Presentation, treatment, and outcomes of unifocal and multifocal osseous vertebral Langerhans cell histiocytosis lesions in patients under 18 years old

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Background

- Langerhans Cell Histiocytosis (LCH) is a rare disease most with initial presentation ranging from isolated skeletal lesions to multisystemic disseminated disease. There are three levels of classification per the Histiocyte society; single-system single-site (SS-s), single-system multiple-site (SS-m), and multisystem (MS) [2]. The prognosis of LCH varies significantly with some cases undergoing complete remission while others present with consistent recurrence, rapid progression, post-disease sequelae or death [3-5]. SS-s predominantly carries a better prognosis with more conservative treatment while MS requires a more aggressive treatment that is more likely to have an inferior outcome.

- Pain with accompanying skeletal lesions is a typical initial presentation [6]. While vertebral lesions are not uncommon sites of unifocal or multifocal lytic lesions due to LCH, few studies have characterized and reviewed outcomes at these sites in a pediatric population. Common presentations of vertebral LCH include back or neck pain with varying levels of more focal neurological symptoms, along with vertebral body compression and soft tissue extension on imaging [7-9]. SS-s and SS-m treatment also has wide variety in treatments including biopsy with observation up to chemotherapy with surgical treatment failing to show superior outcomes and selectively utilized [8,10,11]. No universal standardized protocol exists and treatment protocols are unique to the physician or health system.

- This study aims to (1) clinically and radiographically characterize a series of unifocal (SS-s) and multifocal (SS-m) LCH lesions in the vertebra and (2) determine the success and recurrence rates with different treatment modalities in a pediatric population at a tertiary children's hospital.

Methods

- **Inclusion criteria:** Patients younger than 18 years old with a diagnosis of LCH at a large, Level 1 children's hospital before June 1, 2021, and a unifocal or multifocal LCH skeletal lesion. From these, patients with vertebral lesions were selected.
- **Exclusion criteria:** included bone marrow involvement, multisystemic disease including patients with visceral or organ involvement, other malignant diagnoses, insufficient patient data, or patients with under six months of follow-up. The most common reasons for exclusion were multisystemic cases
- **Final Inclusion**: Thirty-nine patients met the final inclusion criteria from 686 patients diagnosed with LCH..
- **Variables**: Clinical presentations, lesion sites, additional skeletal lesions, biopsy site, radiographic findings, treatments, complications, recurrence rates, and length of follow-up, if present, were reviewed and recorded. We also determined whether the associated skeletal lesion was diagnosed at the time of initial consultation and which intervention was used in clinical care.
- **Data analysis:** Descriptive statistics were estimated and reported as means or medians with range values or counts with percentages.

Results

- **Demographics**: Thirty-nine patients were found to have unifocal (SS-s) or multifocal (SS-m) LCH lesions involving the vertebrae. There were 17 males and 22 females identified. The median age at diagnosis was 6.9 years (0.7-16.7) (**Table 1**).

- **Presentation and Characterization**: The most common clinical presentation was neck or back pain (51%) and difficulty or inability to ambulate (15%). Specific neurologic symptoms such as parasthesias, numbness and weakness were reported in 4 cases (10%). 70 vertebrae were involved in total, including 23 cervical (59%), 24 thoracic (62%), 19 lumbar (49%), and 4 sacral (10%) lesions. There were 14 unifocal (36%) and 25 multifocal cases (64%). The skull/maxillofacial bones (23%), femur (21%), ribs/sternum (18%) and non-sacral pelvis (18%) were the most common affected locations. Other bony lesions include two at the clavicle, one at the tibia, and one at the mandible. 44% of patients had vertebral lesions only. The most common radiographic finding was vertebra plana (44%) and soft tissue extension of lesions (41%) (**Fig. 2, Fig 3**.). Outside of vertebra plana, 8 patients were found to have compression fractures (21%). The most common imaging modalities utilized in each case were x-rays (85%), computed tomography (79%), and MRI (85%).

