International Journal of Research in Medical Sciences
Jacob RK et al. Int J Res Med Sci. 2020 Jun;8(6):2128-2135
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20202255

Original Research Article

Retrospective analysis of clinical manifestations and treatment outcomes of patients diagnosed with langerhans cell histiocytosis from a tertiary cancer hospital in South India

Roshan Koshy Jacob, Shashidhar V. Karpurmath*, Manjunath Nandennavar, Veerendra Angadi

Department of Medical Oncology, Vydehi Institute of Medical Sciences and Research Centre, Bengaluru, Karnataka, India

Received: 20 March 2020
Accepted: 22 April 2020

***Correspondence:**
Dr. Shashidhar V. Karpurmath,
E-mail: shashivk5@gmail.com

ABSTRACT

Background: Langerhans cell histiocytosis (LCH) comprises a diverse group of disorders where pathologic Langerhans cells accumulate in a variety of organs. Aims and objectives of the study is to analyse the clinical manifestations and treatment outcomes of patients diagnosed with LCH in a tertiary cancer hospital in South India.
Methods: Retrospective analysis of the case records of patients presenting with histological proven case of LCH over a period of 7 years from 2011 to 2018, being treated at Vydehi Institute of Medical Sciences and Research Centre.
Results: 10 patients with biopsy proven LCH were included. The median age of diagnosis was 8 years (range 1 to 73 years) and 3 patients aged 18 years or older at the time of diagnosis. The male: female ratio was 3:2. Multisystem involvement was found in 4 patients (40%) and Single system Involvement in remaining 6 patients. Isolated bone lesions were found in 4 patients (40%), 1 patient had isolated Lymph node involvement; 1 patient had oral cavity lesion. None of the 4 patients with multisystem diseases had skin/mucosal involvement; 3 had bony involvement, 2 patients had lung involvement. One patients with multisystem disease expired while 5 patients were lost to follow-up. 4 out of the 10 patients are on regular follow-up and are in remission.
Conclusions: Despite limitation by the retrospective nature, this descriptive study was done to provide further disease information regarding Indian population. Data from this study clearly confirms the known fact that most of the patients with Single System LCH have a very good response rate. Patients with multisystem disease have the highest risk of disease related mortality and morbidity as one among the 4 patients with multisystem disease died just after initiating treatment.

Keywords: Indian, Langerhans cell histiocytosis, Multisystem, Single system

INTRODUCTION

The first descriptions of what authors now recognize as Langerhans Cell Histiocytosis (LCH) appeared in the early 1900s as case reports and case series. Hand-Schüller-Christian disease was described as eosinophilic granulomatous lytic bone lesions, diabetes insipidus, and exophthalmos in young children. Letterer-Siwe disease was described in infants with aggressive and generally fatal systemic disease, including skin, liver, spleen, and bone marrow infiltration by reticuloendothelial cell.[1] Langerhans Cell Histiocytosis (LCH) is a reactive proliferative disease of unknown pathogenesis characterised by infiltration of bone marrow derived pathological Langerhans cells in one or more organs. The involved organs include bone, skin/mucosa, lung,

hypothalamus/ posterior pituitary gland, lymph nodes, liver, spleen, bone marrow and various soft tissues.[2]

A breakthrough in understanding of LCH pathogenesis came with the discovery and validation of recurrent BRAF-V600E mutations in over 50% of LCH lesions. BRAF, a central kinase of the MAPK pathway, regulates critical cellular functions. The BRAF-V600E mutation induces constitutive activation of downstream MAPK/ERK kinase (MEK) and extracellular signal-regulated kinase (ERK) proteins. Whole-exome sequencing and targeted sequencing recently identified recurrent mutations in MAP2K1, encoding MEK1, in 33% to 50% of LCH lesions in which BRAF is not mutated.[3]

