CLINICAL REPORT

Langerhans' Cell Histiocytosis of Temporal Bone: A Study of 11 Egyptian Patients

Asser A ElSharkawy, Mohamed M Sarhan

Departments of ENT Pediatrics Faculty of Medicine, Mansoura University, Mansoura, Egypt (AAE, MMS)

Objective: To describe and analyze 11 cases of Langerhans' cell histiocytosis of the temporal bone of the skull in children in the period between 2002 and 2011.

Materials and Methods: Eleven children with Langerhans' cell histiocytosis of the temporal bone were included. The patients were evaluated by means of CT scan preoperatively. All patients underwent surgical excision of the lesion via mastoidectomy through postauricular approach. Postoperative chemotherapy was given to seven patients: four with residual disease in the mastoid, two with multifocal lesion and the last patient with systemic disease.

Results: The patients were 7 males and 4 females. Involvement was unifocal in 8 cases, multifocal in two cases, and multisystem in one case. Complete surgical excision was achieved in seven patients. With regard to the pathological findings of cases: most of cases were diagnosed as class I histiocytosis (9 patients) (eosinophilic granuloma in 6 patients and classical LCH in 3), followed by class II in 2 cases (hemophagocytic lymphohistiocytosis). Seven patients received standard protocol for Langerhans' cell histiocytosis. Complete response was achieved in 10 cases and one patient died from respiratory failure.

Conclusion: LCH is a rare disease with a wide spectrum of clinical presentations. A high index of suspicion is required to diagnose the disease, especially when an ear disease is refractory to medical treatment. The prognosis for isolated lesions is usually excellent. Complete surgical excision is effective in isolated lesions. Follow up is essential.

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Introduction

Langerhans' cell histiocytosis (LCH) is a proliferative disorder in which the accumulation of pathologic Langerhans cells leads to local tissue infiltration and destruction[1]. LCH is a rare disease with an incidence of .5 to 5 cases per million children per year[2]. Previously, LCH was known as histiocytosis X, a nosologic term for a diverse group of clinical syndromes including eosinophilic granuloma, Hand-Shu¨ ller-Christian disease, and Letterer- Siwe disease[3].

The incidence of otologic manifestations ranges from 11% to 61%. The most common symptoms are otorrhea, mastoid swelling, deafness, and aural polyps eroding the posterosuperior canal wall[4]. Inner ear involvement is very rare[5, 6] .

Classification of diseases involving histocytic and dendritic lesions is difficult and must include a broad range of diseases. Therefore, most proposed systems are incomplete and arbitrary[7]. The classification of histocytic and dendritic cell disorders proposed by the World Health Organization (WHO)[7] is shown in Table- 1.

Corresponding address:
Asser A. Elsharkawy
ORL department, Mansoura University Hospital, Mansoura, Egypt
Tel: +201002223269
Fax:+22267016
Email: assersharkawy@yahoo.com

Table 1. WHO classification of Histiocytosis Syndromes in children

Class	Syndrome
I	Langerhans Cell Histiocytosis
II	Histiocytosis of mononuclear phagocytes other than Langerhans cells
	Hemophagocytic lymphohistiocytosis (familial and reactive)
	Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman),
	Juvenile xanthogranuloma
	Reticulohistiocytoma
III	Malignant histiocytic diseases.

The purpose of this study was to describe and analyze 11 cases of Langerhans' cell histiocytosis of the temporal bone of the skull in children in the period between 2002 and 2011.

Materials and Methods

The study was conducted in ORL department and the hematology/ oncology/BMT unit of Mansoura University Children's Hospital, Mansoura University between 2002 and June 2011. A total of 11 patients with with Langerhans' Cell Histiocytosis of the temporal bone were included in this study. They were 7 males and 4 females with mean age 4.3years (6months - 9.5 years) years.

Otorrhea was the most common otologic symptoms occurring in about 10 children. A postauricular swelling, facial paralysis, and hearing loss were additional symptoms. The hearing loss was typically conductive hearing loss. Sensorineural hearing loss, vertigo and nystagmus suggesting otic capsule involvement was not seen in any child (Table- 2).

