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CASE REPORT

LCH of the Scapula in a 2-Year-Old Masquerading as an ABC: A Case Report and Literature Review

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Abstract:

We describe a unique case of Langerhans Cell Histiocytosis (LCH) arising in the scapula of a 2-year old male child masquerading as an aneurysmal bone cyst (ABC) at clinical presentation and on imaging. Scapular involvement is only occasionally noted in LCH cases. Solitary bone involvement in our patient's age group is uncommon in LCH without multi-organ involvement. Careful pathologic examination and immunohistochemistry was crucial in establishing this diagnosis due to the presence of a solitary lesion with fluid-fluid levels.

Keywords: Langerhans cell histiocytosis, Aneurysmal bone cyst, Scapular, Histiocytes, Hemosiderin, Frozen section, Cerament.

Article History

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1. INTRODUCTION

A rare case of Langerhans Cell Histiocytosis (LCH) of the scapula in a 2-year-old male child who presented with a diffusely enlarged left scapula that was warm to touch with severe pain on movement is described in this study. LCH is an extremely rare histiocytic disorder with an incidence of 2 per million in children, affecting males to females in a 2:1 ratio [1, 2]. Our patient's lesion was initially believed to be an aneurysmal bone cyst (ABC) based on clinical presentation and imaging appearance. ABCs are expansile, non-malignant bone lesions that predominantly affect pediatric populations. They frequently present with localized pain and swelling and upon plain radiography, they will typically appear as lytic expansile solitary lesions of the metaphysis. [3] The average age of presentation is 10.2 years and the most commonly affected sites are the femur, tibia, spine, humerus, and pelvis. [4] Our patient's lesion was determined to be LCH with extensive hemorrhage and focal secondary ABC changes following pathological analysis [5, 6]. Comprehensive workup showed no other bone or organ involvement. There were only two reported cases in the literature of LCH masquerading as an ABC, with this being the third. Additionally, solitary bone involvement at this age and of the scapula is highly atypical in LCH. Hence, our patient is unique due to his lesion's imaging features, clinical presentation, and location.

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2. CASE PRESENTATION

A 2-year-old male child with no significant medical history presented to the pediatrician with 1-month of left shoulder pain, forward positioning of the shoulder, and a protuberant scapula. There was no history of trauma, congenital defects, or other symptoms. Initial radiographs revealed a lytic, expansile, radiolucent scapular body bone lesion (Fig. 1). After orthopedic oncology consultation, coordination of MRI and open biopsy under a single episode of general anesthesia (GA) was planned [7]. MRI with and without Gadolinium revealed the presence of an expansile, multi-loculated, septated lesion involving the scapular body and spine (Fig. 2). Multiple fluid-fluid levels were noted within the lesion, reflecting intralesional blood products. No solid component was apparent on any MRI images. Perilesional intraosseous edema in the surrounding scapula and adjacent periscapular muscles was noted, suggesting either occult pathologic fracture or secondary ABC associated with primary chondroblastoma, LCH, osteoid osteoma/osteoblastoma, or infection [8]. Immediately following MRI, the patient was transported to the OR where an open biopsy was planned. Under general anesthesia, fluoroscopy was used to localize the bone lesion and plan the incision. A 3cm incision was made longitudinally over the body of the scapula extending cephalad to the scapular spine and dissection carried down to the bone. A scalpel blade was utilized to enter the almost non-existent outer cortex. A 1 cm diameter window was created for the biopsy. The tissue obtained consisted of multiple fragments of red-brown tissue. Frozen section favored ABC based on the presence of bloody

and cystic areas associated with histiocytes, bland fibroblasts, osteoclast-like giant cells, and hemosiderin deposition (Fig. 3A, B). The incision was then extended and the entire lesion was completely curetted, leaving only a rim of bone around the native scapula. A high speed bur was used to further extend the margins around the lesion to ensure it was entirely removed. During intralesional curettage, the gross appearance was again felt to be consistent with ABC given the findings of blood-filled pools separated by septations. The resulting defect was filled with synthetic bone filler (Cerament, BoneSupport, Inc) and defect filling was confirmed fluoroscopically .

