CONTENTS

Clinico-biologic profile of Langerhans cell histiocytosis: A single institutional study

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Abstract

CONTEXT: Langerhans cell histiocytosis (LCH) is a rare atypical cellular disorder characterized by clonal proliferation of Langerhans cells leading to myriad clinical presentations and highly variable outcomes. There is a paucity of Indian studies on this subject. **AIM:** To present the experience of management of LCH at a single institution. **SETTINGS AND DESIGN:** This is a retrospective observational study of patients with LCH who presented at the Tata Memorial Hospital between January 1987 and December 2002. **MATERIALS AND METHODS:** Fifty-two patients with LCH were treated in the study period. Due to the long observation period and variability in diagnostic and therapeutic protocols, the patients were risk-stratified based on present criteria. The disease pattern, management approaches and treatment outcomes of patients were recorded. **STATISTICAL ANALYSIS USED:** Statistical analyses were done using Student's *'t'* test, test for proportion and survival estimates based on the Kaplan-Meier method. **RESULTS:** The median age at presentation was 3 years and more than 48% of the patients had Group I disease. Skeleton, skin and lymphoreticular system were the commonly involved organs. Majority (80%) required some form of therapy. The projected overall survival is 63% at 10 years and mean survival is 118 months. Seventeen percent of surviving patients developed long-term sequelae. **CONCLUSIONS:** The clinico-biologic profile of LCH patients in India is largely similar to international patterns except a higher incidence of lymphoreticular involvement. Majority of the patients respond favorably to therapy and have a good outcome, except a subset of Group I patients who warrant enrolment in clinical trials with innovative therapeutic strategies to improve outcome.

Key words: Clinical profile, Langerhans cell histiocytosis, outcome

Introduction

Langerhans' cell histiocytosis (LCH) is a rare, predominantly childhood disease.[1-3] It occurs due to clonal proliferation of bone marrow-derived Langerhans' cells leading to myriad clinical presentations and variable outcomes.[4] The last decade has seen the maximum efforts to categorize LCH into distinct subgroups with predictable behavior, while simultaneously trying to improve outcome.[5-9] We, hereby, present a descriptive analysis of our LCH patients at a large tertiary cancer center reflective of this period and evaluate the utility of recent classification systems to assess the outcome.

Materials and Methods

This is a retrospective observational study whereby the medical records of all patients referred to our hospital from January 1987 to December 2002 with histologically proven diagnosis of LCH established by examination of fresh and review slides were reviewed. Additional Immunochemistry and/or electron microscopy was done whenever required. Minimum investigations done in all cases at presentation included complete blood count (CBC), Biochemical parameters including LFT, RFT, uric acid, LDH, radiology including skeletal survey and chest X-ray, imaging

including ultrasonography abdomen and bone marrow aspirate and biopsy-morphological studies. Detailed investigations of involved systems were done by further special tests such as CT scan/MRI of CNS or thorax, radionuclide scanning, pulmonary function tests, hormonal assays or function tests when indicated by clinical suspicion or indicative abnormal initial investigations. Standard consensus criteria adapted from the LCH trials [Table 1] were retrospectively applied to define organ involvement, classify risk groups and assess treatment response and outcome. The response to treatment and disease status were assessed at the end of 3 and 6 cycles of chemotherapy and again at the end of second-line and/or salvage therapy. When therapeutic intervention entailed observation, surgery, radiation or a point intervention, evaluations were done 3 and 6 months post-intervention to maintain the uniformity of assessment. Similar assessments were made at the last recorded follow-up. Statistical analyses were done by Student's '*t*' test and Test for proportion. Survival estimates were based on the Kaplan-Meier method. Analyses were computed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA). The results were compared with available literature. Since this was a retrospective observational study ethical clearance was not sought.

Results

Fifty-two patients with a confirmed diagnosis of LCH were eligible. The median age was 3 years and median follow-up was 16 months (range 1-183 months) with 35 cases followed for more than 6 months. Patient characteristics are shown in Table 2.