The current classification of LCH is based on extent of organ systems involved at diagnosis. Single system disease (SS) LCH (involvement of one organ or system) most commonly involves skin and bone but can involve other organ systems. Single system involvement can be unifocal or multifocal in nature and usually carries an excellent prognosis. In contrast those patients who have multisystem (MS) or disseminated disease (>2 organ systems involved) have a less favorable prognosis. LCH most commonly presents in infancy and early childhood. Patient frequently have some cutaneous manifestations which may mimic seborrheic dermatitis or eczematous lesions usually of the scalp especially in younger patients. Patients may have skin limited disease that can resolve spontaneously.[4]

LCH cells are large epithelioid cells enriched with ample eosinophilic cytoplasm and indented or reniform nuclei. They are easily identified as they tend to show heavy and diffuse infiltration, particularly in skin and bone. Eosinophils are typically scattered throughout the infiltrate and though they are usually conspiciously present, their presence is not mandated to achieve the diagnosis. Mitotic figures and necrosis are features that can be seen in LCH. However, atypical mitosis and marked pleomorphism are features not seen in LCH and should raise the possibility of Langerhans cell sarcoma.[5]

LCH is diagnosed by clinico-pathological correlation, with the histological presentation as the common characteristic across disease categories. Langerhans cells are composed of eosinophilic to amphophilic cytoplasm, and contain deeply indented, cerebriform nucleus. It is confirmed with reactivity of S-100, CD1A or CD 207 antibodies.[6]

The clinical course and outcome of the patients varied in wide range from single system diseases often cured by surgical curettage to generalized and fulminant diseases resulting in life-threatening organ dysfunction.[7]

The Histiocyte society initiated international randomized clinical trials using standard diagnostic strategies and disease monitoring methods. They used a treatment backbone of vinblastine and steroid. LCH I (1991-1995) compared vinblastine vs etoposide, together with pulse steroid for 6 month duration in patients with MS-LCH. Both the arms were equivalent in all criteria observed. In LCH II (1996-2001) patients were stratified based on risk factors i.e. <2 years of age and/or risk organ involvement. Patients were randomized to receive Prednisone and vinblastine alone or intensified by adding etoposide to the combination. Also 6 Mercaptopurine was given during continuation phase in both groups. The total duration of therapy was 6 months. In both the arms, those patients with risk organ disease had higher survival rate than LCH I suggesting that intensification in therapy improved survival. In LCH III (2001-2008) those with risk organ disease received more intensive treatment by adding methotrexate and by increasing the duration to 12 months. In patients without risk organ disease, they were randomized to receive 6 or 12 month therapy. In patients without risk organ disease, they were randomized to receive 6 or 12 month therapy.[4]

The aim of this study is to characterise the clinical manifestations and treatment outcome of LCH patients by retrospectively analysing the clinical data of patients diagnosed with LCH in Vydehi Institute of Medical Sciences and Research centre.

METHODS

This study is a retrospective analysis of the case records of patients presenting with histological proven case of Langerhans Cell Histiocytosis over a period of 7 years from 2011 to 2018, being treated at Vydehi Institute of Medical Sciences and Research centre, India.

Inclusion criteria

- All cases of Langerhans cell Histiocytosis diagnosed based on histopathology/IHC

Exclusion criteria

- Patients without the histopathological confirmation

This is retrospective case record review. Including 10 patients.

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5% level of significance.

The following assumptions on data is made;

- Dependent variables should be normally distributed
- Samples drawn from the population should be random, Cases of the samples should be independent

Statistical analysis

The Statistical software namely SPSS 22.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

RESULTS

A total number of 10 histologically proven cases of Langerhans Cell Histiocytosis who presented over a period of 7 years from 2011 to 2018 to the Department of Medical Oncology, Vydehi Institute of Medical Sciences, Bangalore were included in the study. The patients were selected according to the inclusion and exclusion criteria as mentioned earlier. All demographic details were noted in the proforma along with investigations carried out initially.

In this study the median age of diagnosis was 8 years (range 1 to 73 years) and 3 patients aged 18 years or older at the time of diagnosis. Data on the age distribution of patients included in the study is shown in Table 1. Most of the patients were in the age group of less than 10 years.

Table 1: Age distribution of patients studied.