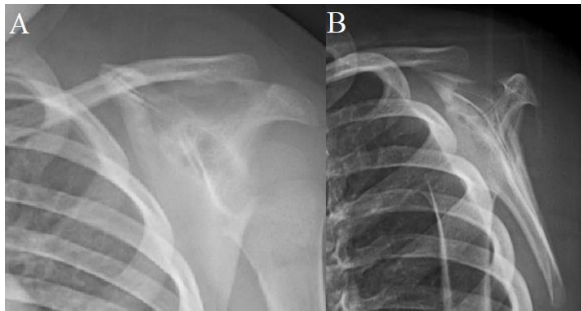


Fig. (1). Initial radiographs. A radiolucent lesion with moth-eaten borders is seen on AP (A) and scapular spine (B) views.

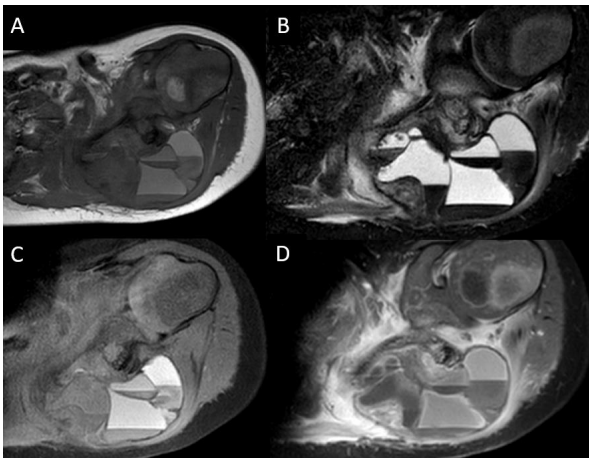


Fig. (2). Baseline MRI of the shoulder. An expansile lesion involving the body of the left scapula is seen. (A) Axial T1 (TR 580, TE 9). (B) Axial STIR (TR4964, TE 60). (C) Axial Pre- (TR 698, TE 9). (D) Axial post-Gadolinium- (TR 698, TE 9). Multiple fluid/fluid levels within the lesion, perilesional edema on the fluid sensitive sequences, and diffuse lesional enhancement all suggested ABC with possible pathologic fracture.

Final pathological analysis showed loose aggregates of histiocytes with nuclear grooving and eosinophilic cytoplasm admixed with osteoclast-like multinucleated giant cells, eosinophils, lymphocytes, and hemosiderin-laden macrophages set in an extensively bloody background (Fig. 4A, B). Blood-filled cystic spaces lined with fibroblasts, multinucleated giant cells, and focal collections of histiocytes with nuclear grooving were also focally identified. Histiocytes were positive for CD1a and S100 by immunohistochemistry, consistent with Langerhans cells (Fig. 4C, D) [9, 10]. Given those findings, the lesion was diagnosed as LCH with extensive hemorrhage and

focal secondary ABC changes rather than primary ABC.

Subsequent evaluation by Pediatric Oncology included staging with skeletal survey and laboratory work. All imaging and laboratory analysis suggested no additional LCH. Observation was elected going forward. At three months post-operation, the patient had no pain, was participating unrestricted in all activities, and had regained full active range of shoulder motion without local tenderness or masses. Three-month scapular radiographs showed graft material incorporation without any recurrence (Fig. 5).

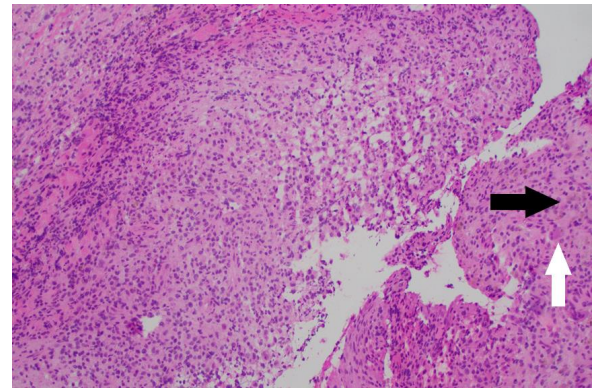


Fig. (3). Frozen section pathology. Low power magnification shows moderately cellular tissue with admixed osteoclast-like giant cells (white arrow) and hemosiderin (black arrow) originally interpreted as ABC.