Clinical features

The skeletal system was the most commonly involved system. The classical lytic lesions, often with adjacent soft tissue swelling, were detected either incidentally or on investigation of a swelling by imaging. Pain occurred in only two patients with lesions in weight-bearing bones. The calvarium accounted for 63% of skeletal involvement followed by lesions of the base of skull bones, maxilla and mandible. "CNS risk" lesions were present in five patients, usually as intracranial extensions of surrounding bony lesions. Two of these subsequently developed diabetes insipidus (DI). The other flat and long bones were infrequently involved. Bone scan done

Table 1: Definitions of risk-organ involvement

	System	Criteria
Risk systems	Hematopoietic	
	(a) CBC	1. Hb < 10 g% or < 9 g% in infants with IDA excluded
		2. Total leukocyte count < 4000/cmm
		3. Platelet count < 100,000/cmm
	(b) Bone marrow aspirate/biopsy	1. Morphology
		2. Positive markers on IHC
	Spleen	1. Palpable > 2 cm confirmed on USG
		2. Infiltrates on USG
	Liver	1. Palpable > 3 cm confirmed on USG
		2. Deranged liver function tests
		3. Ascites or edema
		4. Histopathological confirmation
	Lungs	1. Typical changes on CT thorax
		2. Histopathological confirmation
		3. Suggestive X-rays in a confirmed case
Special sites	CNS risk disease	1. Orbital, temporal bones
		2. Mastoid, sphenoid, zygomatic, ethmoid, maxillary sinuses with intracranial extension on CT/MRI
	Vertebral column	Vertebral lesions with intraspinal extension

IDA - Iron deficiency anemia, CBC - Complete blood count, IHC - Immune histochemistry, USG - Ultrasonography, CT - Computerized tomography, MRI - Magnetic resonance imaging, NB - With modifications from criteria of LCH III trial.

Table 2: Study group characteristics (n = 52)

S. no.	Characteristic	n (%)
1.	Age	Median - 3 years (1 month to 62 years)
2.	Males: females	2:1
3.	Socioeconomic strata	
	Low	31 (59.6)
	Middle	19 (36.5)
	High	2 (3.8)
4.	Organ involvement	
	Skeletal system	46 (92)
	Skin	12 (23)
	Lymphadenopathy	27 (52)
	Lungs	8 (15)
	Hepatic	14 (27)
	Spleen	13 (25)
	Hematological	19 (37)
	Endocrine	5 (9)
	Intestinal	1 (2)
5.	Risk groups	
	Group I	23 (44)
	Group II	7 (13)
	Group III	12 (23)
	Group IV	10 (19)

in selected cases did not have any added diagnostic value over conventional skeletal survey. The frequency of various organ involvement is given in Table 2.

Clinically significant lymph nodes were the second commonest disease site, with cervical nodes involved in 45% patients followed by axillary and inguinal (one-third of cases each) involvement. Mediastinal lymph nodes were enlarged in three patients. Majority (60%) of cases had histopathological confirmation on lymph node biopsy, while another 20% were reported as "Reactive" Lymph nodes. The remaining 20% cases with significant lymphadenopathy did not undergo a node biopsy either due to deep location (mediastinal/abdominal) and/or availability of another easily accessible biopsy site.

Dermal involvement was seen commonly in scalp (75%), face, limbs and trunk (40-60%). Papular rash was the commonest lesion, while seborrheic dermatitis was less frequent. Diffuse skin pigmentation and mucocutaneous ulcers were seen in two patients each.

Approximately half of the cases could be confirmed histopathologically.

Splenomegaly was frequent in our patients (25%). Nineteen cases (36.5%) had hematological involvement based on deranged peripheral blood parameters. Anemia as defined by grouping criteria [Table 1] was common to all, while one had thrombocytopenia. Five had bone marrow involvement on morphological assessments of aspirate smears or marrow biopsy specimens. CD1a studies were not done on any marrow specimen.

Lungs (based on suggestive imaging) were involved in eight patients. Liver involvement was common. Three patients had obstructive hepatitis, of which one went on to develop cirrhosis. Intestinal involvement suggested by profuse chronic diarrhea was seen in one patient.

Endocrine involvement manifested by DI was seen in five cases. One of these patients also had growth retardation suggestive of possible growth hormone deficiency. Other manifestations included chronic suppurative otitis media seen in six, while constitutional symptoms were seen in two patients.