Age in years	No. of patients	%
<10	6	60.0
10-20	1	10.0
>20	3	30.0
Total	10	100.0

Mean ± SD: 20.80±24.47

The male: female ratio was 3: 2. A total of 4 females and 6 males were included in the study, as depicted in Figure 1.

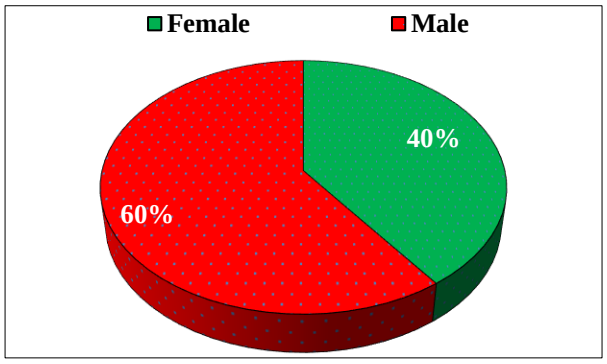

Figure 1: Gender distribution of patients studied

Among the study population of 10 patients, 5 patients presented with head and neck swelling. 2 patient presented with respiratory symptoms. The distribution of presenting symptoms are mentioned in Table 2.

Only 1 patient had proptosis among the 10 patients and this patient had bilateral proptosis. 4 out of the 10 patients had palpable lymph nodes on examination. Skin involvement was seen in 2 of the patients, one patient had generalised rash and 2nd patient had eczema. The clinical signs distributions of the patients studied is mentioned in Figure 2.

Table 2: Presenting symptoms distribution of patients studied.

Presenting symptoms	No. of patients	%
Cough with expectoration, fever	2	20.0
Generalised pruritis	1	10.0
Pain in the left leg 2 years	1	10.0
Proptosis, skin rash	1	10.0
Swelling in Head and Neck region	5	50.0
Total	10	100.0

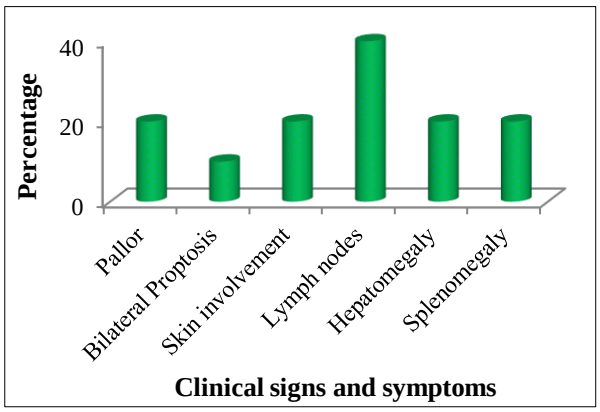

Figure 2: Clinical signs and symptoms distribution of patients studied.

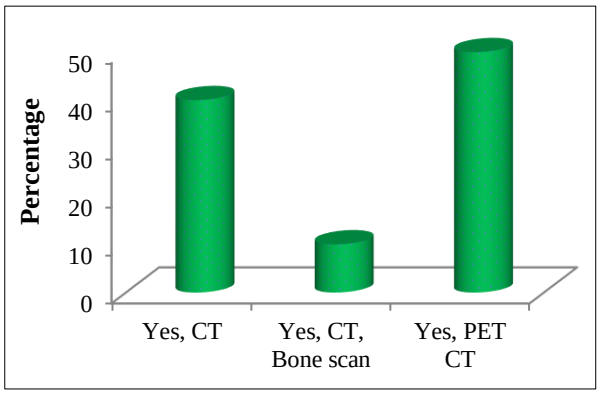

Figure 3: Imaging done.

In this study, 6 out of the 10 patients had anaemia. AST and ALT was found to be elevated in 2 out of the 10 patients while 4 patients had elevated alkaline phosphatase. Blood investigations distributions of the studied patients are mentioned in Table 3.

In this study majority of the patients (50%) underwent PET-CT for staging. 4 patients underwent only CT scan while one patient underwent CT scan and bone scan. The details of the imaging done is mentioned in Figure 3.