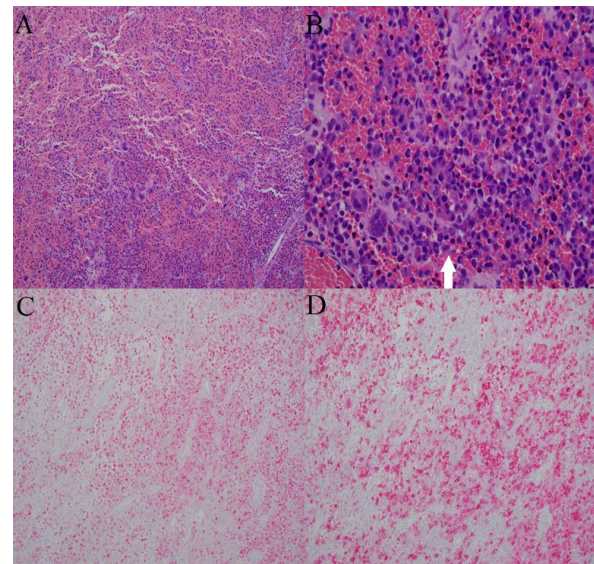


Fig. (4). Final pathology. Low-power magnification shows loose histiocytic aggregates admixed with inflammation and hemorrhage (A). High-power image shows characteristic Langerhans cells (white arrow) with nuclear grooving and eosinophilic cytoplasm admixed with osteoclast-like multinucleated giant cells, and eosinophils (B). Langerhans cells show nuclear and cytoplasmic positivity for S100 (C) and characteristic membranous immunoreactivity for CD1a (D).

3. DISCUSSION

The differential diagnoses (DDX) for this patient shifted

based upon each piece of clinical, imaging, and pathologic evidence obtained. Due to the patient’s age and progressively enlarging, painful intraosseous bone lesion, metastatic neuroblastoma, osteomyelitis, and LCH were considered in the initial DDX. [5, 11 - 15] Inclusion of neuroblastoma metastatic to the bone in our initial clinical-imaging differential diagnosis was due to the young age of the patient with painful aggressive bone involvement. Langerhans cell histiocytosis was considered initially due to the patient’s young age, although the scapula is the least common skeletal site. [16, 17] The MRI findings shifted the differential to primary ABC, secondary ABC, or telangiectatic osteosarcoma [18 - 20]. Imaging findings were inconsistent with metastatic neuroblastoma. In LCH, MRI often shows well-defined lesions with a high T2 and low T1-weighted appearance but only rarely fluid-fluid levels. [17] In this case, the radiographic appearance was atypical of LCH, particularly on MRI. The presence of perilesional edema on MRI, however, suggested the possibility of an associated pathologic fracture, as well as secondary ABC associated with chondroblastoma, LCH, osteoid osteoma/osteoblastoma, or infection. The intra-operative frozen section suggested primary ABC, as no malignant or primary component, and characteristic features of LCH were recognized. Only upon further review of the histology was LCH confirmed. The most distinctive radiographic findings, in this case, were fluid-fluid levels and septations. The most common causes for bone lesions with fluid-fluid levels are shown in Table 1, along with rare causes and a suggested mnemonic for these lesions (GOATS CSF) is as shown in Table 2. LCH is not included in either the suggested differential diagnosis or the mnemonic due to its extreme rarity.

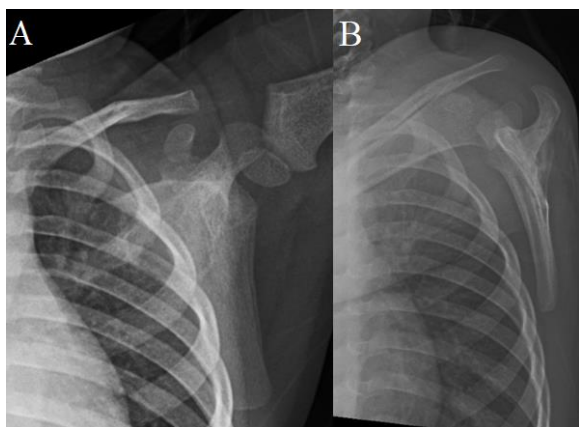


Fig. (5). Follow-up x-ray: The previously visualized lucency in the left scapula now shows radiopaque material representing incorporating synthetic filler.

