ORIGINAL ARTICLE

RADIOLOGIC MANIFESTATIONS OF LANGERHANS CELL HISTIOCYTOSIS IN PEDIATRICS

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ABSTRACT

PURPOSE: To assess and review the radiologic manifestations of pediatric patients diagnosed with Histiocytosis. **METHODS:** A total number of 48 biopsy-proven Langerhans Cell Histiocytosis (LCH) patients (<14 years old) were retrospectively reviewed. As one of diagnostic work up, all the selected patients underwent radiologic studies including radiographic bone survey which were reviewed by radiologist for musculoskeletal and respiratory system findings. **RESULTS:** Lytic bone lesions, lung involvements and generalized osteoporosis were the most common radiologic findings among the patients. 38 of them (79.2%) had bone involvements; skull was involved the most (66.7%), followed by Pelvis (31.3%), Femur (31.3%), Sphenoid (30.0%) and ribs (16.7%). In 10 cases (20.8%) periosteal reaction was seen and 4 cases (8.3%) had metaphyseal lucent band. In the long bones, metaphysis(31.3%) was the most commonly affected, followed by diaphysis (18.8%) and epiphysis (2.0%). One fourth of patients (12 cases) had vertebral involvements. None of these cases had cervical vertebral lesions while in 10 (21.0%) and 7 (14.6%) of them lumbar and thoracic vertebras were involved. Lung involvement was detected in 33 patients (68.8%). The most common involvement patterns were reticulonodular in 30 cases (62.5%), honeycomb with 13 cases (27.1%) and mediastinal widening with 5 cases (10.4%). **CONCLUSION:** Lytic lesions in flat bones like skull are the most common radiologic manifestation of LCH, followed by reticulonodular pulmonary involvement, as well as generalized osteoporosis. Solitary long bone lesions and isolated lung involvement are not common and must be correlated with clinical condition in cases suspicious of LCH.

Keywords: Histiocytosis, Pediatrics, Radiology.

Introduction

Langerhans cell histiocytosis (LCH) or histiocytosis X is a rare disease complex characterized by proliferation of the mononuclear phagocytes and dendritic cell system.[1,3] Up to 5 cases per 1 million have the chance to grow this disease.[1] LCH can affect patients of any age, but males under 15 years are more commonly affected.[4]

The clinical manifestations of LCH show a wide variety depending upon the site and extent of involvement leading to a long and confusion history with enigmatic causes for this disease.[5] These manifestations range from a self limited solitary bone lesion to a fatal multi systemic dysfunction.

LCH was formerly composed of three distinct clinical syndromes: Eosinophilic granuloma, Hand-Schüller-Christian disease and Letterer-Siwe disease. Eosinophilic granuloma is limited to bone in patients usually 5–15 years old. Hand-Schüller-Christian disease is characterized by multifocal bone lesions and extraskeletal involvement of the reticuloendothelial system (RES) and pituitary gland, usually seen in children 1–5 years old. In Letterer-Siwe disease, there is disseminated involvement of the RES with a fulminant clinical course in children less than 2 years old.[6,7] These syndromes show indistinguishable histology

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and all are diagnosed by approving Langerhans cell existence in their lesion. In order to make the definite diagnosis electronic microscopy for detecting Birbeck granules, immunohistochemistry for detecting S100 proteins and CD1a marker should be used.[8]

Although definite diagnosis is made by histopathologic, immunophenotype and enzyme studies, hence to the bone involvement in 80% of cases and pulmonary involvement in one third of cases, radiology still plays a major role in making the diagnosis and in many cases provides the initial findings which raise the clinical suspicion.[9] Meanwhile, the extension of disease after clinical assessment can be determined by imaging.[10] This study was designed to assess and review the radiologic manifestations of pediatric patients diagnosed with LCH in a pediatric hospital.

