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Presentations, treatment and outcomes of unifocal and multifocal osseous appendicular Langerhans cell histiocytosis lesions in a pediatric population

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Langerhans cell histiocytosis (LCH) is a rare disease most commonly presenting in the pediatric population and characterized by neoplastic clonal proliferation of Langerhans dendritic cells with accumulation in various sites, including skeletal and visceral lesions.[1] 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] 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.

While the extremities are not uncommon sites of unifocal or multifocal lytic lesions due to LCH, few studies have characterized and reviewed the eventual outcomes after treatment at these sites in a pediatric population. Recently Mavrogensis *et al*[3] reviewed 66 SS-s treated exclusively with steroid injections and biopsy alone with excellent outcomes. Information regarding treatment and long-term sequelae at these sites is lacking.

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

We obtained institutional review board approval for a retrospective analysis of patients younger than 18 years old with a diagnosis of LCH at Texas Children's Hospital before June 1, 2021. Inclusion criteria included patients with a unifocal or multifocal skeletal lesion. From these, patients with appendicular 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 6 months of follow-up. Six hundred and eighty-six patients diagnosed with LCH from January 1, 1999 to June 1, 2021 were reviewed. The most common reasons for exclusion were multisystemic cases. Patients underwent a skeletal survey and a full body positron emission tomography scan. Diagnosis was usually confirmed by biopsy and histology via a positive CD1a, CD207 (Langerin), or S100 immunoassay in all except several cases prior to electronic medical record usage where there was no test documented. Clinical presentations, lesion sites, additional skeletal lesions, biopsy site, focal classification, radiographic findings, lesion size, 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.

Totally, 30 patients were found to have unifocal (SS-s) or multifocal (SS-m) LCH lesions involving the appendicular skeleton. There were 14 boys and 16 girls identified. The median age at diagnosis was 6.5 years (range: 0.7–16.7 years) (table 1).

The most common clinical presentation was pain, limping, or inability to weight bear (77%). There were 18 unifocal (60%) and 12 multifocal cases (40%). The femur was the most common affected location (53%), followed by the humerus (27%), tibia (23%), and fibula (3%). Most lesions occurred in the diaphysis (59%). Two cases involved both the tibia and femur (7%). Other bony lesions primarily included the skull or maxillofacial bones (17%), pelvis (13%), vertebrae (13%), ribs/sternum (7%), and clavicle (3%). The most common radiographic finding was a lytic bone lesion (73%),

Table 1 Demographics and characteristics

Variable	Counts (percentages)
Sex	
Male	14 (47%)
Female	16 (53%)
Age at diagnosis (years)*	6.5 (0.7–16.7)
Location	
Femur only	14 (47%)
Humerus only	8 (27%)
Tibia only	5 (17%)
Tibia+femur	2 (7%)
Fibula	1 (3%)
Additional skeletal lesions	
Skull/maxillofacial	5 (17%)
Pelvis	4 (13%)
Vertebrae	4 (13%)
Ribs/sternum	2 (7%)
Clavicle	1 (3%)
Classification	
Unifocal	18 (60%)
Multifocal	12 (40%)
Radiographs	
Fractures	4 (13%)
Lytic lesions	22 (73%)
Immunopathology	
CD1a+	23 (77%)
CD68+	7 (23%)
CD207+	19 (63%)
S100+	12 (40%)

*Data are presented with median (range).

with four cases of pathological fractures noted (13%). Size measurements of lesions were not consistently assessed radiographically.

Eight patients (27%) had their lesions resected surgically, five with curettage only (17%) and with curettage only treatment occurring in unifocal (SS-s) cases. Six patients were only treated with a steroid injection (20%). Other cases either had chemotherapy treatment (43%), or no treatment (13%). One patient was treated via low dose targeted radiotherapy and casting. Vinblastine with prednisone was the most common chemotherapy regimen (80% of chemotherapy cohort). The recurrence rate in the entire cohort was 27%. All multifocal patients were treated with chemotherapy, except one patient. The patient went on to have spontaneous resolution of lesions. Only three unifocal patients were treated with chemotherapy as part of the index regimen (17%). The LCH recurrence rate in patients treated with curettage only or steroid injections (figure 1) only was 37%, all at different sites than the original lesion or in a different system. There were no complications from lesion excisions (figure 2). All patients had resolution of symptoms and lesion via follow-up visit symptomatology and imaging