Table 3: Blood investigations

variables		No. of patients (n=10)	%
Hemoglobin (g/dl)	<12	6	60.0
	12-16	2	20.0
	>16	0	0.0
Total Count	<10	2	20.0
	10-12	2	20.0
	>12	4	40.0
Platelets	<350	6	60.0
	350-500	1	10.0
	>500	1	10.0
Neutrophils	<60	3	30.0
	60-80	3	30.0
	>80	1	10.0
Creatinine (mg/dl)	<1.1	9	90.0
	>1.1	0	0.0
Total Bilirubin	<0.5	2	20.0
	0.5-1	5	50.0
	>1	2	20.0
Direct Bilirubin	Nil	4	40.0
	<0.3	3	30.0
	0.3-0.6	2	20.0
	>0.6	1	10.0
Albumin	Nil	3	30.0
	<2.5	0	0.0
	2.5-3.5	1	10.0
	>3.5	6	60.0
SGOT	0	0	0.0
	0-42	7	70.0
	>42	2	20.0
SGPT	0	0	0.0
	0-48	7	70.0
	>48	2	20.0
Alkaline Phosphate	<25	0	0.0
	25-125	5	50.0
	>125	4	40.0

In this study 2 out of the 10 patients had bone marrow involvement, 7 patients had bone lesions, none had brain involvement, one patient had soft tissue involvement and 2 patients had lung involvement.

Table 4: Single system or multisystem.

Single system or multisystem	No. of patients	%
Multisystem	4	40.0
Single System	6	60.0
Total	10	100.0

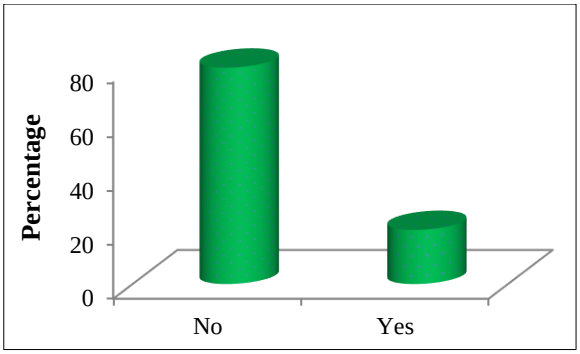

Figure 4: Bone marrow Involved distribution of patients studied.

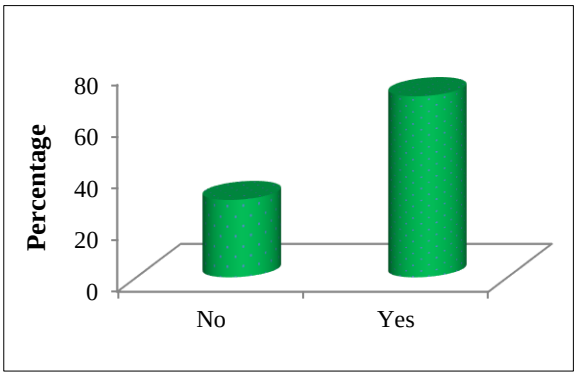

Figure 5: Bone lesions distribution of patients studied.

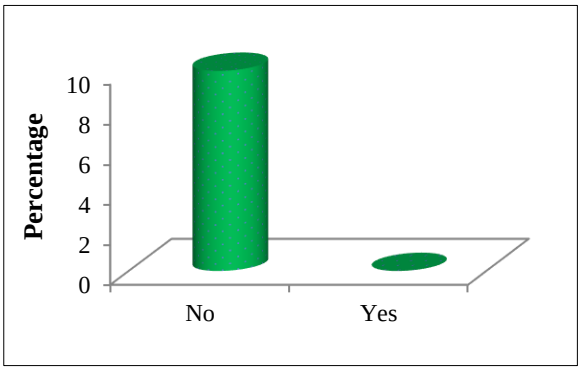

Figure 6: Brain distribution of patients studied.