Materials and Methods

This is a retrospective review on radiological manifestations of 48 biopsy-proven LCH patients (<14 years old), who were admitted to the Mofid children's Hospital, Tehran, Iran. All of these cases were diagnosed by both Pediatric Hematologist-Oncologists contributing in this article. As one of diagnostic work up, all the selected patients underwent radiologic studies including bone survey which include, skull x-ray AP-lateral, cervical and thoracolumbosacral, upper and lower extrimities and pelvic x-rays. An informed consent was obtained from the patients or their parents for children under 14 years. The study protocol was approved by ethics committee of Shahid Beheshti University of Medical Sciences. All of x-rays was reported by one radiologist expert in the field of pediatric radiology.

Results

Of the total number of 48 patients from 6-month-old to 14-year-old, the mean age was 3.5-year-old. 34 (70.1%) were boys and 14 others (29.9%) were girls. Half of these patients were younger than 2 years. (Tab.1) & (Chart 1) show age distribution of these patients.

Lytic bone lesions, lung involvements and generalized osteoporosis were the most common radiologic findings among our patients. (Tab. 2) summarized all kinds of radiologic findings among studied patients.

All 38 (79.2%) patients with bone lesions had flat bone involvements; among them skull was the most common location. All the lesions were lytic, well margined and irregularly bordered in all the cases. Generalized osteoporosis was seen in 32 patients (66.7% of all 48patients); of them 8 ones (16.7%) had no other signs of bone involvement. Reticulonodular pattern was the most common patterns of lung involvement among our patients. Other patterns of lung involvement such as pleural effusion, hyperinflation, pneumothorax and pleural thickening were all less than 10%. Isolate lung involvements were found in only 14.6% of our patients. The cause of mediastinal widening was adenopathy in 4 patients and thymic enlargement in one case. Types of bone lesions and patterns of lung involvement in more details have been summarized in (Tab. 3). In fifteen cases (31.3%) among patients with long bone involvement metaphyseal lesions were found while diaphyseal and epiphyseal lesions were detected in 9 (18.8%) and only 1(2.0%) cases respectively. Three patients had isolated diaphyseal involvement without the metaphysis involved. One fourth of patients (12 cases) had vertebral involvements. None of these cases had cervical bone lesions while in 10 (21.0%) and 7 (14.6%) of patients lumbar and thoracic vertebras were involved. No case with classic pattern of vertebra planna was found. Location of bone involvements in long and flat bones have been shown in (Tab. 4). (Fig. 1-6) describe six LCH cases with various radiologic manifestations.

Age groups	Cases	Percent
2-0	24	50.0
4-2	11	22.9
6-4	5	10.4
8-6	3	6.3
10-8	1	2.1
14-10	4	8.3
Total	**48**	**100**

Table 1: Age distribution of the patients (48 patients).

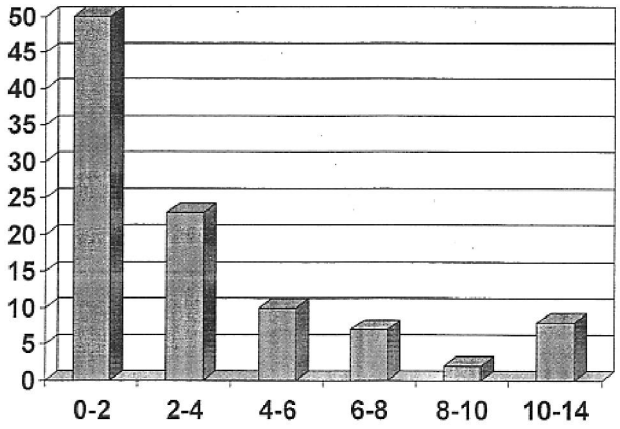

Chart 1: Patient age distribution.

