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Oral Langerhans cell histiocytosis in Malaysian children: a 40-year experience

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Background. Oral Langerhans cell histiocytosis is generally seen in children.

Objective. To determine the clinicopathological features of oral LCH in Malaysian paediatric patients.

Methods. A retrospective study was carried out to determine the clinicopathological features of Langerhans cell histiocytosis (LCH), Letterer–Siwe disease, Hand–Schuller–Christian disease, eosinophilic granuloma, and histiocytosis X occurring in the oral cavity in children, diagnosed histologically in the main oral histopathology laboratory in Malaysia from 1967 to 2007.

Result. There were 17 cases (eight girls and nine boys) with age ranging from 1 to 7 years. There were ten Malays, four Chinese, two Indians, and one of other ethnicity. Thirteen cases presented as gingival swellings with six of these cases accompanied with mobility of the teeth. Nine cases involved the mandible, two in the maxilla, and two cases in both the maxilla and mandible. The radiographic findings were mentioned only in nine cases with presence of bony erosion or destruction of the jaw bones. Four cases had punched-out radiolucencies of the skull. The patients also had other systemic signs and symptoms: skin lesions ($n = 5$), hepatosplenomegaly ($n = 2$), prolonged fever ($n = 2$), diabetes insipidus ($n = 1$), and exophthalmos ($n = 1$). Two cases were known cases of systemic LCH.

Conclusion. The histopathologic features of LCH are easily recognized; however, with the development of immunostaining, the use of CD1a helps in confirming the diagnosis.

Introduction

Langerhans cell histiocytosis (LCH) or formerly known as histiocytosis X encompasses Letterer–Siwe disease, Hand–Schuller–Christian disease, and eosinophilic granuloma which can present as either localized or more generalized clinical features. It is a rare disease that affects five children per million population[1]. It commonly involves the head and neck region. It is caused by proliferation of Langerhans-type histiocytic cells. Treatment is either by surgical excision, chemotherapy, radiation therapy, or combinations of these modalities.

Because there are no other studies on oral LCH in Malaysian paediatric patients, we carried out this study to determine the clinicopathological features of oral LCH diagnosed histologically in the main oral histopathology laboratory over a 40-year period (1967–2007).

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Materials and methods

A retrospective study was carried out on cases of LCH, Letterer–Siwe disease, Hand–Schuller–Christian disease, eosinophilic granuloma, and histiocytosis X diagnosed in the Stomatology Unit, Institute for Medical Research, Kuala Lumpur from 1967 to 2007 for paediatric patients (0–16 years old). All the data regarding the age of presentation, gender, race, clinical presentation, radiographic findings, and diagnoses were retrieved from the computerized data. Immunostaining for CD1a, S100 protein, and CD68 using standard procedure was carried out for all the cases selected.

Results

There were 17 cases (eight girls and nine boys) with age ranging from 1 to 7 years. The patients comprised of ten Malays, four Chinese, two Indians, and one of other ethnicity. The patients' characteristics are summarized in Table 1. There were nine cases involving the mandible, two in the maxilla,

Table 1. Clinical features of 17 cases of oral Langerhans cell histiocytosis.