The onset of involvement of various organ systems with relation to time of presentation showed trends reflective of the biology of the disease [Figure 1]. Most of the patients had consistent temporal pattern of disease progression, with skin and skeletal system being the earliest to get involved and other visceral organs later in the neoplastic continuum heralding an aggressive phase of disease.
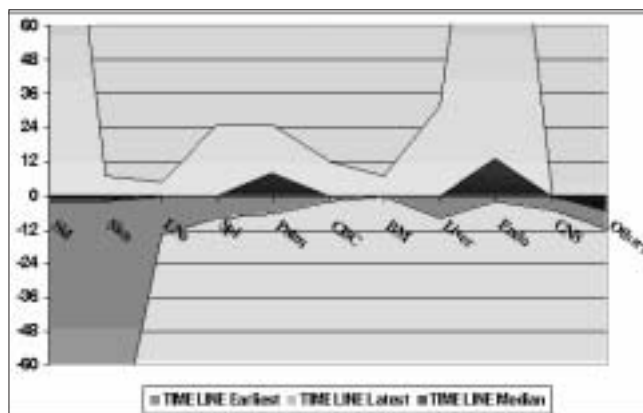

Figure 1: Timeline of detection of involvement of various organ systems
Skl - skeletal, Skn - skin, LN - lymph nodes, Spl - spleen, Pulm - pulmonary, CBC - complete blood counts, BM - bone marrow, Endo - endocrine system, CNS - central nervous system. "0": At time of presentation to our center. Timeline earliest: Time of detection of organ system involvement prior to presentation in months. Timeline latest: Time of detection of organ system involvement after presentation in months. Timeline median: Median time of detection of organ system involvement with relation to time of presentation.

Grouping

Forty-four percent patients (*n* = 23) were classified as Group I with involvement of one or more "risk" organs [Table 1]. Hematopoietic system involvement accounted for the majority (*n* = 19). Significantly, six patients were classified in this group only on the basis of anemia as defined in Table 1. Group II, III and IV lesions formed more than half the patients [Table 2].

Prior treatment

Twenty-nine percent patients had prior treatment at a median of 2 months before presentation (range −27 to −1 month). In half of these, surgery - usually curettage of an isolated bony lesion - had been done. One patient had received radiotherapy. Five patients with multi-system disease had received chemotherapy and three of these had progressive disease at presentation.

Initial treatment

Sixty percent of our patients received chemotherapy as initial treatment. One-fifth (*n* = 10) received radiotherapy, while nine were kept on surveillance. One patient each underwent surgery or intra-lesional steroids as definitive therapy. Etoposide-based chemotherapy (150 mg/m^2/day over 3 days 4 weekly, 1-6 cycles, median 3) was the commonest regime (*n* = 20) usually along with methyl prednisolone (30 mg/kg/day infusion for 3 days 4 weekly, 1-6 cycles, median 3) (*n* = 14) or other drugs (*n* = 6). Cyclophosphamide (400 mg/m^2 IV 3 weekly), vincristine (1.5 mg/m^2 3 weekly) and prednisolone (40 mg/m^2 × 5 days) (COP regime) were used in another 10 patients. A median of 6 cycles was received by all (range 1-6). Twenty-one patients received second-line treatment consisting of radiotherapy (*n* = 4) and polychemotherapy (*n* = 17). The latter group included three cases that received COP, five each of vinblastine (6 mg/m^2) or etoposide with or without steroids (1-6 cycles, median 4) and two each of cyclosporine (5 mg/kg/day for 1-6 month, mean 3.5 month) and cladiribine (0.15-0.35 mg/kg/day × 5 days). Two patients received cyclosporine after failing second-line treatment.

Disease state and response

While 40% had good response and inactive disease at the end of 6 cycles/month from initial therapy, 33% had progressive disease. Of the 21 patients requiring second-line treatment, about 50% showed a complete response and clinically inactive disease, 30% had progression and the rest had stable disease.

Outcome

Majority of patients (58%) were in CR at last follow-up, 13% had stable disease and the remaining 29% had progressive disease. Of these, five died of the disease in hospital and the remaining patients opted for best supportive care only. Overall survival of the study cohort was 62.78% and mean survival was 118 months [Figure 2].

Patients with Group I disease had the worst outcome, with almost all the fatalities belonging to this group. Fatalities included cases classified in this group on the basis of anemia alone. The projected overall survival at 10 years in Group I was 35% as compared to 68% in Group II and almost 100% in the other groups. The outcome of non-Group I patients remained excellent irrespective of the treatment offered [Figure 3].