Table 1. Demographics and statistics

Variable	Counts /percentages
Sex	
Male	17 (44%)
Female	22 (56%)
Age at diagnosis (years)*	6.9 (0.14-14.8)
Additional skeletal lesions	
Skull/maxillofacial	9 (23%)
Femur	8 (21%)
Non-sacral pelvis	7 (18%)
Ribs/sternum	7 (18%)
Clavicle	2 (5%)
Tibia	1 (2.5%)
Mandible	1 (2.5%)
Classification	
unifocal	14 (36%)
multifocal	25 (64%)
Radiographs	
Vertebra plana	17 (44%)
Soft tissue extension	16 (41%)
Compression fracture	8 (21%)
Immunopathology	
CD1a+	22 (56%)
CD68+	8 (21%)
CD207+	23 (59%)
S100+	15 (39%)

*given as median and range

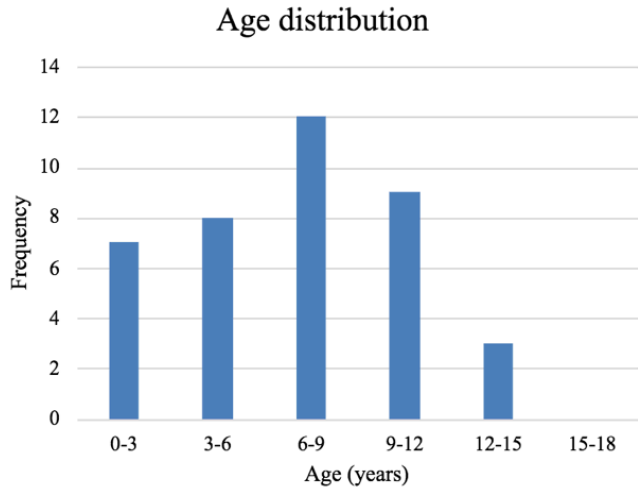

Figure 1. Age distribution in vertebral LCH lesions

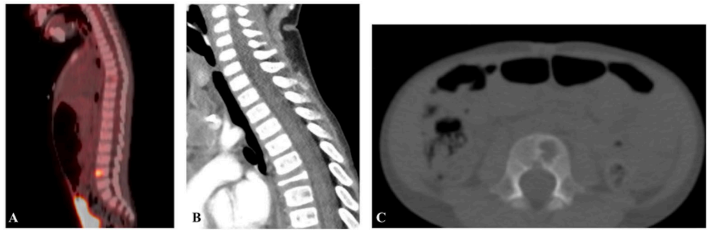

Figure 2. 1 y/o male presenting with no back, neck pain, or neurologic symptoms. (A) Sagittal view positron emission topography (PET) scan demonstrating notable radiotracer uptake at T7 and L4 (B), sagittal computed tomography (CT) scan demonstrating continued vertebral plana at T7, and (C) axial CT depicting bony destruction of vertebral body at T7.

Results (continued)

- **Treatments and Outcomes:** Most patients were treated with chemotherapy (82%). Other treatments included curettage or excision (2 cases), steroid injection (2 cases), radiotherapy (2 cases) and surgical fixation only with observation (1 case) (**Table 2**). Vinblastine with prednisone was the most common chemotherapy regimen (72% of chemotherapy cohort) followed by cytarabine (41%). The recurrence rate in the entire cohort was 10%, mostly multifocal except for one recurrence in a unifocal case. All multifocal patients were treated with chemotherapy, except one patient who underwent an excisional biopsy only. The patient went on to have spontaneous resolution of lesions. 88% of multifocal patients underwent chemotherapy compared to 60% of unifocal patients. There were two cases with operative treatments involved due to spine instability; one patient underwent a C7-T1 fusion with only follow-up (**Figure 4**), and another had a T5-T7 fusion along with chemotherapy. There were no complications from surgical treatment. One patient was still undergoing chemotherapy treatment at 1.6 years of follow-up but was lost to additional follow-up. All other patients had resolution of lesions. One patient (treated with radiotherapy) had mild disc space narrowing with radiotherapy and recurrent back pain on 6.7 years follow up. All patients had resolution of symptoms and lesions. Median length of follow-up was 5.2 years (0.6-16.8). There was no mortality in this cohort.

Table 2. Treatment and outcomes

Variable	Counts/percentages
Treatment	
Chemotherapy	32 (82%)
Curettage or excision	2 (5%)
Steroid injection only	2 (5%)
Radiotherapy only	2 (5%)
Surgical fixation only	1 (2.5%)
Chemotherapy involved in treatment	
Vinblastine + prednisone	23 (59%)
Cytarabine	13 (33%)
Clofarabine	4 (10%)
Methotrexate	2 (5%)
Cladribine	1 (2.5%)
Recurrence rate (any site)	
All	(4 (10%)
Total follow-up (years)*	3.6 (0.54-16.1)

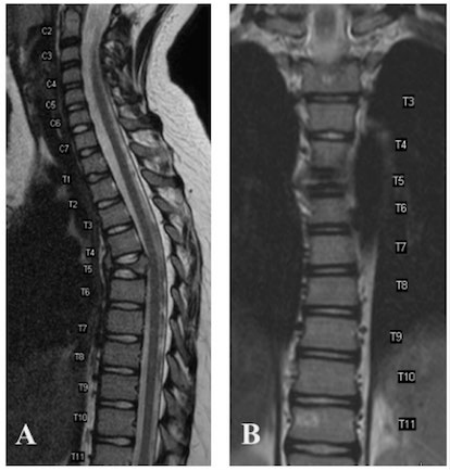

Figure 3. 9 y/o female presenting with back pain and multiple vertebral lesions. (A) Sagittal and (B) coronal MRI demonstrating T5 vertebral plana with soft tissue extension and spinal cord compression.