Case	Age	Gender	Race	Clinical presentation	Radiographic findings	Other signs and symptoms
1	5	M	M	Swelling left mandible	Radiolucency from tooth 37 to left ramus	–
2	2	M	O	Swelling right mandible, maxilla;	Bone destruction over right mandible, maxilla	Hepatosplenomegaly
				mobility of teeth; gingival swelling		
3	2	F	C	Gingival swelling on right mandibular; mobility of teeth	NA	Hepatosplenomegaly, prolonged fever, malaise
4	1	M	C	Swelling left mandible	Radiolucency of mandible	Known case; radiolucency of ribs, femur, humerus, skull
5	3	M	M	Gingival swelling on palatal; mobility of teeth	NA	Loss of weight
6	3	F	I	Swelling left mandible	NA	Skin lesions
7	1	F	C	Swelling left maxilla	NA	–
8	4	M	C	Swelling right mandible; gingival swelling	Bony erosion over right mandible	Diabetes insipidus
9	2	M	M	Gingival swelling on palatal; mobility of teeth	Bony destruction over right alveolus, antrum, floor of orbit	Skin rashes, exophthalmos right eye, scalp lesions
10	2	F	M	Gingival swelling	NA	Purpuric spots on palm, prolonged fever
11	4	M	I	Gingival swelling; left mandible expansion	NA	–
						–
12	7	M	M	Gingival swelling anterior mandible; mobility of teeth	Bony erosion around lower anterior teeth	
13	1	F	M	Gingival swelling	Cyst-like cavity on right mandible	Punched-out radiolucency of skull
14	2	F	M	Gingival swelling; periodontal destruction both maxilla and mandible	Bony destruction both maxilla and mandible	Punched-out radiolucency of skull, recurrent otitis, pruritis on scalp
15	1	M	M	Gingival swelling on palatal	NA	Pruritis on scalp
16	5	F	M	Gingival swelling, mobility of teeth	Radiolucency from lower left first molar to right first molar	Known case
17	2	F	M	Gingival swelling	NA	Multiple osteolytic lesion on skull, humerus

M: Malay, C: Chinese, I: Indian, O: Others.
M: Male, F: Female.
NA: Not available.

and two cases in both the maxilla and mandible. Intra-orally, 13 cases presented as gingival swellings with six of them accompanied with tooth mobility. Three cases had swelling of the mandible (Fig. 1), whereas only one case had maxillary swelling. For radiographic findings of the jaw bones, nine cases presented with bony erosion or destruction (Fig. 2), whereas in the other eight cases, the findings of the radiograph were not mentioned. Four cases had punched-out radiolucencies of the skull. Two cases which were known case of LCH presented as multiple osteolytic lesion of skull, humerus, ribs, and femur. Systemic signs and symptoms include skin lesions ($n = 5$) with three cases presented as pruritis on the scalp and one case as purpuric spots on the palm. Other signs and symptoms include hepatosplenomegaly ($n = 2$), prolonged fever ($n = 2$), diabetes insipidus ($n = 1$), otitis ($n = 1$), weight loss ($n = 1$), and exophthalmos ($n = 1$).

Histologically, all the cases showed diffuse sheets of histiocyte-like cells with indistinct cytoplasmic outlines and rounded or indented vesicular nuclei, and with varying numbers of interspersed eosinophils, polymorphs, and lymphocytes (Fig. 3).

Immunohistochemistry staining was carried out in 11 of the cases including those from the pre-immuno era. In six cases, the wax blocks

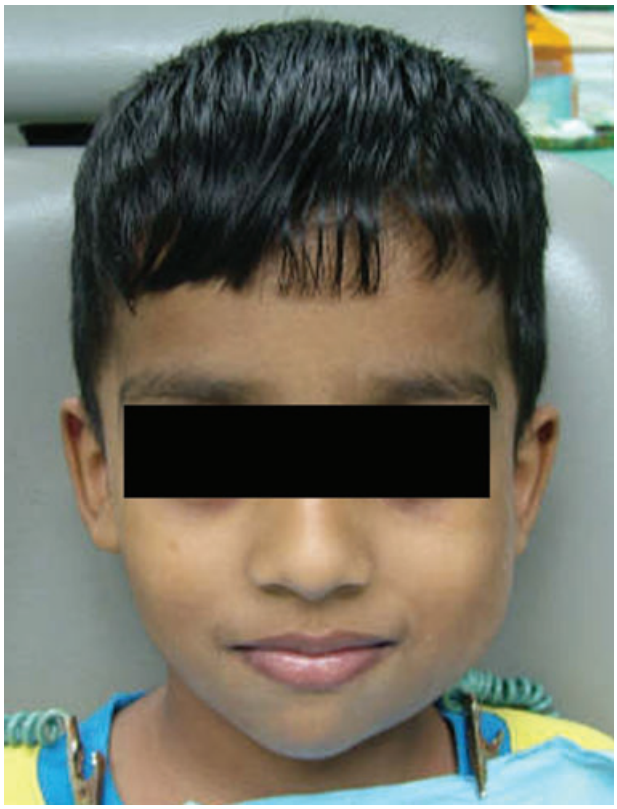

Fig. 1. Patient presented with swelling on the left mandible.

were not available. All cases showed strong positivity with CD1a and S100 protein, whereas for CD68 only highlights the macrophages.