Table 2. Incidence of symptoms and signs of otologic LCH

Symptoms	No of cases (%)
Otorrhea	10/11 (90.9%)
Postauricular swelling	4/11 (36.7%)
Aural polyp	3/11 (27.7%)
Lower motor facial paralysis	1/11 (9.2%)

Preoperative assessment

A sheet for each patient was done including the following: age at presentation, sex, residence, mode of presentation, histopathological diagnosis, radiological diagnosis, laboratory investigations, therapy given, and the final outcome of the disease.

All the children were admitted in ORL department with initial diagnosis of chronic suppurative otitis media (cholesteatoma) (9 cases) and mastoid abscess (two cases) was suggested. Preoperative CT revealed a soft tissue mass filling mastoid and middle ear with variable portion of bone destruction in most cases with a possible diagnosis of cholesteatoma. Preoperative audiological evaluations were done; pure tone audiometry (PTA) for elder children (9 patients) and ABR for the two younger ones. Two children underwent blood transfusion due to anemia before surgery.

Surgical intervention

All children were subjected to surgical intervention. They were operated under general anesthesia with standard post auricular incision and transverse incision in young infant to avoid injury of the superficial facial nerve. After elevation of the periosteum, a complete mastoidectomy was done with removal of the soft tissue mass from the mastoid and middle ear if possible. During exploration, a fleshy firm mass with a varying degree of necrosis and bleeding was detected filling a varying amount of the mastoid with exposure the deep structures of the temporal bone. Complete surgical excision of the tumor was achieved in seven patients with residual tumor in four patients (Table- 3).

Radical mastoidectomy was done in two cases while modified radical mastoidectomy was done for nine cases (Table- 3). All cases had a wide meatoplasty for easy cleaning of the mastoid cavity and follow up of the disease. The excised tissues were sent for histopathological diagnosis.

Post surgical management and follow up

Postoperative CT scan with contrast was done for all cases (6 - 8 weeks postoperative) after the diagnosis.

Table 3. Characteristics of the study patients

Patient	Gender/ age	Clinical stage	Duration of symptoms	Surgery	Postoperative	Outcome chemotherapy
1	M/3.4 y	Unifocal LCH (RT temporal bone)	3 months radical	Modified mastoidectomy (residual tumor)	Yes	Complete response
2	F/ 6.7 y	Unifocal LCH (RT temporal bone)	4months	Modified radical mastoidectomy (complete excision)	No	Complete response
3	M/9.5 y	Unifocal LCH (LT temporal bone)	5months	Modified radical mastoidectomy (complete excision)	No	Complete response
4	M/ 2.7y	Mulifocal LCH (LT temporal bone and femur bone)	4months	Radical mastoidectomy (complete excision)	Yes	Complete response
5	F / 6 m	Multifocal LCH with mulisystem dysfunction	3weeks	Modified radical mastoidectomy (complete excison)	Yes	Died (20months)
6	F/6y	Unifocal LCH (LT temporal bone)	4months	Modified radical mastoidectomy (complete excision)	No	Complete response
7	M/3y	Unifocal LCH (LT temporal bone)	5months	Radical mastoidectomy (complete excision)	No	Complete response
8	M/2.5y	Mulifocal LCH (LT temporal bone and tiba bone)	4months	Modified radical mastoidectomy (complete excision)	Yes	Complete response
9	F/4y	Unifocal LCH (RT temporal bone)	2months	Modified radical mastoidectomy (residual tumor)	Yes	Complete response
10	M/5y	Unifocal LCH (RT temporal bone)	5months	Modified radical mastoidectomy (residual tumor)	Yes	Complete response
11	M/4 y	Unifocal LCH (RT temporal bone)	3months	Modified radical mastoidectomy (residual tumor)	Yes	Complete response

The patients were transferred to the hematology unit at pediatric hospital where they received standard protocol for Langerhans' cell histiocytosis consisting of 6 weeks of induction chemotherapy with vinblastin, etoposide, and prednisolone followed by 46 weeks maintenance with 6-mercaptopurine with pulse vinblastin, etoposide, methotrexate, and prednisolone[8]. The patients were followed up regularly at the ORL department for the care of the mastoid cavity and for detection of any recurrent disease.