Radiologic findings	Number	Percent
Lytic bone lesion	38	79.2
Lung Involvement	33	68.8
Generalized Osteoporosis	32	66.7
Organomegaly	13	27.1
Brain Atrophy	10	20.8
Periosteal Reaction	10	20.8
Mediastinal Widening	5	10.4
Metaphyseal Lucent Band	4	8.3
Sclerotic lesion	3	6.3
Pathologic Fracture	1	2.1

Table 2: Radiologic findings of 48 patients with langerhans cell histiocytosis (LCH).

Bone or lung involvements	Number (n=48)	Percent
Bone lesions		
Flat Bones	38	79.2
Long bones	19	39.6
Vertebrae	12	25.0
Lung involvements		
Reticulonodular Pattern	30	62.5
Honeycomb Pattern	13	27.1
Mediastinal Widening	5	10.4
Interstitial Pattern	4	8.3
Pelural Effusion	3	6.3
Hyperinflation	2	4.2
Pleural Thickening	1	2.1
Pulmonary Edema	1	2.1
Pneumothorax	1	2.1

Table 3: Types of bone lesions and patterns of lung involvement in the patients.

Flat or long bones	Number (n=48)	Percent
Flat bones		
Skull (frontal, parietal and occipital bone)	32	66.7
Pelvis	15	31.3
Sphenoid	11	22.9
Rib	8	16.7
Scapula	3	6.3
Mastoid, temporal bone	2	4.2
Clavicle	1	2.1
Long bones		
Femur	15	31.3
Humerus	5	10.4
Ulna	5	8.3
Tibia	4	10.5
Radius	1	2.1
Phalanx	1	2.1
Metatarsus Metacarpus	1	2.1

Table 4: Location of bone involvements in long and flat bones in the patients.

Discussion

In this study radiologic manifestation of 48 pediatric patients with biopsy-proven LCH were reviewed. In consistence with other studies our results showed predominance of male gender with a male/female ratio of 2.4/1.[4,11,12] The peak incidence of LCH is at 1-4 years of age;[13] all of our studied patients were younger than 14 years old and half of them (24 cases) were under 2 years.

LCH can involve various organs and presents with various clinical manifestations. Here we focus on radiologic findings of bone and lung involvements of this disease.

Bone Involvement

Flat and long bones

Bone lesions are commonly found in patients with LCH with a predilection for flat bones.[7,14,15] In more than half of the cases of LCH skull, pelvis, spine, mandible and ribs are involved;[7,14,15] among them skull is the most common site.[16] About 4/5 of our patients (79.2%) had bone involvements in whom at least one flat bone was involved while only half of them had long bone involvements. In our patients Skull was involved the most (66.7%), followed by Pelvis (31.3%), Femur (31.3%), Sphenoid (30.0%) and ribs (16.7%) (Fig. 1-3).

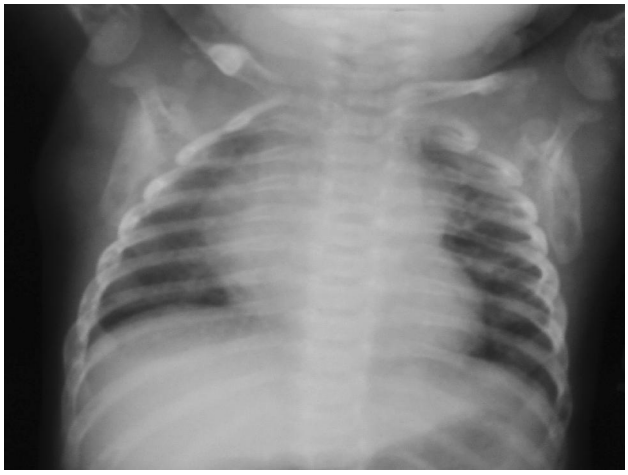

Figure 1: A 4-month-old infant with histiocytosis. CXR reveals bilateral scapular and rib lytic lesions.