Discussion

Oral LCH can affect any age group; however, it is mainly seen in children. Seventeen cases of paediatric oral LCH were reported during the 40-year period in our laboratory with age range from 1 to 7 years, and a mean age of 2.8 years. In contrast, three cases of histiocytosis X were reported in an analysis on oral pathology lesions in children over a 30-year period[2]. In another study, there were four patients with oral lesions from a group of 33 children managed in a 16-year period[3]. For the ethnic distribution, most of our patients are Malays; however, this is proportionate to the racial demographics of this country. Comparison with other studies cannot be made because there aren't any other studies done in this part of the region.

There are three clinical types of LCH: (i) eosinophilic granuloma, a localized form which affects older children and adults; (ii) Letterer–Siwe disease having clinical features such as mucocutaneous lesions; seborrheic dermatitis-like lesions; involvement of the lungs, liver, and spleen; and it is usually can be seen in the first year of life; and (iii) Hand–Schuller–Christian disease which involves children of age 2–6 years old characterized by osteolytic lesions, exophthalmos and diabetes insipidus[1]. Because we only received specimens from oral biopsies, we really could not tell the clinical type of the LCH of our patients unless the clinicians disclose the full clinical signs and symptoms of the patients in the request biopsy forms.

The systemic manifestations of LCH include skin lesions, alterations of the long bones and skull, diabetes insipidus, exophthalmos, pulmonary involvement, otitis, anaemia, and fever[3,4]. Lymph node involvement was also noted[3]. In our study, two cases were known cases of systemic LCH, and ten cases presented with other systemic signs and symptoms. Five of our patients presented with skin lesions with three affecting the scalp. Minguez *et al.*[4] reported 90% of their patients presented skin lesions with the scalp being

Fig. 2. Orthopantomogram showing unilocular radiolucency with irregular margin at left angle extending to left ramus.

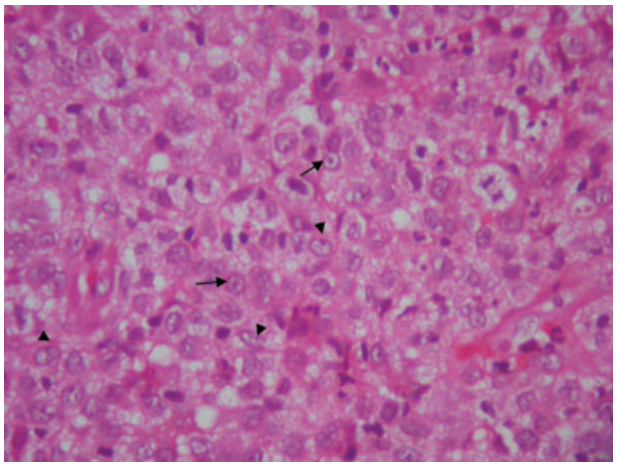

Fig. 3. Sheets of histiocyte-like cells with indistinct cytoplasmic outlines and rounded (arrow) or indented vesicular nuclei (arrowhead) (H&E ×400).

involved the most, whereas in another study[5] 50% of patients had skin lesions. From our data, otitis was seen in one patient. In comparison, Minguez *et al*. reported seven patients to have otitis[4]. Hepatosplenomegaly was also seen in two of our patients.