Based on MRI, our patient was felt to most likely have an ABC, a benign bone lesion most commonly affecting children and presenting with localized pain, swelling, and even pathologic fracture. [21, 22]. Plain radiography typically reveals expansile radiolucencies circumscribed by a thin layer of periosteal bone, as evident in this case. On MRI, numerous blood-filled channels with fluid-fluid levels divided by septations were observed. [4, 23]. Both plain film and MRI findings in our patient suggested ABC, with the differential diagnosis, including secondary ABC and telangiectatic

osteosarcoma. [24 - 26]. Histopathology of ABC shows cavernous blood-filled spaces without endothelial lining, benign giant cells, spindle cells, and thin strands of woven bone. [27].

Table 1. Bone Lesions with Fluid-Fluid Levels on MRI.

Aneurysmal Bone Cyst (ABC)	
Primary ABC	
Secondary ABC	
	Giant cell tumors
	Chondroblastoma
	Osteoblastoma
Simple Bone Cyst (after fracture)	
Telangiectatic Osteosarcoma	
Uncommon Causes	
	Metastases (esp. Renal Cell and Lung primaries)
	Synovial sarcoma
	Synovial hemangioma
	Myositis ossificans
	Adamantinoma
	Neurogenic tumors

Gaillard F. Fluid-fluid containing bone lesions. <https://radiopaedia.org/articles/fluid-fluid-level-containing-bone-lesions-2?lang=us>

Table 2. Mnemonic for Musculoskeletal Lesions with Fluid-Fluid Levels on MRI.

G	Giant cell tumors
O	Osteoblastoma
A	Aneurysmal bone cyst
T	Telangiectatic osteosarcoma
S	Sarcomas (esp. synovial)
C	Chondroblastoma
S	Simple bone cyst and synovial hemangioma
F	Fibroxanthoma (non-ossifying fibroma)

Bell DJ, Chen T. Fluid-fluid level containing musculoskeletal lesions (mnemonic). <https://radiopaedia.org/articles/fluid-fluid-level-containing-bone-lesions-mnemonic?lang=us>

Only the final histology review provided a firm diagnosis of LCH. The change in diagnosis was based upon morphologic identification of the characteristic Langerhans cells confirmed by expression of CD1a and S100. In retrospect, the tissue fragments on the frozen section slides with the loose Langerhans cell histiocytic clusters admixed with osteoclast-like giant cells and hemosiderin deposition were originally misinterpreted at the time of the frozen section evaluation as being fibrous septae with bland fibroblasts and osteoclast-like giant cells similar to those seen in ABC. Both frozen section artifacts and the unusual presence of intra-tumoral blood-filled cystic spaces played a significant role in misinterpretation at the time of the frozen section evaluation. The presence of blood lakes within the tumor ultimately explained the fluid-fluid levels and septations noted on MRI.

The pathological cells of LCH are the Langerhans cells, which are characterized by their ovoid or shape, unobtrusive nucleoli, lobulated nuclei, and eosinophilic cytoplasm. [13]. The background stroma in LCH demonstrates eosinophils,

neutrophils, and monocyte-derived histiocytes. Langerhans cells of LCH lack dendritic cell processes, unlike normal skin Langerhans cells. [13]. However, similar to skin Langerhans cells, the pathologic cells of LCH express the markers CD1a, S100, and CD207 (langerin). Diagnosis of LCH is ultimately based on pathology results, with fine-needle aspiration or core biopsy usually sufficient to yield the required material for diagnosis. [28, 29]. However, the identity of the Langerhans cells must be confirmed via positive immunostaining for CD1a, S100, or CD207 (langerin) or electron microscopy identification of Birbeck granules. [30 - 32]. Furthermore, over 50% of patients with LCH carry an oncogenic BRAF V600E mutation. [33, 34]. Our patient was not evaluated for BRAF mutation. The V600E mutation is not specific for LCH, as it is also found in melanoma, hairy cell leukemia, and Erdheim-Chester disease (another disorder of histiocytes). [33, 35 - 37].