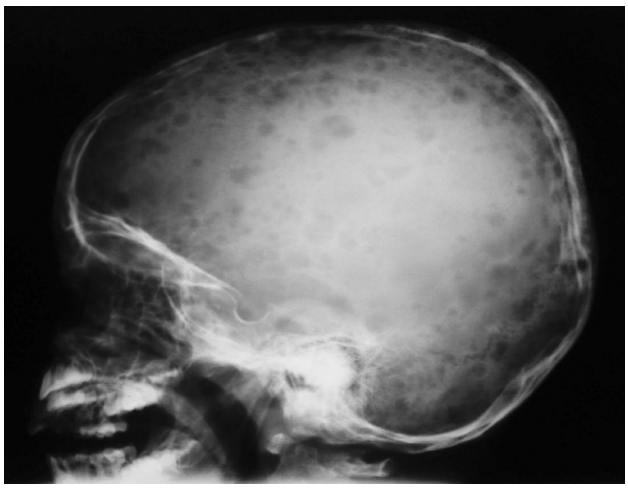

Figure 2: A 4-year-old boy with histiocytosis. Lateral skull X-ray reveals multiple lytic lesions in calvarial bones.

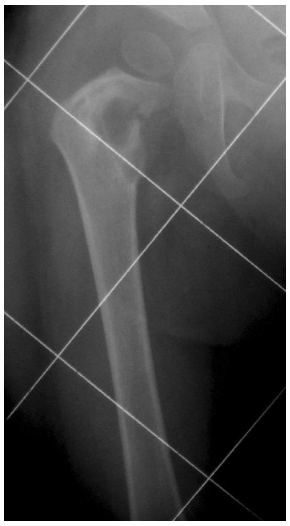

Figure 3: A 9-month-old boy with histiocytosis. X-Ray reveals lytic lesion in right femur with pathologic fracture on medial side of femoral neck.

Generalized osteoporosis was seen in 32 patients (66.7% of all 48patients); of them 8 ones (16.7%) had no other signs of bone involvement.

It is assumed that in more than one third of patients long bone lesions can be detected; among them femur is the most common site, followed by Tibia and Humerus.[7] Similar pattern was found among our patients. In the long bones, the metaphysis (31.3%) was most commonly affected, followed by the diaphysis (18.8%) and epiphysis (2.0%). Three patients had isolated diaphyseal involvement without the metaphysis involved. In contrast to our result, the diaphysis has been reported as the most common affected site (58%), followed by the metaphysis in Stull study.[7] Epiphysial lesions are rare and can be mistaken by chondroblastoma or abscess.[17,18]

The radiologic appearance of lesions depends upon the site of involvement and the pattern of the disease. In the early stage, lesions may appear rapidly, show an aggressive pattern with poorly defined margin with a wide zone of transmission and laminated periosteal reaction.[19,20] In this stage the lesions should be differentiated from other similar lesions such as osteomyelitis, leukemia, lymphoma and Ewing sarcoma. In chronic phase specially while receiving treatment in responders, lesions may present with a more benign pattern with well defined sclerotic margins, a narrow zone of transmission and a mature or absent periosteal reaction.[20] Patterns of diseases like giant cell tumor, fibrous dysplasia, healing metastasis, intraosseous hemangioma, bone cysts and enchondroma may be similar to the latent phase of LCH.

In the skull, osteolytic sharp lesions with well defined margins or “punched out” lesions are characteristic. Button sequestrum is a residual fragment of intact bone that may be sometimes seen within skull lesions in LCH, as well as infection, dermoid and epidermoid cysts and radiation necrosis.[21,22]

Among our patients, in 10 cases (20.8%) periosteal reaction was seen; however 4 cases (8.3%) had metaphyseal lucent band. We also had one case with pathologic fracture in neck of Femur. In similar studies periosteal reaction has been mentioned as one of possible patterns of bone involvement,[23] but metaphyseal lucent band has not been widely assessed.

