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ORIGINAL ARTICLE

Overview of Langerhans Cell Histiocytosis among Children

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ABSTRACT

Aim: To analyze clinical manifestations, course and outcome of Langerhans Cell Histiocytosis in children in resource limited settings lacking salvage therapy.
Study design: Observational retrospective study
Place and duration of study: Department of Haematology/Oncology, The Children's Hospital, Lahore Pakistan from 1st January 2011 to 31st December 2018.
Methodology: Sixty-five patients with age range from<1 to 8 years included analysing their age, gender, clinical classification, course of therapy and outcome. The major treatment was composed of either prednisolone and vinblastine or cytarabine pulses.
Results: There were 59% males and 41% females. Forty-seven (72%) patients presented with multi system-LCH with 49% Risk Organ involvement. Most of them 42 (65%) had bone lesions while 15patients (23%) presented with central nervous system involvement. Forty patients (61%) have completed treatment, 11(17%) left against medical advice and 12(18%)patients expired due to progressive disease and worsening infection. Only 2 patients were put on palliation with progressive brain parenchyma disease. 22 patients (34%) had reactivations of disease requiring therapy for more than one-year (p-value=0.06), while 15 (23%) patients received two cycles of initiation therapy before continuation therapy started. The treatment initiated >6 months after the onset of symptoms in 48 (74%) patients.
Conclusion: Early diagnosis and timely initiation of therapy are of utmost importance to reduce mortality and morbidity. There is a dire need of social support to reduce treatment abandonment in low-middle-income countries LMIC.
Keywords: Paediatric Langerhans cell histiocytosis, Resource-limited settings, Delayed diagnosis, Abandonment

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare histiocytic disorder, with myriad of clinical features from unifocal bony lesion to widespread disease and life-threatening sequelae.[1,2]The incidence of LCH is 2-9/million per year inchildren[1,2], with peak diagnosis is around 1-4 years.[2,3]Children at all ages can suffer from LCH; however, multisystem disease is more common among infants. This can involve not only soft tissues but also the bony compartment of particularly head and neck region. In addition, patients can have manifestations in skin, lymphoid tissue, bone marrow and central nervous system (CNS)[1-4]

Langerhans cell histiocytosis is considered a neoplasm of myeloid origin having a clonal proliferation of CD1a and CD207 cells with BRAF mutations. 25% cases have been reported to have mutations in MAPK/ERK pathway.[3]The disease has been reclassified from an immune disorder to a neoplasm and led to the development of new targeted therapies. Current treatment regimens provide cure in 80% of these patients. However, disease recurrence has been observed in 30-50% of the patients.[2]Barres et al also suggested LCH to be considered an inflammatory myeloid neoplasia.[5] Currently, LCH is categorized into three distinct groups according to the site and system involvement. There can be single system involvement with a single site as well as multiple sites. In addition, multiple systems can be involved simultaneously. However majority patients have involvement of a single system. Skeletal system is predominantly involved in single system (SS). Multi system LCH (MS-LCH)may present either with or without organ involvement. Skin, bones, lymph nodes, and the pituitary gland are included in low-risk, whereas bone marrow, liver, spleen are classified as high-risk organs.[4]Approximately half of MS-LCH patients have more than one risk organ (RO) involvement.[6]

Various studies have been done to determine the clinical spectrum, outcome, and prognostic factors of LCH worldwide but there is scarce data available from Pakistan. This study aims to highlight the challenges faced in treating this rare paediatric disease with lack of salvage therapies in the form of targeted therapies like nucleoside analogues and BRAF inhibitors for long term cure and reduced reactivation rates.

PATIENTS AND METHODS

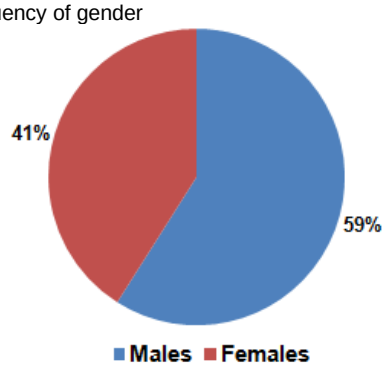
This observational retrospective study was done at Department of Haematology/Oncology, Children's Hospital & ICH, Lahore Pakistan from 1st January 2011 to 31stDecember 2018. Patients in all ages and of both genders were included. Each patient was thoroughly