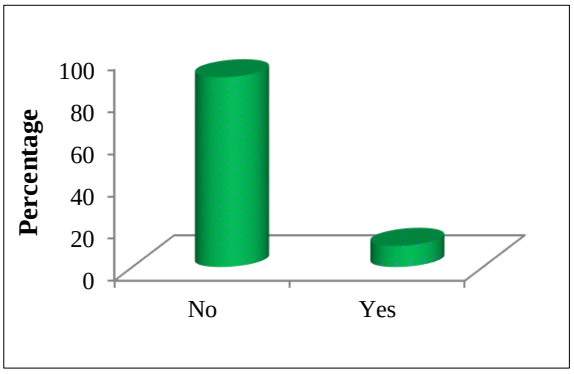

Figure 7: Soft tissue involvement distribution of patients studied.

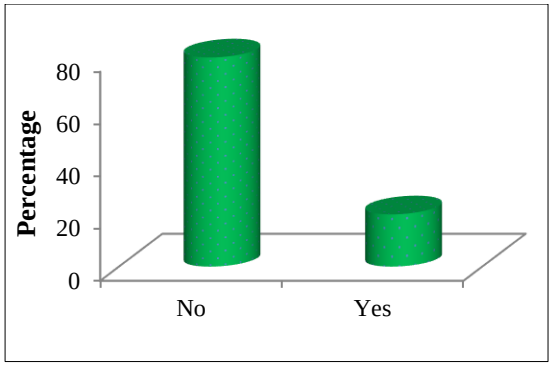

Figure 8: Lung involvement distribution of patients studied.

The details regarding the diagnosis distribution is mentioned below in Figure 4 to Figure 8. Among the 10 patients studied, 4 patients had multisystem disease while 6 patients had single system disease as shown in Table 4.

In this study 8 out of the 10 patients underwent treatment of which 4 patients received only chemotherapy as per the LCH-3 protocol, 3 patients underwent surgery followed by chemotherapy as per LCH-3 protocol and 1 patient underwent only surgery. This is depicted in Table 5 and 6.

Table 5: Treatment taken distribution of patients studied.

Treatment Taken	No. of patients	%
No	2	20.0
Yes	8	80.0
Total	10	100.0

Table 6: Regimen used distribution of patients studied.

Regimen used	No. of patients	%
Nil	2	20.0
LCH-3	4	40.0
Surgery	1	10.0
Surgery, LCH-3	3	30.0
Total	10	100.0

Table 7: Interim assessment done distribution of patients studied.

Interim assessment done	No. of patients	%
No	4	40.0
Yes	6	60.0
Total	10	100.0

Among the 7 patients who undertook chemotherapy, interim assessment was done in 6 of the patients of which 5 patients were in Complete Remission, 1 patient had Partial Remission and 1 patient had progressive disease as shown in Table 7 and Table 8. End of treatment assessment was done only in 2 of these patients and both these patients were in Complete Remission which can be noted in Table 9 and 10.

Table 8: Interim response distribution of patients studied.

Interim response	No. of patients	%
No	3	30.0
CR	5	50.0
PR	1	10.0
Progression	1	10.0
Total	10	100.0

Table 9: End of treatment assessment.

End of treatment assessment	No. of patients	%
No	8	80.0
Yes	2	20.0
Total	10	100.0

Table 10: End of treatment response.

End of treatment response	No. of patients	%
Nil	8	80.0
CR	2	20.0
Total	10	100.0

Among 4 out of the 10 patients are alive and in complete remission, 3 of these patients are on regular follow-up. 5 patients are lost to follow-up while 1 patient with multisystem disease expired while on treatment. This is depicted in Table 11.

Table 11: Status at last follow-up.