Spine

In the pediatric spine, the thoracic vertebrae are the most common site, followed by lumbar and cervical spine.[14,24] Vertebral body is mainly involved that may lead to its collapse with the characteristic "vertebra planna" appearance. One fourth of our patients showed vertebral involvement; among them lumbar spine was the most common site (20.8%), followed by thoracic spine (14.6%) (Fig. 4).

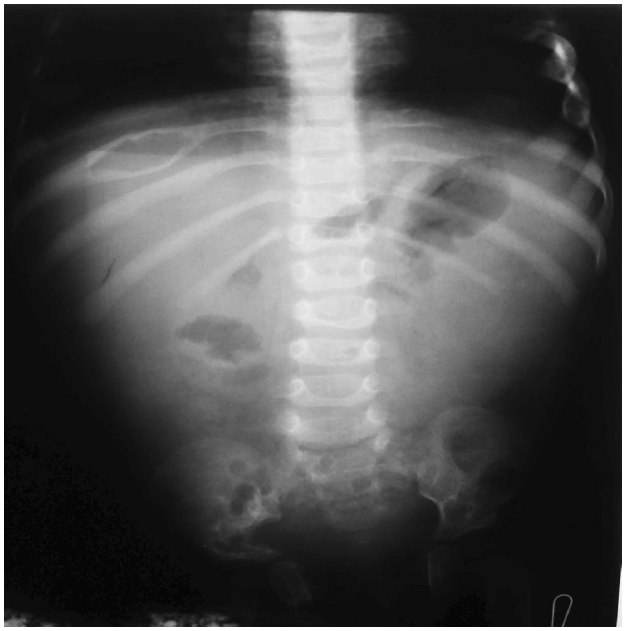

Figure 4: An 8-month-old boy with histiocytosis. Plain abdominal X-Ray reveals right side 9th rib lytic expansile lesion with partial compress FX inT12 & L2 and reduce height of L3 with bilateral iliac bones lytic lesions

Surprisingly we could not detect any case of cervical spine involvement. No case with classic pattern of vertebra planna was found. Garg S et al in an assessment of 26 patients with LCH involving the spine found a particularly high prevalence of lesions in the cervical spine, but similar to our findings they revealed that more severe lesions often led to asymmetric collapse rather than the classic view of vertebra plana.[24]

Lung

Although LCH is approximately three times more common in children than adults, its pulmonary involvement mainly affects adults.[25] Pulmonary LCH accounts for only less than 10% of childhood LCH. A considerable proportion of children with LCH (about half of them) are asymptomatic, and the prognosis of the disease seems to depend upon the absence or presence of involvemement in other organs.[26] Lung involvement was detected in 33 patients (68.8%). The most common involvement patterns were reticulonodular in 30 cases (62.5%), honeycomb's with 13 cases (27.1%) and mediastinal widening in 5 cases (10.4%). The cause of mediastinal widening was adenopathy in 4 patients and infiltration of thymus with histiocytes in one case. Other patterns of lung involvement such as pleural effusion, hyperinflation, pneumothorax and pleural thickening were all less than 10% (Fig. 5 and 6).

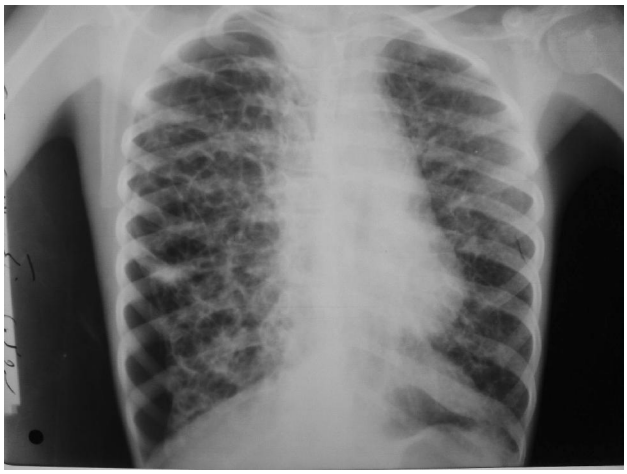

Figure 5: A 3-year-old girl with histiocytosis. CXR reveals interstitial pattern with cystic and honeycombing appearance.