Following diagnosis, imaging is required to stage the extent of involvement. A skeletal survey, skull films, and chest radiographs are often sufficient. [18] However, depending on suspected systemic involvement, CT, PET, and/or MRI may also be useful. [38 - 40] In our case, pediatric oncology did not recommend additional staging evaluation due to the lack of signs indicative of recurrent disease or multisystem disease. For isolated skeletal involvement, no additional treatment beyond surgery is necessary, although careful observation is prudent to ensure that additional lesions do not arise, particularly in young patients such as our case. [7, 41] While there is no universally accepted treatment protocol for LCH apart from cranial locations, minimally invasive and localized approaches are typically preferred. [28] Solitary bone lesions have a good prognosis with curettage with low rates of recurrence, particularly among pediatric patients. [42, 43] In patients with multifocal bone involvement, corticosteroids and vinblastine are typically used with good results and they are well tolerated. [7] Our patient was treated in Stratum VI (Natural History and Management) protocol in the LCH-IV International Collaborative Treatment Protocol for Children and Adolescents with Langerhans Cell Histiocytosis (www.cancer.gov/clinical_trials/NCT02205762). [44]

CONCLUSION

Other reports of similar presentations are rare. Only two cases have been reported. One 8-year-old girl was discovered to have an occipital bump. MRI showed an expansile, destructive, and lytic mass located with multiple fluid-filled levels favoring an ABC as in our case. However, upon excision and biopsy, the characteristic features of LCH were found. [45] The second report involved a 2-year-old male patient with ABC secondary to LCH, and on the occiput. [46] Thus, the current report is the first documented instance of LCH masquerading as an ABC outside of the skull. In conclusion, we present an unusual case of LCH with extensive hemorrhage mimicking primary ABC on imaging modalities. Hemorrhagic LCH is an entity that should be considered in the differential diagnosis of bone lesions with fluid-fluid levels. Pathologic examination and a thorough immunohistochemical workup play a vital role in establishing this rare and challenging diagnosis.

LIST OF ABBREVIATIONS

LCH = Langerhans Cell Histiocytosis

ABC = Aneurysmal Bone Cyst
GA = General Anesthesia
DDX = Differential Diagnosis

CONSENT FOR PUBLICATION

We have obtained consent to publish from the patient.

STANDARD OF REPORTING

CARE guidelines have been used for conducting this research.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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None declared.