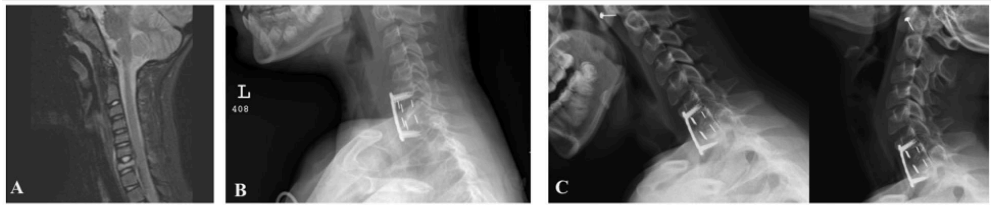

Figure 4. 7 y/o female presenting with neck pain extending into the right hand, right sided weakness and decreased sensation, and right sided torticollis. (A) Sagittal MRI demonstrating vertebra plana at C7 with soft tissue invasion and cord compression and (B) sagittal radiograph after C7-T1 fusion. (C) Sagittal radiograph of flexion (left) and extension (right) 7.5 years after fusion.

Discussion

Presentation

- From the 686 patients originally queried for a diagnosis of LCH, there were 39 patients with single system vertebral lesions (5.6%), including 14 unifocal (2%). All except three patients were under 12 years old.
- Neck or back pain was the most common clinical presentation. Specific neurologic symptoms besides pain demonstrating spinal cord involvement such as weakness, parasthesias and numbness were relatively few (10%). These neurologic complications have been reported with widely varying numbers across the literature. Greenlee et al. [15] reported 2 out of 11 patients with complications, while Lee et al. [16] reported only one in 22. Other reports range from 37% in cervical lesions only [7] to 18% and 49% in larger series [8,9]. Some reports in our cohort are limited due to age as not all patients are unable to indicate the extent of their symptoms.

Imaging:

- The most common imaging characteristic of vertebral LCH besides a lytic lesion is a compression fracture with complete (vertebra plana) or incomplete vertebral body collapse [7-9,16-21]. Though initial lesions are typically seen on X-ray as lytic or sclerotic, further imaging via computed tomography (CT) or magnetic resonance imaging (MRI) may show prevertebral, paravertebral, or epidural soft tissue extension.
- A larger series by Xu et al. [8] showed 57% soft tissue extension overall, with 52% in their pediatric subset, via MRI. Similarly Huang et al [9] all found 67% overall, with 70% in their pediatric subset, via MRI. MRI's should always be acquired to ensure the extent of disease is recognized.

Treatment and outcomes*:*

- Chemotherapy, radiotherapy, excision or curettage, surgery, and steroid injections are all options for management. There is not strong evidence prioritizing one treatment over the other in less aggressive cases. Some studies show observation only in unifocal lesions often leads to regression [22-25]. Chemotherapy in multifocal presentations involving the vertebrae also leads to good outcomes with few recurrences [8,9]. Two patients in our study underwent surgical fixation.. Xu et al. [8] reviewed outcomes in their cohort, with 35.2% of the patients undergoing surgical treatment for vertebral LCH before 2009, and 10.7% undergoing surgical treatment with a conservative treatment protocol. Surgical treatment included excision, curettage, or other invasive procedures. There were no significant differences in outcomes.

Limitations

- Retrospective nature which relies on chart review of available imaging and documentation, and timeline for resolution of symptoms was not consistently documented. This case series was limited by the infrequency of single system osseous vertebral lesions and would benefit from a multi-institutional randomized trial comparing treatment options and outcomes of vertebral LCH lesions. There are only 39 patients that fit the criteria for our series. Three patients had under one year of follow up.

Conclusion

- Vertebral lesions are common in the setting of LCH. Chemotherapy is often utilized as treatment of these lesions regardless of unifocal or multifocal osseous presentation, with good outcomes and low recurrence rates. However other treatments such as observation only and steroid injections may be a better option with smaller and less widespread lesions due to side effects and length of treatment with chemotherapy. Standardized treatment protocols are not in place and will vary between institutions. Determination of more invasive treatments including surgical excision or fixation will need to be considered on a case by case basis, and should be held as a last resort.

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