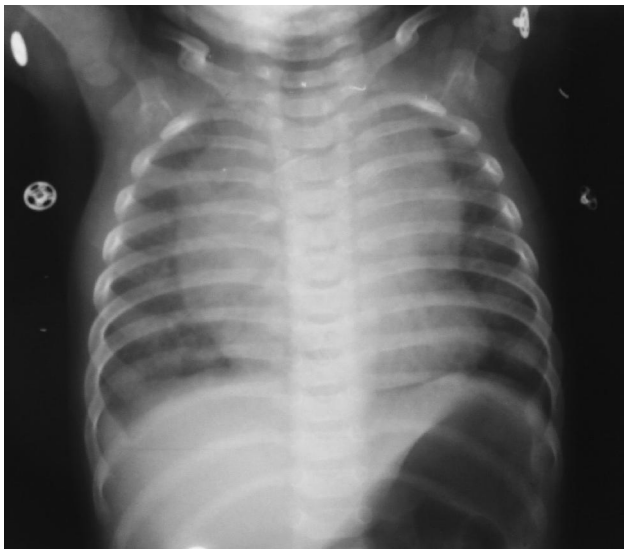

Figure 6: A 6-month-old boy with histiocytosis. CXR reveals mediastinal widening due to thymic infiltration by histiocytic cells.

Lung involvements and its frequent pattern in LCH among our patients were similar to the previous studies.[9,27] Isolated lung involvements without bone

lesions are rare[28] and were found in only 14.6% of our patients. Brain atrophy was seen in 10 patients (20.8%); of whom 4 had no signs of skull involvement. The brain atrophy may be as a result of histiocyte proliferation and demyelination of unknown etiology.[29] One of the mentioned radiologic patterns of disease is floating teeth which clinically was observed in just one patient,a three-year-old boy which floating teeth was part of the clinical manifestation. CT scan was not performed for all of the patients and because of inadequacy of data, their findings were not assessed among our patients and we only focused on radiographic findings of the patients. Studies with more sample size and applying more sensitive imaging like high resolution CT for pulmonary involvement will be helpful to obtain a clearer view.

Conclusion

Lytic lesions in flat bones like skull are the most common radiologic manifestation of LCH, followed by reticulonodular pulmonary involvement, as well as generalized osteoporosis. Cervical spine involvement is not so common among LCH patients in Iran. Solitary long bone lesions and isolated lung involvement are not common and must be correlated with clinical condition in cases suspicious of LCH.

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References

1. Glotzbecker MP, Carpentier DF, Dormans JP. Langerhans cell histiocytosis. UPOJ 2002;**15:** 67–73.

2. Behrman RE,et al. Nelson Textbook Of Pediatrics.17th ed. USA:Elsevier, Science;2004.

3. Egeler RM, D'Angio GJ. Langerhans cell histiocytosis. J Pediatr. 1995;**127:**1–11.

4. Broadbent V, Egeler M, Nesbit ME. Langerhans cell histiocytosis: clinical and epidemiological aspects. Br J Cancer. 1994;**70:**S11–6.

5. Coppes-Zantinga A, Egeler RM. The Langerhans cell histiocytosis X files revealed. Br J Haematol. 2002;**116(1):**3–9.

6. Hoover KB, Rosenthal DI, Mankin H. Langerhans cell histiocytosis. Skeletal Radiol. 2007;**36:** 95–104.

7. Stull MA, Kransdorf MJ, Devaney KO. Langerhans cell histiocytosis of bone. RadioGraphics .1992; **12:** 801–23.

8. Philip A.Pizzo,et al. Principles and practice of pediatric oncology.5th ed.USA: Lippincott:2006.

9. Ouzidane L, Benjelloun A, Saaidi B, Ksiyer M. Radiological aspects of histiocytosis X , J Radiol. 1993 Dec;**74(12):**629–40.