LCH also involves the head and neck region especially the jaws which are involved twice as frequently as the oral soft tissues and the mandible is three times more frequently affected than the maxilla[1]. Nine cases in our study involved the mandible, whereas two affected the maxilla. This finding concurs with others[1]. For jaw lesions, radiologically they usually have a unilocular radiolucent appearance varying from well-demarcated borders to poorly defined borders[1]. The extensive loss of alveolar bone produces the characteristic 'teeth floating in air' appearance with sharply demarcated rounded radiolucencies surrounding the roots[6]. Other than the jaw bones, the skull bones are also involved[1]. In our series, there were four cases which presented as radiolucencies of the skull. In Campos *et al*.'s study, out of 33 children, 23 had osteolytic lesions with the skull being the most commonly affected[3]. For oral soft tissues, other signs and symptoms include gingival bleeding, aphthae, maxillary osteolytic lesions, oral candidiasis, and orofacial swelling[4]. Thirteen of our cases presented as gingival swellings with six of these cases accompanied with tooth mobility. In ten paediatric patients with chronic disseminated histiocytosis, five cases had oral lesions as the first manifestation of the diseases[4], whereas in another series[5] three of eight patients had oral involvement at onset and later followed by systemic involvement.

LCH is a fairly easy histologically recognized disease. Microscopically, the lesion is composed of mixed infiltrate of macrophages, lymphocytes, eosinophils, and Langerhans cells. The hallmark feature is the presence of Langerhans cells characterized by cells with either cleaved, small reniform nuclei, or with large grooved or 'coffee bean' nuclei. Eosinophils are a consistent feature especially in jaw lesions which usually located near or around foci of Langerhans cell or macrophages[7].

CD1a and S100 protein are two markers used widely for identifying Langerhans cells. Our data showed all the cases which have been immunostained with CD1a and S100 protein were strongly positive with both the markers. Even those cases from the pre-immuno time were equally positive as well. This finding demonstrates LCH can be simply diagnosed histologically by the oral pathologists, and the use of immunostaining with CD1a and S100 protein aids in confirming the diagnosis. We also stained our cases with CD68, and the results showed that the marker only highlights the macrophages. CD68 is a lysosomal antigen expressed at high levels in monocyte/macrophage, and at low levels in immature skin Langerhans cells and down-regulated on maturation[8]. Currently, a new antibody langerin (CD207) which is more specific and sensitive against Langerhans cell is commercially available. Langerin (CD207) is a new antibody directed against a type II Ca^{++}-dependent lectin associated with Birbeck granules[9,10]. Another diagnostic test which is not performed in our laboratory is the electron microscopic detection of Birbeck granules which are characterized by elongated clubs or tennis racket resembling shapes and having a laminar structure[11].

The patients' further management and follow-up are not investigated in our study because the information was not available. According to a review done by Satter and High[12], patients with suspected LCH must undergo multidisciplinary evaluation such as a thorough physical examination, laboratory

evaluation which include complete haematologic panel and urine osmolality, and skeletal and chest radiograph. For the protocol of patient's treatment, clinical stratification based upon the extent of the disease has been suggested[12]. Basically, treatment consists of surgical excision, chemotherapy, radiation therapy, or combinations of these treatment modalities. In a case report of a 2.9-year-old boy involving the maxilla and mandible with no extraskeletal manifestations, the treatment consisted of oral chemotherapy and administration of methylprednisolone by intralesional infiltration[13].

The patient's prognosis depends mainly upon involvement of multiple organ systems. Young patients presenting with disseminated disease and organ dysfunction have the highest mortality[12]. Patient's response to chemotherapy during the 6-week induction phase has been shown to be the single best prognostic indicator[12]. Ten years post-treatment of a child showed no signs of the lesion with complete resolution occurred at 6 months post-treatment[13].

Conclusion

Although LCH is a rare disease, it can also present in the oral cavity. Our records showed 17 cases of paediatric oral LCH over a period of 40 years. Dentists should be aware of the possibility of LCH especially in young children presenting with gingival swellings and mobility of teeth. The histopathologic features of LCH are easily recognized; however, with the development of immunostaining, the use of CD1a helps in confirming the diagnosis. Another diagnostic test is the presence of Birbeck granules on electron microscopic examination.

What this paper adds

- Because there aren't any other studies done in this part of the region, we carried out this study to determine the clinicopathological features of oral LCH diagnosed histologically in the main oral histopathology laboratory in Malaysian paediatric patients.

Why this paper is important to paediatric dentists

- LCH is a rare disease that affects five children per million population, and oral presentation in paediatric patients is commonly seen in children.
- Dentists should be aware of the possibility of LCH especially in young children presenting with gingival swellings and mobility of teeth.

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