REFERENCES

- [1] Guyot-Goubin A, Donadieu J, Barkaoui M, Bellec S, Thomas C, Clavel J. Descriptive epidemiology of childhood Langerhans cell histiocytosis in France, 2000-2004. *Pediatr Blood Cancer* 2008; 51(1): 71-5. [<http://dx.doi.org/10.1002/pbc.21498>] [PMID: 18260117]
- [2] Malpas JS. Langerhans cell histiocytosis in adults. *Hematol Oncol Clin North Am* 1998; 12(2): 259-68. [[http://dx.doi.org/10.1016/S0889-8588\(05\)70509-8](http://dx.doi.org/10.1016/S0889-8588(05)70509-8)] [PMID: 9561899]
- [3] Vergel De Dios AM, Bond JR, Shives TC, McLeod RA, Unni KK. Aneurysmal bone cyst. A clinicopathologic study of 238 cases. *Cancer* 1992; 69(12): 2921-31. [[http://dx.doi.org/10.1002/1097-0142\(19920615\)69:12<2921::AID-CNCR2820691210>3.0.CO;2-E](http://dx.doi.org/10.1002/1097-0142(19920615)69:12<2921::AID-CNCR2820691210>3.0.CO;2-E)] [PMID: 1591685]
- [4] Cottalorda J, Kohler R, Sales de Gauzy J, *et al.* Epidemiology of aneurysmal bone cyst in children: A multicenter study and literature review. *J Pediatr Orthop B* 2004; 13(6): 389-94. [<http://dx.doi.org/10.1097/01202412-200411000-00008>] [PMID: 15599231]
- [5] Mankin HJ, Hornicek FJ, Ortiz-Cruz E, Villafuerte J, Gebhardt MC. Aneurysmal bone cyst: A review of 150 patients. *J Clin Oncol* 2005; 23(27): 6756-62. [<http://dx.doi.org/10.1200/JCO.2005.15.255>] [PMID: 16170183]
- [6] Kransdorf MJ, Sweet DE. Aneurysmal bone cyst: Concept, controversy, clinical presentation, and imaging. *AJR Am J Roentgenol* 1995; 164(3): 573-80. [<http://dx.doi.org/10.2214/ajr.164.3.7863874>] [PMID: 7863874]
- [7] 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(2): 175-84. [<http://dx.doi.org/10.1002/pbc.24367>] [PMID: 23109216]
- [8] Yildiz C, Erler K, Atesalp AS, Basbozkurt M. Benign bone tumors in children. *Curr Opin Pediatr* 2003; 15(1): 58-67. [<http://dx.doi.org/10.1097/00008480-200302000-00010>] [PMID: 12544273]
- [9] Dziegiel P, Dolilńska-Krajewska B, Dumańska M, *et al.* Coexpression of CD1a, langerin and Birbeck's granules in Langerhans cell histiocytoses (LCH) in children: Ultrastructural and immunocytochemical studies. *Folia Histochem Cytobiol* 2007; 45(1): 21-5. [PMID: 17378241]
- [10] Allen CE, Li L, Peters TL, Leung H-CE, Yu A, Man T-K, *et al.* Cell-specific gene expression in Langerhans cell histiocytosis lesions reveals a distinct profile compared with epidermal Langerhans cells. *J Immunol Baltim Md* 1950; 184(8): 4557-67.
- [11] Peltola H, Pääkkönen M. Acute osteomyelitis in children. *N Engl J*