Results

The study was conducted in ORL department and hematology/ oncology/BMT unit of Mansoura University Children's Hospital, Mansoura University between 2002 and 2011. A total of 11 patients with Langerhans' Cell Histiocytosis were included in this study. They were 7 males and 4 females with mean age 4.5 years (6months-9.5 years). Eight (72.7%) patients had unifocal LCH (one temporal bone affection only),

multifocal LCH (one temporal bone and femur) was present in two patient (18.1%) and Multifocal LCH with mulisystem dysfunction was present in one patient (9.2%). Patients' data are included in Table- 3.

The most frequently encountered clinical presentations were otorrhea (90.1%), followed by postauricular swelling (36.4%) and lower motor neuron facial paralysis in one patient (9.1%). The otologic manifestations included conductive hearing loss in all patients with no sensorineural hearing loss, external auditory canal (EAC) polyps (three patients) (Table-2).

Preoperative computed tomography (CT) was performed for all patients as part of the work-up for detection of the extent of the lesion. It showed an osteolytic soft tissue mass in the temporal bone with a preliminary diagnosis of cholesteatoma with mastoid abscess in two patients. On reviewing the CT after the histopathological diagnosis, no sclerotic margins were found around the tumor. This radiological sign was overlooked due to rare incidence of the tumor (Fig 1&2).

Seven patients received standard protocol for Langerhans' cell histiocytosis; two patients with multifocal LCH, one patient with multifocal LCH with multisystem dysfunction, and four patients with unifocal LCH with residual temporal bone disease. Complete response was achieved in 10 cases (90.9%). Poor response was observed in one child with multifocal LCH with mulisystem dysfunction and she died from respiratory failure (20 months) (Table 3).

The patients were reviewed in outpatient clinic of ORL and Hamatology unit twice weekly for the first 2 months, monthly for 3 next months and every 6 months after surgery during the follow up period. The follow up period ranged from 2 to 9 years with a mean of 5.7 years.

Ethical considerations

All procedures including obtaining written informed consents from the parents of the patients were conducted in accordance with the recommendations of the ethics committee of the faculty of medicine Mansoura University.

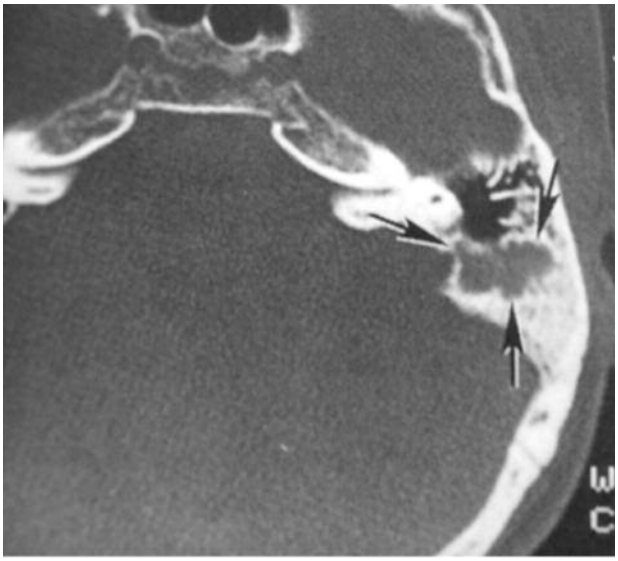

Figure 1. irregular lytic lesion in the mastoid bone.

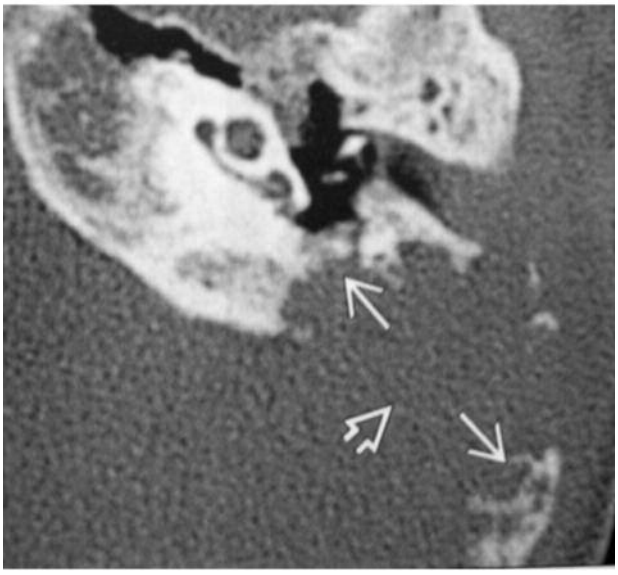

Figure 2. Axial CT scan shows a destructive lesion with punched-out regions of the left mastoid (white arrow). The sigmoid plate is completely eroded (open arrow).