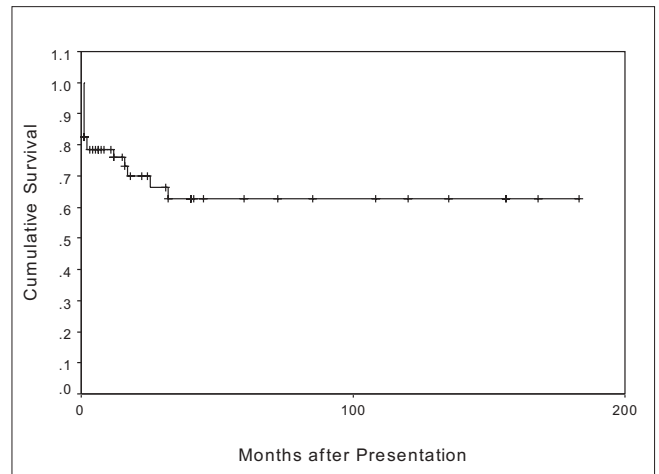The outcome was also assessed according to the initial treatment offered, as this was more reflective of the

Figure 2: Overall survival
Overall survival: 62.78% (SE - 7.88%); mean survival 118.51 months (±13.41, 95% CI 92.23-144.78 month).

Figure 3: Survival by grouping
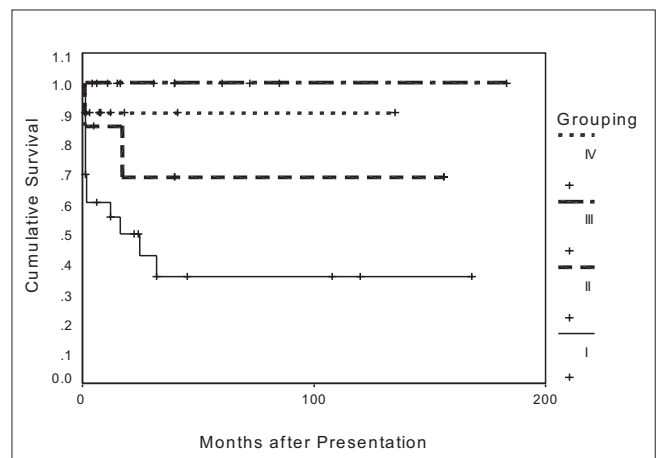**Group I survival: 35.53% (SE - 11.52%); mean survival 65.71 months (±17.95, 95% CI 30.53-100.90 months). Group II survival: 68.57% (SE - 18.63%); mean survival 110.03 months (±27.15, 95% CI 56.81-163.25). Difference in survival between groups I and II was statistically significant (*P* = 0.0012). Groups III and IV had no mortality. The solitary event in group IV was a loss to follow-up.**

risk assessment at the time of diagnosis. Predictably, the chemotherapy group did the worst, as this was offered to those perceived to be most at risk [Figure 4].

Thirty-four surviving patients who were followed-up for at least six months were evaluated for sequelae. At a median follow-up of 40 months (range 6-183), six patients (17%) had sequelae. DI occurred in two patients. Both were among five patients who had "CNS risk" disease at diagnosis. Two patients had suboptimal scholastic performance. Both had received radiotherapy for skeletal lesions in the calvarium. One of these patients also had obesity. One patient each had pulmonary (restrictive lung disease) and hepatic sequelae (cirrhosis). In the latter, death occurred as a result of the sequelae.

Discussion

LCH is a rare childhood malignancy. Only 52 cases were registered over the last 17 years at our center, which gets at least 20,000 new cases of malignancies per year in all age groups (Hospital Registry). There has been unprecedented progress in the understanding of this enigmatic disease over the past few years by means of collaborative trials and large single institutional studies.[1,5-8] Foremost is that multi-organ involvement has worse outcome than single-organ disease and needs some form of cytotoxic therapy and among those with multi-organ disease, some patients are more "at risk" for disease progression, sequelae and death.[5-11]

Clinical features in our patients were similar in nature and extent to those reported in most large series. Skeletal involvement with or without other sites occurs in 80 to 100% of patients in most large series and

Figure 4: Survival by treatment option
Chemotherapy group survival: 50.40% (SE - 10.38%); mean survival 90 months (±16.06, 95% CI 58.52-121.48 months); other therapies survival: 85.71% (SE - 07.64%); mean survival 157 months (±13.90, 95% CI 129.76-184.24 months).

was 92% in our series.[10,12,13] Radionuclide scanning provided no additional benefit as against its suggested complementary role in recent studies.[14-17]

Dermal involvement (25%) was less common in contrast to 35-50% cases in most series.[12,17] This is likely to be due to underdiagnosis of minor lesions such as seborrheic dermatitis. Lymphadenopathy was more common as compared to less than 10% in literature.[18] This, to some extent, may have been contributed by the high incidence of reactive adenopathy in our country, but warrants further investigation.