investigated for his complete blood count, liver and renal function tests, serum albumin, ferritin, coagulation profile, LDH, skeletal surveys, ultrasonography of abdomen, radiographs of chest and skull. In addition, tissue biopsy followed by its immunohistochemistry with CD1a and S100 wherever applicable along with bone marrow biopsy were also done. Complex radiological investigations including CT scan, MRI of brain and hormonal assays if required, were also carried out. The first line treatment composed of intravenous vinblastine and oral steroids as initiation therapy for 6-12 weeks and Continuation phase for 6-12 months and for refractory cases intravenous cytarabine pulses 120-150mg/m^2 for 5 days every 3-4 weeks for 6 months to 1 year. The salvage therapies in the form of adenosine analogues (clofarabine and cladribine), BRAF/MEK inhibitors and allogenic stem cell transplantation were not available due to financial constraints. The data was entered and analyzed through SPSS 20.

RESULTS

Thirty-eight (59%) were males and 27(41%) were females with M:F ratio of 1.4:1 (Fig. 1). Among total, 49/65(75%) were >2years and 25% < 2 Years old (Table 1). Time interval to reach the clinical diagnosis was more than 6 months in 48 patients (74%). At the initial presentation, majority of the patients 47(72%) had multi system involvement. Whereas multifocal bone involvement was present in 27 patients (42%), and unifocal bone involvement was seen in 29 patients (45%). Risk organ involvement was present in 32(45%) children. Patients presented with CNS involvement were only 15 (23%). Regarding treatment majority of the patients 40 (61%) had completed treatment, whereas 11 of them (17%) abandoned treatment during therapy and 12(18%) children expired. Palliative therapy was given to 2 patients with progressive brain parenchymal disease (Fig. 2). Twenty-one (32%)had reactivation of disease with therapy for more than one year (p-value=0.06) [Table 2]. Fifteen (23%) were given two cycles of initiation therapy due to inadequate response before continuation therapy started. The most common skin manifestations in our study were red scaly popular lesions, seborrheic dermatitis, petechiae with purpuric macules and vesiculopustular lesions with generalized distribution. The diagnosis was confirmed by histopathology and immunohistochemistry of tissue biopsies (Figs. 3-5)

Fig. 1: Frequency of gender



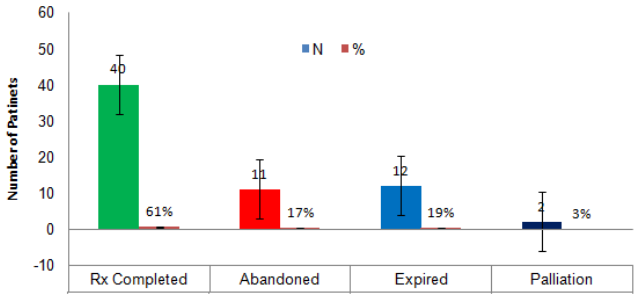


Fig. 2: Frequency of outcome

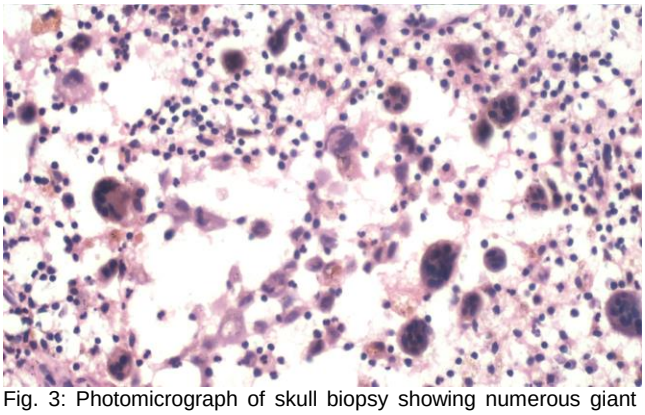


Fig. 3: Photomicrograph of skull biopsy showing numerous giant cells, inflammatory infiltrate and histiocytes

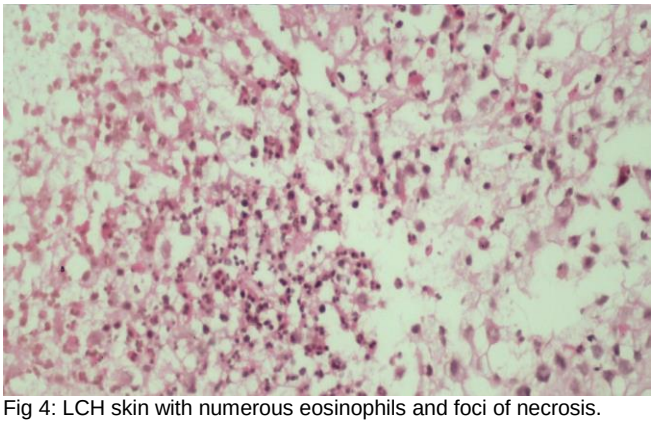


Fig 4: LCH skin with numerous eosinophils and foci of necrosis.