Discussion

The proliferating cells of LCH are the histiocytes, which include dendritic cells and mononuclear phagocytes, and these are derived from the bone marrow and they migrate into the peripheral tissues after a period in the circulation. The essential biological function of dendritic cells is to present antigens to CD4 lymphocytes and, thus, to initiate the immune response[9]. The Langerhans'

cells are a subpopulation of the dendritic histiocytes, primarily located in the basal layer of the epidermis. The function of normal Langerhans cells is cutaneous immunosurveillance. These cells can migrate to the regional lymph nodes and potentially present antigen to paracortical T cells and cause their transformation to interdigitating dendritic cells. Some cancer cells are demonstrated to cause disruption of dendritic cell function, thus blocking development of tumor-specific immune responses and allowing tumors to evade recognition. In LCH, there is a proliferation of Langerhans' cells that are phenotypically similar to the dendritic cells of the skin and involve nearly all the organs of the body[10].

The etiology of LCH is unknown and debated. There is little evidence to support an infectious agents (especially human herpes virus 6)[11]. It has been suggested that abnormal immune regulation may be involved because of decreased T-cell function and increased production of cytokines, which have implications for Langerhans' cell maturation and migration and for the development of fibrosis. The monoclonal origin of all disease forms of LCH has also been demonstrated, and this suggested a neoplasic process[12]. Nevertheless, the absence of aneuploidy and of any correlation between the severity of the disease and the monoclonal origin does not seem to be compatible with this theory and would indeed seem to suggest a reactive process[1].

Preoperative diagnosis of the LCH is difficult and requires a high degree of suspicion as the symptoms and signs of otologic LCH can mimic those of acute and chronic infectious ear disease. Even with the aid of CT scans the diagnosis may be confusing. Thus the definite diagnosis of LCH is based on typical histopathological findings of the langerhans' cells (Fig 3). These cells are characterized by elongated, coffee bean-shaped nuclei, and a pink or clear cytoplasm[9].

In this study, the frequency of symptoms was otorrhea (90.9%) followed by mastoid swelling (36.7%) and facial nerve affection (9.2%). This agrees with most authors who reported that otorrhea and postauricular swelling are the commonest symptoms of LCH[1 ,13,14,15].

In this study acute lower motor neuron facial nerve paralysis was detected in one patient. During surgical exploration, the tumor was eroding the mastoid bone with affection of the facial canal and exposure of the facial sheet to which the tumor was attached. Facial nerve affection had been reported as a symptom of the LCH by *Cunningham et al [13] and Goldsmith et al* [14]. They reported that the tumor tissue does not invade the nerve tissue but rather appears to interrupt the blood supply of the facial nerve by destruction of the bony canal of the facial nerve. In this study, there was no other cranial nerves affection.

There is a lot of controversy in the literature whether temporal bone affection is a part of mulifocal LCH affection or unifocal LCH affection. In a study conducted by AL-Molhim et al[16] in 19 Saudi children they reported that 14 cases had multifocal disease and five cases had unifocal disease. In the present study, 3 cases had unifocal disease, one with multifocal disease, and one with multisystem disease. Bilateral temporal bone affection was recorded a 2 year old boy and was described by *Kleinjung et al* [15] *But in* this study only one temporal bone was affected by LCH.