- Med 2014; 370(4): 352-60.
[<http://dx.doi.org/10.1056/NEJMra1213956>] [PMID: 24450893]
- [12] Newman B, Hu W, Nigro K, Gilliam AC. Aggressive histiocytic disorders that can involve the skin. *J Am Acad Dermatol* 2007; 56(2): 302-16.
[<http://dx.doi.org/10.1016/j.jaad.2006.06.010>] [PMID: 17097374]
- [13] Nakamine H, Yamakawa M, Yoshino T, Fukumoto T, Enomoto Y, Matsumura I. Langerhans cell histiocytosis and langerhans cell sarcoma: current understanding and differential diagnosis. *J Clin Exp Hematop* 2016; 56(2): 109-18.
[<http://dx.doi.org/10.3960/jslrt.56.109>] [PMID: 27980300]
- [14] Loneragan GJ, Schwab CM, Suarez ES, Carlson CL. Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma: Radiologic-pathologic correlation. *Radiographics* 2002; 22(4): 911-34.
[<http://dx.doi.org/10.1148/radiographics.22.4.g02j115911>] [PMID: 12110723]
- [15] Lin PP, Thenappan A, Deavers MT, Lewis VO, Yasko AW. Treatment and prognosis of chondroblastoma. *Clin Orthop Relat Res* 2005; 438(438): 103-9.
[<http://dx.doi.org/10.1097/01.blo.0000179591.72844.c3>] [PMID: 16131877]
- [16] Tsirakis G, Kaparou M, Kanellou P, Kontakis G, Alexandrakis MG. Langerhans cell histiocytosis in the right scapula in a young man. 2012.
- [17] Song YS, Lee IS, Yi JH, Cho KH, Kim DK, Song JW. Radiologic findings of adult pelvis and appendicular skeletal Langerhans cell histiocytosis in nine patients. *Skeletal Radiol* 2011; 40(11): 1421-6.
[<http://dx.doi.org/10.1007/s00256-010-1078-y>] [PMID: 21190020]
- [18] Meyer JS, De Camargo B. The role of radiology in the diagnosis and follow-up of Langerhans cell histiocytosis. *Hematol Oncol Clin North Am* 1998; 12(2): 307-26.
[[http://dx.doi.org/10.1016/S0889-8588\(05\)70512-8](http://dx.doi.org/10.1016/S0889-8588(05)70512-8)] [PMID: 9561902]
- [19] Hiorns MP, Owens CM. Radiology of neuroblastoma in children. *Eur Radiol* 2001; 11(10): 2071-81.
[<http://dx.doi.org/10.1007/s003300100931>] [PMID: 11702143]
- [20] Cochran L-A, Prince M, Clarke K. Langerhans' cell histiocytosis in the paediatric population: Presentation and treatment of head and neck manifestations. *J Otolaryngol* 2003; 32(1): 33-7.
[<http://dx.doi.org/10.2310/7070.2003.35266>] [PMID: 12779259]
- [21] Copley L, Dormans JP. Benign pediatric bone tumors. Evaluation and treatment. *Pediatr Clin North Am* 1996; 43(4): 949-66.
[[http://dx.doi.org/10.1016/S0031-3955\(05\)70444-2](http://dx.doi.org/10.1016/S0031-3955(05)70444-2)] [PMID: 8692589]
- [22] Park HY, Yang SK, Sheppard WL, et al. Current management of aneurysmal bone cysts. *Curr Rev Musculoskelet Med* 2016; 9(4): 435-44.
[<http://dx.doi.org/10.1007/s12178-016-9371-6>] [PMID: 27778155]
- [23] Creager AJ, Madden CR, Bergman S, Geisinger KR. Aneurysmal bone cyst: Fine-needle aspiration findings in 23 patients with clinical and radiologic correlation. *Am J Clin Pathol* 2007; 128(5): 740-5.
[<http://dx.doi.org/10.1309/VB1M9D9H7QG6L3R4>] [PMID: 17951194]
- [24] Murphey MD, wan Jaovisidha S, Temple HT, Gannon FH, Jelinek JS, Malawer MM. Telangiectatic osteosarcoma: Radiologic-pathologic comparison. *Radiology* 2003; 229(2): 545-53.
[<http://dx.doi.org/10.1148/radiol.2292021130>] [PMID: 14512511]
- [25] Liu JJ, Liu S, Wang JG, et al. Telangiectatic osteosarcoma: A review of literature. *Oncotargets Ther* 2013; 6: 593-602.
[PMID: 23745051]
- [26] Discepolo F, Powell TI, Nahal A. Telangiectatic osteosarcoma: Radiologic and pathologic findings. *Radiographics* 2009; 29(2): 380-3.
[<http://dx.doi.org/10.1148/rg.292085150>] [PMID: 19325054]
- [27] Rapp TB, Ward JP, Alaia MJ. Aneurysmal bone cyst. *J Am Acad Orthop Surg* 2012; 20(4): 233-41.
[<http://dx.doi.org/10.5435/JAAOS-20-04-233>] [PMID: 22474093]
- [28] Yasko AW, Fanning CV, Ayala AG, Carrasco CH, Murray JA. Percutaneous techniques for the diagnosis and treatment of localized Langerhans-cell histiocytosis (eosinophilic granuloma of bone). *J Bone Joint Surg Am* 1998; 80(2): 219-28.
[<http://dx.doi.org/10.2106/00004623-199802000-00009>] [PMID: 9486728]