Status at last follow-up	No. of patients	%
Died	1	10.0
Alive, in remission	3	30.0
Alive, in remission (updated over phone)	1	10.0
Lost in follow up, phone number not reachable	5	50.0
Total	10	100.0

DISCUSSION

Langerhans cell histiocytosis (LCH) is caused by the infiltration of bone marrowderived pathological Langerhans cells in one or more organs. The involved organs include bone, skin/mucosa, lung, hypothalamus/posterior pituitary gland, lymph nodes, liver, spleen, bone marrow and various soft tissues.[1]

In a retrospective study done in Taiwan, 35 biopsy proven patients of LCH were identified between 1990

and 2006. Median age was 3 years (Range 2 months to 58 years). Male:Female ratio was 3:2. Multisystemic involvement was found in 15 patients (42.8%) and isolated bone lesions were found in 12 patients (34.2%), 3 patients had isolated cutaneous involvement; the remaining 5 patients had solitary lymph node, lung, thyroid gland, submandibular gland or extraocular soft tissue involvement, respectively. Ten of the 15 patients with multisystemic diseases had skin/mucosal involvement; 10 had bony involvement. All three patients that expired had multisystemic disease. In another case series of 13 cases of LCH of the oral cavity, majority of 61.53% (8/13) of cases occurred in infants and adolescents with female predominance (61.53%). Out of all the lesions, 61.53 % occurred intraosseously; with majority 53.82% (7/13) presenting on the posterior mandible and 15.38% (2/13) in the anterior mandible. Five lesions extended to involve more than one site. Radiologically all intraosseous lesions presented as osteolytic lesions with ill-defined or well defined margins.[2]

In another retrospective analysis done in Children's Hospital New Orleans during 2005-2014, a total of 41 patients who were diagnosed and treated for Langerhans cell histiocytosis were studied. The distribution by year of diagnosis at certain time frames are even throughout the 10 year duration. Out of the total 41 patients, 20 (49%) presented with single system involvement and 21 (51%) presented with multisystem disease. Of those with single system involvement, 17 (42%) presented with bony involvement and 3 (7%) presented with only skin manifestations. Of those 17 patients who had bony disease, 13 (76%) presented with unifocal bone involvement and 4 (24%) presented with multifocal bony lesions. 21 patients presented with multisystem disease at presentation. 13 (62 %) presented with risk organ involvement and 8 (38%) patients did not have risk organ involvement. Of the patients with risk organ involvement, the most common site was liver (11 patients), spleen (7 patients) and bone marrow disease (4 patients). Out of 41 total patients 22 patients (54%) were male and 19 patients (46%) were female. The age of diagnosis ranged from 0.2 years to 16 years with a mean age of presentation of 2.1 years. 22 (54%) of this patients were younger than 2 years at presentation. Of the 13 patients with unifocal bone disease, 9 patients were treated by orthopedic service with curettage only. 4 of these patients received chemotherapy as part of their treatment. All 4 patients with single system - multifocal bone lesions were treated with chemotherapy. All of these patients had either "Special Site" or "CNS risk "lesion involvement. Of the 3 patients who presented with skin lesions only, 2 were treated with chemotherapy and one received treated local treatment.[4]

In a study done by Eden et al, 13 cases of LCH of oral cavity were studied. The majority of 61.53% (8/13) of cases occurred in infants and adolescents with female predominance (61.53%). Out of all the lesions, 61.53 % occurred intraosseously with majority 53.82% (7/13) presenting on the posterior mandible and 15.38% (2/13) in the anterior mandible. Five lesions extended to involve more than one site. Radiologically all intraosseous lesions presented as osteolytic lesions with ill-defined or well defined margins. Histopathologically, all lesions at first glance resembled an infection/chronic inflammatory process and contained mixed inflammatory cells including eosinophils. Round mononuclear cells, containing eosinophilic cytoplasms and peripheral indented cerebriform nuclei were only observed under higher magnification. Immunohistochemical investigations with S-100 antibody revealed nuclear and cytoplasmic positivity in mononuclear cells confirming these cells as Langerhans cells. All the patients were treated with complete surgical excision with or without chemotherapy/radiotherapy. They concluded that LCH of oral cavity may have a broad spectrum of clinico-pathological presentations, high degree of clinical awareness is required to arrive at the definitive diagnosis.[6]