Similarly, splenic involvement was much higher (25%) in our patients as compared to 5% at presentation in a French series.[12] Conversely, pulmonary involvement (15%) was less frequent, compared to 50% of patients in a large series that also included patients with isolated abnormal pulmonary function tests.[19]

Hepatomegaly is often present in systemic disease and pathological changes might be present in the liver on histology, even in the absence of liver dysfunction.[20] In our series, a quarter of the patients with multi-systemic disease had hepatomegaly. Only one with associated hepatic dysfunction developed cirrhosis.

DI afflicts nearly one-third of all patients with multi-system LCH and can develop at any time during the course of the illness.[5,6,13,18,21,22] This was reflected in our patients where it occurred in five patients at a variable time during the disease course (median 11 months; range 20-31 months). The regular and prospective use of water-deprivation test in our study cohort might have ensured maximum detection of cases. CNS risk lesions predated DI in two of five cases.

In the present study, risk perception remained a matter of interpretation that varied over time and observer. We, therefore, retrospectively applied uniform risk and response criteria as per the current understanding to make the analysis more meaningful. The projected overall survival of all cases at 10 years was just over 60% with a mean observation time of 118.15 months [Figure 2]. The survival of patients with multi-system risk disease (Group I) was just over 30% [Figure 3]. The occurrence of patients classified in this group solely for anemia underlines the importance of this finding in LCH. This group compared poorly to Group II patients with 68% survival, the only other group to have any mortality at all. Here too, the only two patients, who died shortly after presentation, had one of the risk-organs involved pre-terminally. It is likely that involvement of these systems was missed at initial assessment. Prior treatment is unlikely to have
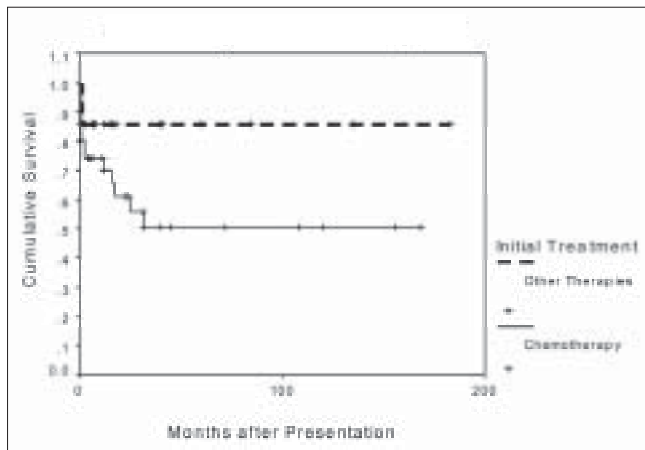
impacted the outcome as two-thirds were low-risk at presentation and had received only local therapy. In the analysis by treatment group too, early mortalities occurred in the radiotherapy/other therapies group only in two patients with risk-organ systems involved [Figure 4]. In our study, as in literature, approximately one-third of patients had poor prognosis, with survival just above 30%, irrespective of the type of systemic therapy given. These patients were correctly identified using the current criteria of high-risk-organ system involvement, despite the limitations of applying such criteria retrospectively.[5-11]

In the earliest European studies, patients with multi-system disease and evidence of organ dysfunction were considered "at risk" and had an overall survival of 81%. However, dissimilarity in the grouping criteria prevents any meaningful comparison with these studies.[23] Furthermore, the stratification of patients into responders and non-responders early in their treatment at 6 weeks closely identified poor prognostic groups.[5,7,12,24] The importance of early response could not be assessed in our study due to its retrospective nature.

Sequelae in LCH have usually been limited to bony deformities, teeth loss and endocrine disorders.[8,13] No bony deformities were seen in our patients, while endocrine disorders were seen in a few patients.