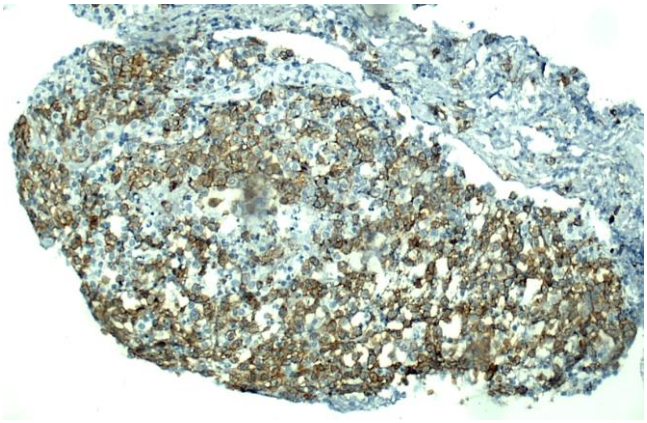


Fig 5: LCH lymph node showing atypical histiocytic proliferation (CD1a X 200)

Table 1: Clinical Characteristics

Variable	No.	%	P value
Age (years)			
<2	16	25.0	0.000
>2	49	75.0	
Classification			
Single system (SS)	18	28.0	0.217
Multisystem (MS)	47	72.0	
Lytic lesions			
Present	42	65.0	0.218
Not present	23	35.0	
Bone lesions			
Multifocal	27	42.0	0.213
Unifocal	29	44.0	
NA	9	14.0	
Risk organ +	32	49.0	0.000
Not involved	33	51.0	
CNS lesions	15	23.0	0.061
No CNS lesions	60	77.0	

Table 2: Clinical Course

Variable	No.	%	P value
Rx started (duration of symptoms)			
<6 m	17	26.0	0.031
>6 m	48	74.0	
Initiation Rx			
6 weeks	39	60.0	0.000
12 weeks	15	23.0	
Not applicable	11	17.0	
Continuation Rx			
>1 year	27	42.0	0.000
<1 year	14	22.0	
Reactivation			
Yes	22	34.0	0.000
No	18	28.0	

P-value measured for outcome and the clinical course and characteristics.

DISCUSSION

This study has given an overview of paediatric LCH in resource limited settings in a public sector hospital in Pakistan with 25% of children presenting at ages less than 2 years with male preponderance. In contrast to Narula et al[7], who noticed median age of the patients as 36 months in their population. However male predominance was observed in their study group like our study. Kim et al[6] also observed median age of the patients as 65 months in their population.

In our study bone was involved in 65% children with 42% having multifocal bony lesions and reactivation in 34% cases (Table 1). Like Narula et al[8], who also observed predominantly involvement of bones and skull. However, Dhar et al[9], in contrast observed mainly involvement of skin followed by bones.

Prognosis of LCH is highly dependent on the involvement of body systems. Single-system LCH has a better prognosis with a 100% 5-year survival and <20% recurrence risk whereas MS-LCH has more risk of relapses and complications requiring more aggressive management.[10] In our study, majority patients (72%) had MS-LCH at initial presentation and only 28% presented with SS-LCH with 84% survival, two abandoned treatment and one expired (Table 1). In contrast 54% of MS-LCH completed treatment and are well and the rest either abandoned treatment, put on palliation, or expired due to progressive disease and complications of treatment.In contrast, Dhar et al[9] showed only 32% of the total patients with multisystem LCH at the time of presentation. Complications developed in few patients resulted in mortality of 8% in their population group.[10]

McClain et al[11] noticed involvement of CNSin 23% of cases including diabetes insipidus and parenchymal brain lesions. Out of their total population, 60% completed the treatment and two cases were given palliative treatment due to aggressive brain parenchymal disease. However, only three patients abandoned treatment. CNS lesions range from granulomatous, non-granulomatous with or without calcification and atrophy and neurodegeneration, best defined by MRI brain.[11,12]

