred to as histiocytosis X (4), with three clinical subtypes, namely eosinophilic granuloma, Hand-Schüller-Christian's disease, and Letterer-Siwe's disease. Practically every organ can be involved by LCH, and significant overlapping has been observed studying the presentations of the three clinical subtypes mentioned above. In this study, the current reclassification was applied. In our series, the 18 LCH patients with skull involvements were firstly classified as 12 cases of monosystem form and 6 cases of multi-system form, and the 12 cases of mono-system form further subdivided into 10 cases of unifocal and 2 cases of multifocal types. In our opinion, the new classification is more convenient to evaluate the effectiveness of treatment and prognosis of LCH compared with the former one.

Clinical presentations

LCH arises from an abnormal proliferation of histiocytes, and most commonly presents as a solitary lesion in the skull, whereas femur, mandible, ribs, pelvis, and spine are other common locations (5-7). Our series consisted of 18 cases (14 males, 4 females; mean age, 9.4 years; range, 0.9 to 64 years), and there was an obvious male predominance (male/female ratio, 3.5:1). A skull mass with or without tenderness was the most common chief complaint (13 cases, 72.2%), and the frontal bone was the most frequent affected locations of skull (6 cases, 33.3%) in our series. In the skull, the typical appearance of a LCH lesion is a well-defined lytic lesion, with nonsclerotic margins, involving both inner and outer table, resulting in a double-contour appearance, sometimes associated with an adjacent soft tissue mass (*Figure 1*). A "button sequestrum" was once thought to be characteristic of skeletal LCH (*Figure 2*), but it may be seen in metastatic disease, radiation necrosis, dermoid and epidermoid cysts, fibrous dysplasia and meningioma (8,9).

Treatment

All 18 patients were treated for their disease, and the choice of treatment was based on the disease extent. For the ten cases with unifocal lesion of skull, local resection, irradiation and observation had been utilized respectively. Systemic therapy had been used in the other eight cases with multifocal bone lesions or multisystem lesions. For the unifocal bone lesions, surgery resection is a typical treatment. Involvement of the skull base has been rarely reported. In our series, surgery resection was performed

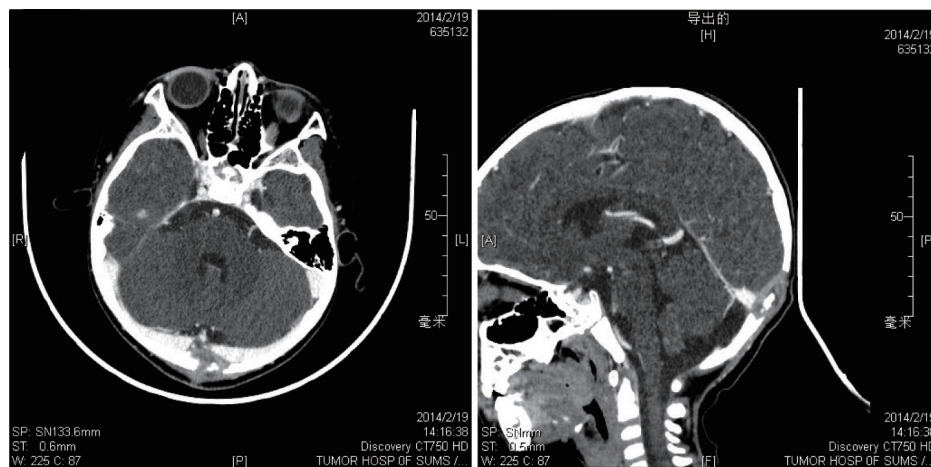


Figure 2 CT scan of one boy demonstrating a “button sequestrum” lesion in the frontal cranium. CT, computed tomography.

in eight unifocal skull lesions, including four involvements in calvarium bone and four involvements in the skull base. Complete remission was obtained in seven of eight, but one involvement in orbit recurred 24 months after surgery resection. It is clear that surgery resection is very effective for single skull bone lesions, but as a complex surgical area, the involvement affected in skull base was more challenging than that in calvarium bone. Though some authors recommend chemotherapy in case of involvement of the orbit and the temporal bone instead of surgical resection, according to our experience, based on the experienced surgeons and the choosing of optimal approach, surgery intervention is the mainstay treatment to unifocal skull bone lesion, and the approach should allow wide enough exposure of the tumor for achieving complete resection and manage the eventual complications (10). A low dosage of radiotherapy is also an effective treatment for the LCH lesions. In our series, a low dosage of radiotherapy allowed for a complete remission of an occipital lesion and a second time remission of recurrent orbital LCH lesions.