A conductive hearing loss is commonly present in otologic LCH secondary to soft tissue infiltration of the mastoid and middle ear, secondary bacterial infection and obliteration of the external canal by the aural polyps. Tympanic membrane perforation may occur in the presence of secondary infection[13] Cunningham et al . Otic capsule appears more resistant

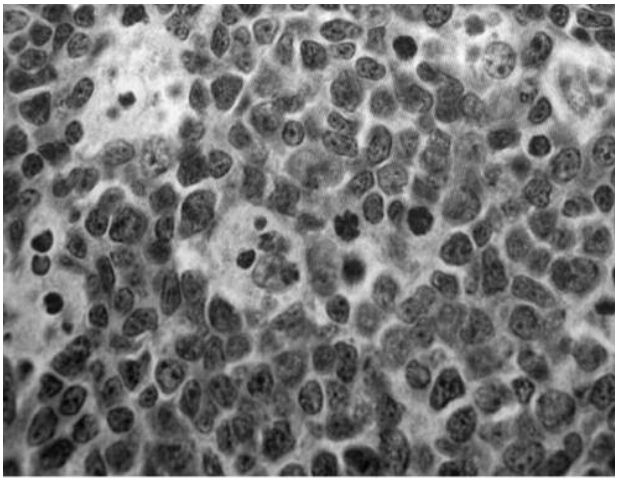

Figure 3. Tissue specimen showing masses of histiocytic cells and numerous eosinophils in a fibroconnective tissue background. The histiocytes have a small amount of pale pink cytoplasm and irregular nuclear contours. (Hematoxylin and eosin stain)

to infiltration by the histiocytosis, but labyrinth destruction with vertigo and SNHL has been reported.[1, 15, 17]. In this study the hearing loss was conductive hearing loss in all children with no cases of SNHL.

In this study no preoperative biopsy was taken, and the diagnosis of LCH was done after the surgical exploration and the biopsy. Although the preoperative CT scan was done for all cases, the preliminary possible diagnosis was cholesteatoma in all patients with mastoid abscess in two patients.

Management of temporal bone LCH remains controversial. Up till now there is no well established protocol for the treatment of LCH. Radical or limited surgical interventions (aural polypectomy and curettage), intralesional steroids injection, chemotherapy and radiotherapy have been used. These modalities can be used either alone or in combinations, depending upon the extent and severity of the disease[17].

In this study, the patients were subjected to surgical treatment in the form of mastoidectomy with complete removal of the mass from the mastoid the middle ear in seven cases. Residual mass was left in four cases: three patients the tumor was attached firmly to the dura of the posterior fossa dura with endolymphatic sac and lateral sinus, and the last patient the tumor was extending to the retrofacial air cells with attachment to the facial nerve sheath.

Complete surgical removal of the tumor in unifocal LCH was effective and the sole treatment in two cases with strict follow up till now with no recurrence. In the remaining cases chemotherapy was effective in controlling the disease with complete cure with no complications in two cases.

In a study conducted in Italy on 90 patients, they were divided into two groups: poor prognosis, comprising 11 children with organ dysfunction, and good prognosis, made up of 79 patients without organ dysfunction. Eighty-four patients were evaluated for treatment results. Two of the 11 poor prognosis patients had a complete response (18.2%), while six died and three survived with recurrent disease. The overall incidence of disease-related disabilities was 47.7%, while that of diabetes insipidus was 20%[18]. AL-Molhim et al [16] reported in his retrospectve study of 19 Saudi children with histiocytosis that three patients died, three had recurrence and eight patients had various disabilities. Overall disease free survival was (84.2%). Another study conducted in Argentina by Braier et al [19] on 123 patients reported that 13 patients with multiple-organ dysfunction died without response to a variety of regimens of therapy.

Among the studied cases, only one patient (9.2%) died by respiratory failure 20 months from diagnosis. This patient had mulifocal LCH with mulisystem dysfunction and with class II tumor. Like another study conducted in Argentina by[17] Braier et al[19] on 123 patients, 17 (14%) died; of these,: 13 died by organ dysfunction and 1 by chronic relapsing progressive disease and myelofibrosis. The median age at diagnosis of the patients who died was 10.9 months. Fifteen out of 17 had visceral or skin involvement. All 13 patients with multiple-organ dysfunction and died without response to a variety of regimens.

In conclusion, LCH is a rare disease with a wide spectrum of clinical presentations. A high index of suspicion is required to diagnose the LCH, especially when an ear disease is refractory to medical treatment. CT scan is extremely helpful, but the diagnosis relies on the identification of the Langerhans' cells in biopsy specimens. Treatment options are numerous and must be tailored to the patient's particular disease. The prognosis for isolated lesions is usually excellent. Complete surgical excision is effective in isolated lesions. Follow up is essential.

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