In a study done in Chandigarh, 5 patients of LCH were included in a study. Male to female ratio was 3:2 with mean age of 9.4 months. Two out of 5 patients had obvious skull swelling; however, radiography of the skull revealed lytic lesion of skull in 4 cases and 2 had skin rashes. Hepatomegaly was present in 4 cases and 2 of whom also had lymphadenopathy and splenomegaly. All patients had anaemia at the time of presentation. Bone marrow aspiration and trephine biopsy in all 5 cases revealed infiltration by large histiocytes with abundant cytoplasm and coffee bean shaped nucleus. Nodules of these Langerhans cells with admixture of eosinophils were seen on trephine biopsy. Immunohistochemistry showed positivity for CD1a stain.[7]

Tseng et al, reported a case with gradual onset of polyuria and polydipsia at 18 years of age and central diabetes insipidus was diagnosed. Pituitary magnetic resonance imaging (MRI) revealed mild prominent pituitary stalk. Desmopressin was prescribed. Nine years later, progressed photophobia, blurred vision, headache and galactorrhea developed. Pituitary MRI revealed a 0.6 cm infundibular nodule with hypothalamus involvement and perifocal edema. She received Gamma knife therapy. Her symptoms improved and the size of the pituitary lesion decreased. A palpable mass over right retromandibular region was found when she was 29 years old. Aspiration cytology showed histiocytes. Excision biopsy reported Langerhans cell histiocytosis. Bone scan revealed osteolytic lesions at T10 level of vertebra. Whole body computed tomography reported bronchiectasis at bilateral lung base with multiple tiny nodules and some minor cystic-like lesions. She received adult Langerhan cell histiocytosis LCH-A1 protocol therapy with vinblastine and prednisolone. Radiotherapy over T10 spine was performed. She was kept on hormone supplement for panhypopituitarism. The right neck mass and pulmonary cystic lesions shrank gradually. Swelling over thyroid

gland was noted several months later. Fine needle aspiration cytology from the thyroid revealed infiltration of Langerhans cell. The thyroid size decreased after intensive chemotherapy and radiotherapy.[8]

Rao et al, reported a case of 5 year old with a chief complaint of swelling in the left side of the face since 1 and ½ months. Panoramic imaging showed an ill-defined osteolytic lesion extending from the distal aspect of tooth bud of mandibular left permanent second molar till the coronoid process and sigmoid notch of the mandible. Computed tomography (CT) scan of the patient showed areas of ill-defined destruction and pathologic fracture of the ramus of the mandible. Aggressive periosteal reaction was noted giving a sun ray-like appearance. Histopathological examination of incisional biopsy specimen showed extensive proliferation of histiocytes with indistinct cytoplasmic borders and rounded vesicular nuclei with interspersed eosinophils suggestive of LCH. Immunohistochemistry showed positivity for CD68, CD1a, and S-100 confirming the diagnosis. Positron emission tomography revealed no active lesion elsewhere in the body. The patient was treated with surgical corticotomy under general anesthesia of the affected side with extraction of the left mandibular second and third molar tooth buds and child is currently under periodic follow-up.[9]

Case of a 3-year-old boy was reported by Rao DG et al. Child had presented along with his mother with the chief complaint of painful gingival growth in the upper and lower, right and left regions of jaw since 1 month. Intraoral examination exhibited a diffused, erythematous swelling over attached gingiva with respect to 55, 65, 75 and 85 over buccal aspect and 55 and 65 with a palatal aspect. Mucosa over the swelling was ulcerated covered with necrotic slough with tiny bleeding spots with 55, 65, 75 and 85. Orthopantogram revealed multiple areas of bone loss in the left mandibular region. Axial and coronal computed tomography [CT] revealed multiple soft tissue density lesions with irregular and punched out bony destruction noted involving left mandibular, left side of occiput, right maxillary and right temporal bone. Three-dimensional CT revealed multiple osteolytic lesions in relation to maxillary alveolar process, body and ramus of the left side of the mandible. Histopathology revealed hypercellular discohesive singly scattered Langerhans cells which are having abundant eosinophilic cytoplasm with characteristic retiform, convoluted nuclei with distinct longitudinal grooves. Also seen are binucleated and multinucleated cells with similar nuclear features. Background is showing a variable number of lymphocyte, eosinophils and plasma cells and occasional mitosis. The definitive diagnosis of LCH involving multiple bones was considered. It was correlated on the basis of clinical, radiographical and histopathological findings. The patient was referred to the nearby cancer institute for further treatment.[10]