For the multifocal bone lesions or multisystem lesions of LCH, chemotherapy is an effective treatment. In our series, complete remission was obtained in five of eight patients who received multiple cycles of chemotherapy. Vinblastine and prednisone were reported as the standard treatment for children (11). But Cantu *et al.* reported that cytosine arabinoside (ARA-C) was an effective and minimally toxic treatment for LCH bone lesions in adults, and in contrast, vinblastine/prednisone results in poor overall responses and excessive toxicity (12). There were still very few publication

literatures providing enough data on long term follow-up, toxicity data, or comparison of responses among various chemotherapy.

Spontaneous remission of LCH lesions has been reported previously (13,14). In our series, such spontaneous remission was also observed in a unifocal skull lesion with a follow-up of 51 months. De Angulo *et al.* reported eight cases of solitary calvarial LCH who were managed with observation, and only one required surgical intervention. They suggested a short period of observation may be useful in the initial management of solitary calvarial LCH lesion to avoid a surgical procedure (14). There is no enough publication literature on multicenter prospective trial to confirm these findings and determine guidelines or indications for surgery to manage these cases.

Conclusions

The unifocal-monosystem of LCH of the skull is a clinicopathological entity with a good outcome, and resection, irradiation or purposeful observation are also can be been utilized as the choice of treatment. For the multifocal bone lesions and multisystem lesions of LCH, chemotherapy is an effective treatment as a systemic therapy. There is no enough publication literature to determine guidelines or indications for managing this disease.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the ethics committee of Sun Yat-sen University Cancer Center and written informed consent was obtained from all patients.

References

- Smith T. Skull-cap showing congenital deficiencies of bone. *Trans Path Soc Lond* 1865;16:224-5.
- Jaffe R, Weiss LM, Facchetti F. Tumors derived from Langerhans cells. In: Swerdlow SH, Campo E, Harris NL, et al. editors. *WHO classification of tumours of haematopoietic and lymphoid tissues*. 4th edition. Lyon: IARC Press, 2008:358-60.
- Histiocytosis syndromes in children. Writing group of the Histiocyte Society. *Lancet* 1987;1:208-9.
- Lichtenstein L. Histiocytosis X; integration of eosinophilic granuloma of bone, Letterer-Siwe disease, and Schüller-Christian disease as related manifestations of a single nosologic entity. *AMA Arch Pathol* 1953;56:84-102.
- Hoover KB, Rosenthal DI, Mankin H. Langerhans cell histiocytosis. *Skeletal Radiol* 2007;36:95-104.
- Kamimura M, Kinoshita T, Itoh H, et al. Eosinophilic granuloma of the spine: early spontaneous disappearance of tumor detected on magnetic resonance imaging. Case report. *J Neurosurg* 2000;93:312-6.
- Park SH, Park J, Hwang JH, et al. Eosinophilic granuloma of the skull: a retrospective analysis. *Pediatr Neurosurg* 2007;43:97-101.
- Stull MA, Kransdorf MJ, Devaney KO. Langerhans cell histiocytosis of bone. *Radiographics* 1992;12:801-23.
- Rawlings CE 3rd, Wilkins RH. Solitary eosinophilic granuloma of the skull. *Neurosurgery* 1984;15:155-61.
- López F, Llorente JL, Suárez C. Surgical treatment of eosinophilic granuloma of the infratemporal fossa: a successful treatment option. *Acta Otolaryngol* 2012;132:558-62.
- Gadner H, Grois N, Pötschger U, et al. Improved outcome in multisystem Langerhans cell histiocytosis is associated with therapy intensification. *Blood* 2008;111:2556-62.
- Cantu MA, Lupo PJ, Bilgi M, et al. Optimal therapy for adults with Langerhans cell histiocytosis bone lesions. *PLoS One* 2012;7:e43257.
- Oliveira M, Steinbok P, Wu J, et al. Spontaneous resolution of calvarial eosinophilic granuloma in children. *Pediatr Neurosurg* 2003;38:247-52.
- De Angulo G, Nair S, Lee V, et al. Nonoperative management of solitary eosinophilic granulomas of the calvaria. *J Neurosurg Pediatr* 2013;12:1-5.

Cite this article as: Zhang XH, Zhang J, Chen ZH, Sai K, Chen YS, Wang J, Ke C, Guo CC, Chen ZP, Mou YG. Langerhans cell histiocytosis of skull: a retrospective study of 18 cases. *Ann Palliat Med* 2017;6(2):159-164. doi: 10.21037/apm.2016.11.04