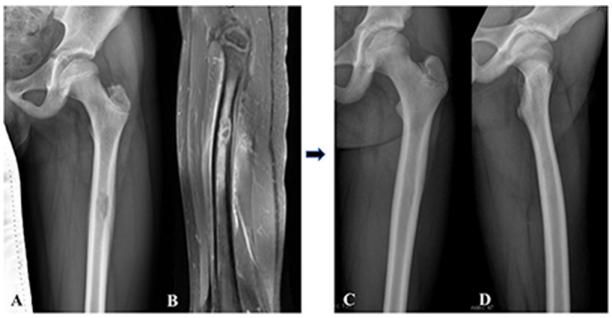

Figure 1 Presentation with left-sided leg pain treated with a steroid injection. (A) AP radiograph and (B) coronal MRI demonstrating a femoral diaphysial lucency. (C) AP and (D) lateral radiographs 1.9 years after initial diagnosis. AP, anteriorposterior; MRI, magnetic resonance imaging.

per chart review. The median length of follow-up was 5.2 years (range:0.6–16.8 years) (table 2).

From the 686 patients originally queried for a diagnosis of LCH, there were 30 patients with single-system appendicular lesions (4.4%), including 18 unifocal (SS-s) LCH lesions (2.6%). Most lesions (53%) occurred in the femur, similar to other large LCH series.[4] The diaphysis as the most common site of occurrence in long bones is also described in some studies. Fractures and additional pathologies such as soft tissue edema and infiltration, endosteal scalloping, and periosteal reactions at LCH sites are common.

Treatment of LCH may involve chemotherapy, radiotherapy, excision (wide or curettage), oral steroids, intralesional steroid injection, and monitoring. Multisystemic cases are almost always treated via chemotherapy.[4 5] Multifocal cases are often treated via chemotherapy secondary to presentation. Unifocal cases have wider variation in treatment. Steroid injections have been shown to be an effective treatment in solitary lesions.[3 5 6] Mavrogensis *et al*[3] examined 66 isolated pediatric appendicular lesions treated with biopsy and steroid injections only. Of the lesions 95% had reconstitution of bone.

A study by Rivera *et al*[7] reviewed 39 single-system osseous lesions where lesions treated with biopsy alone achieved symptom resolution faster than curettage or

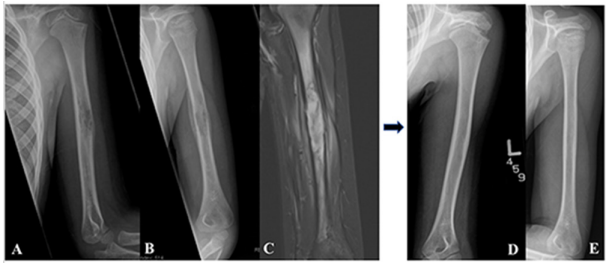

Figure 2 Presentation with left-sided arm pain treated via curettage only. (A) AP radiograph, (B) lateral radiograph, and (C) coronal MRI demonstrating a humeral diaphysial lucency. (C) AP and (D) lateral radiographs 1.9 years after initial diagnosis. AP, anteriorposterior; MRI, magnetic resonance imaging

Table 2 Treatment and outcomes

Variable	Counts (percentage)
Treatment	
Curettage only	5 (17%)
Curettage total	8 (27%)
Steroid injection only	6 (20%)
Chemotherapy only	13 (43%)
Biopsy only	4 (13%)
Radiotherapy	1 (3%)
Chemotherapy involved in treatment	
Vinblastine+prednisone	11 (37%)
Cytarabine	3 (10%)
6-mercaptopurine	3 (10%)
Methotrexate	2 (7%)
Clofarabine	1 (3%)
Cladribine	1 (3%)
Recurrence rate (any site)	
All	8 (27%)
Curettage or steroid only	4 (37%)
Total follow-up (years)*	5.2 (0.6–16.8)

*Data are presented with median (range).