- [29] Kumar P, Singh A, Gamanagatti S, Kumar S, Chandrashekhara SH. Imaging findings in Erdheim-Chester disease: What every radiologist needs to know. *Pol J Radiol* 2018; 83: e54-62.
[<http://dx.doi.org/10.5114/pjr.2018.73290>] [PMID: 30038679]
- [30] Wilson AJ, Maddox PH, Jenkins D. CD1a and S100 antigen expression in skin Langerhans cells in patients with breast cancer. *J Pathol* 1991; 163(1): 25-30.
[<http://dx.doi.org/10.1002/path.1711630106>] [PMID: 2002421]
- [31] Valladeau J, Ravel O, Dezutter-Dambuyant C, et al. Langerin, a novel C-type lectin specific to Langerhans cells, is an endocytic receptor that induces the formation of Birbeck granules. *Immunity* 2000; 12(1): 71-81.
[[http://dx.doi.org/10.1016/S1074-7613\(00\)80160-0](http://dx.doi.org/10.1016/S1074-7613(00)80160-0)] [PMID: 10661407]
- [32] Titgemeyer C, Grois N, Minkov M, Flucher-Wolfram B, Gatterer-Menz I, Gadner H. Pattern and course of single-system disease in Langerhans cell histiocytosis data from the DAL-HX 83- and 90-study. *Med Pediatr Oncol* 2001; 37(2): 108-14.
[<http://dx.doi.org/10.1002/mpo.1178>] [PMID: 11496348]
- [33] Badalian-Very G, Vergilio J-A, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. *Blood* 2010; 116(11): 1919-23.
[<http://dx.doi.org/10.1182/blood-2010-04-279083>] [PMID: 20519626]
- [34] Berres M-L, Lim KPH, Peters T, et al. BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. *J Exp Med* 2014; 211(4): 669-83.
[<http://dx.doi.org/10.1084/jem.20130977>] [PMID: 24638167]
- [35] Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature* 2002; 417(6892): 949-54.
[<http://dx.doi.org/10.1038/nature00766>] [PMID: 12068308]
- [36] Long GV, Menzies AM, Nagrial AM, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. *J Clin Oncol* 2011; 29(10): 1239-46.
[<http://dx.doi.org/10.1200/JCO.2010.32.4327>] [PMID: 21343559]
- [37] Emile J-F, Abba O, Fraitag S, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. *Blood* 2016; 127(22): 2672-81.
[<http://dx.doi.org/10.1182/blood-2016-01-690636>] [PMID: 26966089]
- [38] Zaveri J, La Q, Yarmish G, Neuman J. More than just Langerhans cell histiocytosis: A radiologic review of histiocytic disorders. *Radiographics* 2014; 34(7): 2008-24.
[<http://dx.doi.org/10.1148/rg.347130132>] [PMID: 25384298]
- [39] Chaudhary V, Bano S, Aggarwal R, et al. Neuroimaging of Langerhans cell histiocytosis: A radiological review. *Jpn J Radiol* 2013; 31(12): 786-96.
[<http://dx.doi.org/10.1007/s11604-013-0254-0>] [PMID: 24122527]
- [40] Schmidt S, Eich G, Geoffray A, et al. Extraosseous langerhans cell histiocytosis in children. *Radiographics* 2008; 28(3): 707-26.
[<http://dx.doi.org/10.1148/rg.283075108>] [PMID: 18480480]
- [41] Héritier S, Jehanne M, Leverger G, et al. Vemurafenib Use in an Infant for High-Risk Langerhans Cell Histiocytosis. *JAMA Oncol* 2015; 1(6): 836-8.
[<http://dx.doi.org/10.1001/jamaoncol.2015.0736>] [PMID: 26180941]
- [42] Ghanem I, Tolo VT, D'Ambra P, Malogallowkin MH. Langerhans cell histiocytosis of bone in children and adolescents. *J Pediatr Orthop* 2003; 23(1): 124-30.
[<http://dx.doi.org/10.1097/01241398-200301000-00025>] [PMID: 12499958]
- [43] Karagoz Guzey F, Bas NS, Emel E, Alatas I, Kebudi R. Polyostotic monosystemic calvarial and spinal langerhans' cell histiocytosis treated by surgery and chemotherapy. *Pediatr Neurosurg* 2003; 38(4): 206-11.
[<http://dx.doi.org/10.1159/000069100>] [PMID: 12646740]
- [44] North American Consortium for Histiocytosis. LCH-IV, International Collaborative Treatment Protocol for Children and Adolescents With Langerhans Cell Histiocytosis - Full Text View Available from: <https://clinicaltrials.gov/ct2/show/NCT02205762>
- [45] Krishnan C. Langerhans cell histiocytosis masquerading as aneurysmal bone cyst. *J Clin Oncol* 2011; 29(24): e688-90.
[<http://dx.doi.org/10.1200/JCO.2011.35.5875>] [PMID: 21709198]
- [46] Roncaroli F, Consales A, Galassi E, Bernardi B, Valeri B. Occipital aneurysmal bone cyst secondary to eosinophilic granuloma. *Pediatr Neurosurg* 2001; 35(2): 103-6.
[<http://dx.doi.org/10.1159/000050399>] [PMID: 11549922]