Acknowledgment

References

1. Oberman HA. Idiopathic Histiocytosis - a clinicopathological study of 40 cases and review of the literature on eosinophilic granuloma of bone, Hand Schuller-Christian disease and Letterer-Siwe disease. Pediatrics 1961;28:307-27.
2. Egeler RM, D'Angio GJ. Langerhans cell Histiocytosis. J Pediatr 1995;127:1-11.
3. Malpas JS, Norton AJ. Langerhans cell histiocytosis in the adult. Med Pediatr Oncol 1996;27:540-6.
4. William CL, Busque L, Griffith BB, Favara BE, McClain KL, Duncan MH, *et al*. Langerhans cell Histiocytosis (histiocytosis-X) - a clonal proliferative disease. N Engl J Med 1994;331:154-60.
5. Minkov M, Grois N, Heitger A, Potschger U, Westermeier T, Gadner H. Treatment of multisystem Langerhans cell histiocytosis: Results of the DAL-HX 83 and DAL-HX 90 studies. Klin Padiatr 2000;212:139-44.
6. Braier J, Chantada G, Rosso D, Bernaldez P, Amaral D, Latella A, *et al*. Langerhans cell histiocytosis: Retrospective evaluation of 123 patients at a single institution. Pediatr Hematol Oncol 1999;16:377-85.
7. Gadner H, Grois N, Arico M, Broadbent V, Ceci A, Jakobson A, *et al*. Histiocyte society. A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. J Pediatr 2001;138:728-34.
8. Kusumakumary P, James FV. Permanent disabilities in childhood survivors of Langerhans cell histiocytosis. Pediatr Hematol Oncol 2000;17:375-81.
9. Broadbent V, Gadner H, Komp DM, Ladisch S. Histiocytosis syndromes in children II: Approach to complete clinical and laboratory evaluation of children with Langerhans cell histiocytosis. Med Pediatr Oncol 1989;17:492-5.
10. Lahey E. Histiocytosis X: An analysis of prognostic factors. J Pediatr 1975;87:184-9.
11. KusumaKumary P, Priyakumari T, Chellam VG, James FV, Nair MK. Langerhans cell histiocytosis in children less than 2 years of age. Indian Pediatr 1999;36:29-36.
12. The French Langerhans' Cell Histiocytosis Study Group. A multicentre retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between 1983 and 1993. Arch Dis Child 1996;75:17-24.
13. Willis B, Ablin A, Weinberg V, Zoger S, Wara WM, Mathay KK. Disease course and late sequelae of Langerhans cell histiocytosis: 25 year experience at the University of California, San Fransisco. J Clin Oncol 1996;14:2073-82.
14. Crone-Munzbrock W, Brassow F. A comparison of radiographic and bone scan findings in histiocytosis X. Skeletal Radiol 1983;9:170-3.
15. Dogan AS, Conway JJ, Miller JH, Grier D, Bhattathiry MM, Mitchell CS. Detection of bone lesions in Langerhans cell histiocytosis: Complementary roles of scintigraphy and conventional radiography. J Pediatr Hematol Oncol 1996;18:51-8.
16. Meyer JS, Harty MP, Mahboubi S, Heyman S, Zimmerman RA, Womer RB, *et al*. Langerhans cell histiocytosis: Presentation and evolution of radiologic findings with clinical correlation. Radiographics 1995;15:1135-46.
17. Munn S, Chu UA. Langerhans cell histiocytosis of the skin. Hematol Oncol Clin North Am 1998;12:247-58.
18. 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;37:108-14.
19. Ha SY, Helms P, Fletcher M, Broadbent V, Pritchard J. Lung involvement in Langerhans cell histiocytosis: Prevalence, clinical features and outcome. Pediatrics 1992;89:466-9.
20. Arico M, Egeler RM. Clinical aspects of Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998;12:247-58.
21. Nanduri VR, Bareille P, Pritchard J, Stanhope R. Growth and endocrine disorders in multisystem Langerhans cell histiocytosis. Clin Endocrinol (Oxf) 2000;53:509-15.
22. Dunger DB, Broadbent V, Yeoman E, Seckl JR, Lightman SL, Grant DB, *et al*. The frequency and natural history of diabetes insipidus in children with Langerhans-cell histiocytosis. N Engl J Med 1989;321:1157-62.
23. Lahey E. Histiocytosis X - comparison of three treatment regimes. J Pediatr 1975;87:179-83.
24. Minkov M, Grois N, Heitger A, Potschger U, Westermeier T, Gadner H, *et al*. Response to initial treatment of multisystem Langerhans cell Histiocytosis: An important prognostic indicator. Med Pediatr Oncol 2002;39:581-5.