Despite limitation by the retrospective nature, this descriptive study was done to provide further disease information regarding Indian population. There is scarcity of data from India of patients diagnosed with LCH. Data from this study clearly confirms the known fact that most of the patients with Single System LCH have a very good response rate. Patients with multisystem disease have the highest risk of disease related mortality and morbidity as one among the 4 patients with multisystem disease died just after initiating treatment. Although authors have presented retrospective series of 10 cases from a single centre, more studies including multicentre prospective randomised controlled trials should be done in the Indian population to have a better understanding of the biology of the disease, response to treatment and prognosis.

ACKNOWLEDGEMENTS

I take this opportunity to thank a number of people who have been an integral part in the completion of this study. I offer my utmost and heart-felt thanks and respect to my professor, teacher and guide Dr. Shashidhar VK, Professor and Head of department of Medical Oncology, Vydehi Institute of Medical Sciences and Research Centre, Bangalore, for lending me his constant support, encouragement, motivation and invaluable guidance. I am also thankful to Dr. Manjunath IN and Dr Veerendra for their support in times of need or otherwise.

I profusely thank my colleagues for unflinchingly sharing the work and providing help which was much needed. I also extend my gratitude towards my radiation oncology and surgical oncology colleagues for their support in times of need.

Lastly I thank all the patients who have given consent to be a part of this study and without whom it would not have been possible.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Allen C, Merad M, McClain K. Langerhans-Cell Histiocytosis. New Engl J Medi. 2018;379(9):856-68.
2. Shih Y, Lin W, Shih I. Langerhans Cell Histiocytosis in Taiwan: A Retrospective Case Series in a Medical Center. Dermatol Sinica. 2009;27:93-102.
3. Allen C, Ladisch S, McClain K. How I treat Langerhans cell histiocytosis. Blood. 2015;126(1):26-35.
4. Menghani H, Morrison C. Treatment and Survival Analysis for pediatric patients with Langerhans Cell

Histiocytosis - A Single Institution Review. Pediatr Blood Cancer. 2016 June 1;63:S18-S18.
5. Demellawy D, Young J, Nanassy J, Chernetsova E, Nasr A. Langerhans cell histiocytosis: a comprehensive review. Pathology. 2015;47(4):294-301.
6. Eden P, Abeyasinghe WA, Mufees MB, Jayasooriya PR. A series of 13 new cases of langerhans cell histiocytosis of the oral cavity: a master of disguise. Age. 2017;6(15):16-25.
7. Mahendra K, ManUpdesh Singh S, Shano N. Bone marrow infiltration in Langerhan's cell histiocytosis - An unusual but important determinant for staging and treatment. Int J Hematol- Oncol Stem Cell Res. 2015;9(4):193-7.
8. Tseng F, Kuo C. Langerhans cell histiocytosis: a case report. Endocr Abstr. 2014
9. Rao S, Hegde S, Gopinath Thilak P, Babu G, Ajila V, Shetty U, et al. Langerhans cell histiocytosis in a 5-year-old girl: A case report and review of literature. Ind J Medi Paediatr Oncol. 2019;40(5):176
10. Rao D, Trivedi M, Havale R, Shrutha S. A rare and unusual case report of Langerhans cell histiocytosis. J Oral Maxillof Pathol. 2017;21(1):140.

Cite this article as: Jacob RK, Karpurmath SV, Nandennavar M, Angadi V. Retrospective analysis of clinical manifestations and treatment outcomes of patients diagnosed with langerhans cell histiocytosis from a tertiary cancer hospital in South India. Int J Res Med Sci 2020;8:2128-35.