In our study, among the children less than 2 years 38% achieved complete remission, 37% abandoned and 25% expired as demonstrated to be higher risk when presented at younger age.In the present study, only 49% of the total children had risk organ involvement with only one third able to complete treatment and rest were expired or abandoned treatment. In contrast,Narula et al[7]showed few cases with RO+ and benefited with longer maintenance of 18 months in addition to oral etoposide for 21 days in each 28 days cycle. Gadner et al also described high mortality rate associated with MS-LCH with RO+. However, they observed that intensified treatment regimens can be beneficial to the patients in reducing the mortality rate.[13]

In the present study, a gap of more than 6 months was observed between the onset of disease symptoms and the start of therapy in 74% of the cases. The reason of this gap was diagnostic delay as the patients usually presented with cutaneous and other manifestations of less severe intensity. That resulted in delay in initiation of therapy. Initiation RX was given for 12 weeks in 23% cases based on early response and continuation treatment was extended to more than one year in almost half of the cases. Similarly, Dhar et al faced the same problem of diagnostic delay especially in patients presenting with SS-LCH. Such patients were misdiagnosed as seborrheic dermatitis in 68% of the total cases.[9]

Similarly, Uppal et al[14] described the mean time interval to reach the final diagnosis of 9 months with range of 1-30 months. Meanwhile, these patients received symptomatic therapy for many months without any improvement. Therefore, the threshold to suspect LCH should be reduced, prompting timely management and better possible outcome. As LCH is an uncommon disease and should be suspected in children having unexplained clinical features of lung, CNS, skin, and bone delaying the final diagnosis and consequently resulting in more complications.[15]

Kim et al[16] showed that majority of their patients (69.5%) had SS-LCH, followed by MS-LCH without involvement risk organs MS-RO- in 14.1% and MS-RO+ in16.4% cases with 5-year overall survival (OS) rates in these groups were 99.8%, 98.4%, and 77.0%, respectively and likewise increased 5-year reactivation rates from 17.9%, 33.5%, and 34.3%.Conversely, in our study in SS-LCH reactivation is 28%, in MS-LCH 34% and 33% in the

total cases (p value <0.05).These reactivations are usually less severe in extent and severity than the primary disease and thus did not result in high mortality. Continued efforts are needed to decrease reactivations, but unfortunately the toxicity of the treatment of LCH cannot be ignored.[17,18]In LCH reactivation is not uncommonwith relapses in 20% to 50% of patients. Generally, in both groups of patients with low-risk SS-LCH having reactivation of multifocal bone disease or low-risk MS- LCH/RO-, reactivations happen in approximately one-third of patients with good response to second-line regimens. Patients with high-risk disease MS-LCH RO+and those with inadequate response to standard treatment protocols have poor survival, though they respond to intense regimens with cladribine and high dose cytarabine pulses, stem cell rescue and BRAF inhibitors.[2,19]Although survival is highly dependent on whether risk organs are involved or not, tremendous progress has been made in the management of LCH, with significant improvement of survival in high risk LCH up to around 90%.[17]

Our study showed that among patients having MS-RO+ (n=32, 49%) of total cohort only 34% completed treatment and are doing well. Of the remaining, 32 % abandoned treatment andthe rest of 34% expired. The patients without RO involvement 88% completed treatment and are well, one patient expired, one abandoned and two patients were put on palliation due to advanced disease and poor response to treatment regimens available in the resource limited settings.Jain et al[15] observed with a cohort of 28 LCH patients that majority of their patients achieved complete remission with only around 18% of them relapsed and were in remission after second line treatment protocol and only6/28 patients had progressive disease with 7% abandonment and 14% expiries and 7% lost to follow up.In the present study also showed the same problem of abandonment of treatment. This poses one of the greatest challenges for providing standard of care therapies for childhood cancer affecting up to 50–60% of children as are the other challenges like lack of health education, reduced access to healthcare, and poor socioeconomic environment causing delayed diagnosis in Low-middle-income LMIC countries, augmented by insufficient number of population-based cancer registries in the region.[19-21]

CONCLUSION

To improve the long-term survival of these LCH patients in resource limited settings it is imperative to ensure early diagnosis, efficient referral systems, effective psychosocial support to minimize abandonment and efficient supportive care to reduce morbidity and mortality.

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