chemotherapy. They determined that more aggressive surgical management is not needed for unifocal osseous lesions. Ghanem *et al*[8] reviewed 26 unifocal osseous lesions receiving only a diagnostic biopsy or with additional curettage and found good outcomes in all but one patient. Our study did find a 37% recurrence rate in patients treated with curettage or steroid injections alone, but all recurrences occurred at sites separate from the original lesion indicating that steroid and curettage at the affected sites were efficacious. Our recurrence rate with steroid injections seemed high but many patients had very long follow-up (5 years+) and we counted recurrence as any reappearance of LCH in any system. We did not find any defining features in patients undergoing these compared with only a biopsy. Chang *et al*[9] reviewed 40 steroid injections in 36 patients and found them to be a safe and effective treatment, but their patients had short and variable lengths of follow-up.

Few studies have focused on LCH osseous lesions completely through treatment and management, or subsequent follow-up assessment. As LCH is often highly treatable with many patients exhibiting favorable outcomes, timely diagnosis and management are essential.

A weakness of our study is its retrospective nature which relies on chart review of available imaging and documentation. This retrospective case series was limited by the infrequency of appendicular lesion presentations and would therefore benefit from a randomized trial comparing treatment options and outcomes of single osseous appendicular LCH lesions. Furthermore, there were only 30 patients that fit the criteria for our series. Many appendicular lesions were likely excluded from our study due to strict inclusion criteria. Though most literature reports of LCH are case reports and smaller case series, our study cohort is still of a relatively low quantity. One patient had under 1 year of follow-up.

Contributors EUE: study design, chart review, data organization, statistical analysis, manuscript preparation, guarantor. PM: data organization, chart review, manuscript preparation. ES: data organization, chart review, manuscript preparation. NB: study design, data organization, statistical analysis, manuscript preparation. NM: study design, manuscript preparation.

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Patient consent for publication As this was a retrospective chart review with minimal risk, the need to obtain individual consents was waived by the institutional review board.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Baylor College of Medicine's institutional review board (IRB, H-50819) on 3/2/2022.

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REFERENCES

1 Kim BE, Koh K-N, Suh JK, *et al*. Clinical features and treatment outcomes of Langerhans cell histiocytosis: a nationwide survey from Korea histiocytosis Working Party. *J Pediatr Hematol Oncol* 2014;36:125–33.
2 Haupt R, Minkov M, Astigarraga I, *et al*. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. *Pediatr Blood Cancer* 2013;60:175–84.
3 Mavrogenis AF, Abati CN, Bosco G, *et al*. Intralesional methylprednisolone for painful solitary eosinophilic granuloma of the appendicular skeleton in children. *J Pediatr Orthop* 2012;32:416–22.
4 Abdelaal AHK, Sedky M, Gohar S, *et al*. Skeletal involvement in children with langerhans cell histiocytosis: healing, complications, and functional outcome. *SICOT J* 2020;6:28.
5 Egeler RM, Thompson RC Jr, Voûte PA, *et al*. Intralesional infiltration of corticosteroids in localized Langerhans' cell histiocytosis. *J Pediatr Orthop* 1992;12:811–4.
6 Sahin C, Ucpinar BA, Oc Y, *et al*. Radiologic findings of scapular Langerhans cell histiocytosis successfully treated with CT-guided corticosteroid injection. *J Coll Physicians Surg Pak* 2020;30:754–6.
7 Rivera JC, Wylie E, Dell'Orfano S, *et al*. Approaches to treatment of unifocal Langerhans cell histiocytosis: is biopsy alone enough? *J Pediatr Orthop* 2014;34:820–4.
8 Ghanem I, Tolo VT, D'Ambra P, *et al*. Langerhans cell histiocytosis of bone in children and adolescents. *J Pediatr Orthop* 2003;23:124–30. Available: https://journals.lww.com/pedorthopaedics/pages/articleviewer.aspx?year=2003&issue=01000&article=00025&type=Fulltext
9 Chang CY, Guimares JB, Joseph G, *et al*. Percutaneous CT-guided corticosteroid injection for the treatment of osseous langerhans cell histocytosis: a three institution retrospective analysis. *Skeletal Radiol* 2022;51.