10. Mahboubi S, Meyer JS, Harty MP, et al. Langerhans cell histiocytosis: presentation and evolution of radiologic findings with clinical correlation. RadioGraphics, 1995;**15:**1135–46.

11. Chhabra UD, Desai SS, Jambhekar NA. Langerhans' cell histiocytosis: a clinicopathological study of 50 cases , Indian J Pathol Microbiol. 2004 Jul;**47(3):**370–6.

12. Al-mulhim I, Sabbah RS, Al-Akkad S. Hystiocytosis-X in Saudi children. Indian J Cancer 1991;**28(2):**53–60.

13. Webb DKH. Histiocytic syndromes. In Lilleyman J, Hann I, Blanchette V eds. Pediatric Hematology, 2nd edn. London: Churchill Livingstone, 1999; 356–361.

14. Seibert DJ. Eosinophilic granuloma. Pediatric case of the day. AJR. 1994;**162:**1473–4

15. Bollini G, Jouve JL, Gentet JC, et al. Bone lesions in histiocytosis X. J Pediatr Orthop. 1991; **11:** 69–477.

16. Imashuku S, Kinugawa N, Matsuzaki A, et al. Langerhans cell histiocytosis with multifocal bone

lesions: comparative clinical features between single and multi-systems. 2009 Nov;**90(4):**506–12.

17. Gardner DJ, Azouz EM. Solitary lucent epiphyseal lesions in children. Skeletal Radiol. 1988;**17:** 497–504

18. Usui M, Matsuno T, Kobayashi M, et al. Eosinophilic granuloma of the growing epiphysis. Clin Orthop. 1983;**176:**201–5

19. Hung PC, Wang HS, Jaing TH, et al. From normal to abnormal MR findings within three weeks in a solitary pelvic Langerhans histiocytosis. Skeletal Radiol. 2003;**32:**481–4

20. Kumar R, David R, Oria R, et al. Radiologic features of eosinophilic granuloma of bone. AJR Am J Roentgenol, 1989;**153:**1021–6.

21. Tordeur M, Wybier M, Laporte JL, et al. Button sequestrum in a case of localized Langerhans cell histiocytosis of the ilium: case report. Can Assoc Radiol J. 2000;**51:**90–2.

22. Mitnick JS, Pinto RS. Computed tomography in the diagnosis of eosinophilic granuloma. J Comput Assist Tomogr. 1980;**4:**791–3.

23. Strada M, Tesoro Tess JD, Cozzi G, Musumeci R. Histiocytosis X: radiologic evaluation of 52 patients, Radiol Med (Torino). 1983 May;**69(5):**296–303

24. Garg S, Mehta S, Dormans JP. Langerhans cell histiocytosis of the spine in children. Long-term follow-up. 2004 Aug;**86-A(8):**1740–50.

25. Vassallo R, Ryu JH. Pulmonary Langerhans' cell histiocytosis. 2004 Sep;**25(3):**561–71.

26. Odame I, Li P, Lau L, Doda W, et al. Pulmonary Langerhans cell histiocytosis: a variable disease in childhood. 2006 Dec;**47(7):**889–93.

27. Kilborn TN, The J, Goodman TR. Paediatric manifestations of langerhans cell histiocytosis: A review of the clinical and radiological findings , Clinical Radiology. 2003;**58:** 269–78.

28. David G, Nathan, et al. Nathan and Oski's hematology of infancy and childhood. 6th ed. USA: W.B.Saunders Company, 2003.

29. Barthez MA, Araujo E, Donadieu J. Langerhans cell histiocytosis and the central nervous system in childhood: evolution and prognostic factors. Results of a collaborative study. J Child Neurol. 2000 Mar;**15(3):**150–6.