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Oral Burkitt's lymphoma in children: the Moroccan experience

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Abstract. Thirty-seven children with Burkitt's lymphoma of the oral region diagnosed between 1998 and 2005 were reviewed. There were 31 boys and 6 girls. The mean age at diagnosis was 6.64 years (range 2–15 years) with a mean delay to diagnosis of 41 days (range 10 days–2 months). There was a predominance of maxillary over mandibular involvement: 1.44:1. Complaints included exophytic mass with dental displacement (100%), abdominal pain (68%), nerve palsy (28%) and orbital swelling (21%). Toothache as initial complaint led to dental extraction in 12 cases. According to the Murphy classification, there were 4 stage II, 11 stage III and 22 stage IV tumours; 43% and 41% had bone marrow and central nervous system involvement, respectively. After chemotherapy, complete remission was seen in 59% of cases. Remission in two children was relatively brief, lasting no more than 3 months. After a median follow-up of 45 months (range 9–99 months), the disease-free survival rate was 54%. In conclusion, in this series, oral presentation of Burkitt's lymphoma was a component of more widely disseminated disease. The pattern seemed to fall between that of the endemic and the sporadic types. Even with intensive chemotherapy, patients with advanced disease maintained a poor prognosis.

Key words: Burkitt's lymphoma; oral location; children; Morocco.

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Non-Hodgkin's lymphomas (NHL) are tumours of the immune system with a variable range of incidence depending on age, geographic location, race and Epstein–Barr virus (EBV) exposure. According to their clinical and cytological characteristics, they are classified into low, medium and high grades of malignancy. High-grade NHL affects mainly young people, while low-grade malignancies are more frequent in advanced age[1]. The majority of lymphomas arise in lymphoid tissue, especially the cervical nodes, and only 24% arise at extranodal sites[5]. The most frequent extranodal locations include gastrointestinal tract, skin, bones and Waldeyer's ring, with a greater frequency of concomitant relapse in the gastrointestinal tract and Waldeyer's ring[1,19]. Only rarely do these lesions arise in the oral cavity. The most common sites are the hard palate, gums, salivary glands and tongue[4,20].

Immunohistochemical features of NHL are subdivided into T-cell and B-cell lymphomas. Oral extranodal lymphomas are predominately of B-cell origin (92%), and less commonly of T-cell origin (8%)[4,20]. Burkitt's lymphoma (BL) is a high-grade B-cell non-Hodgkin's lymphoma which occurs as endemic, sporadic and human immunodeficiency-associated subtypes[2,15]. It accounts for 3–5% of all lymphomas[15]. There is a high incidence of BL (endemic or African BL) in endemic regions such as equatorial Africa and Papua New Guinea, where it accounts

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Table 1. Clinical features of BL[3,8,14,18]

	Endemic	Sporadic
Epidemiology	Africa	USA, Europe
Incidence	50–70% of all childhood malignancies	3–6% of all childhood malignancies
Age at incidence	5–8	10–12
EBV titres	90–95%	15–67%
Clinical presentation	Jaw and facial bone diseases 50–100% Abdominal diseases 25%	Jaw diseases 6–40% Abdominal disease 72–90%
Treatment outcome	54–79%	76–90%

for almost half of all childhood cancers[3,15]. Elsewhere in the world, BL occurs with a much lower frequency, and is referred to as sporadic or American BL[2]. The two forms of the disease have different clinical presentations. Age distribution, abdominal and jaw involvement, central nervous system (CNS) dissemination and EBV incrimination prompted the subdivision of this malignant condition (Table 1). The aim of this paper is to discuss cases of oral lymphoma diagnosed at the authors' institution and to compare them to the described endemic and non-endemic forms.

Patients and methods

A retrospective study was undertaken of cases of oral BL diagnosed between 1998 and 2005 at the Pediatric Hemato-Oncology Department of Rabat. Tumours of the pharynx, parotid and sinuses were excluded. The study only included patients in whom the lymphoma was identified in the oral region on initial diagnosis. The diagnosis in each case was based on histopathological findings. Staging of the disease was determined according to Murphy's classification[11] (Table 2). CNS disease was defined as the presence of blasts in cerebrospinal fluid, cranial nerve palsy not related to facial tumour, clinical signs of spinal compression or an intracranial mass.

The patients were reviewed for age, sex, delay before hospitalization, location of tumour, treatment and outcome. Disease extension was assessed by a physical examination, blood cell count, panoramic radiograph of the jaws, cranial computed tomography, chest X-ray, abdominal ultrasound, bone marrow (BM) aspirate and lumbar puncture.

Chemotherapy was administered by means of combined agents according to the French LMB regimen (Fig. 1). Neuro-meningeal (NM) prophylaxis consisted of intrathecal injections of high-dose methotrexate, high-dose Ara-C and hydrocortisone. Irradiation of the skull (24-Gy) was indicated in three cases. Survival was calculated from the first day of chemotherapy to death due to any cause or to the last follow-up contact for patients who were alive.

Results

Of a total of 452 NHL at all sites, 37 (8%) cases of intraoral BL were recorded. The clinical presentation of these patients is summarized in Table 3. The ages of the patients ranged from 2 to 15 years, with a mean of 6.64 years. There was a predominant presentation in males (31 boys and 6 girls); the male-to-female ratio was 5.1:1. Median delay to diagnosis was 41 days (10 days, 2 months). The most common symptoms seen at diagnosis were a fast-growing gingival mass (that may or may not be ulcerated), associated with toothache or dental displacement (100%), abdominal pain (68%), nerve palsy (28%) and orbital swelling (21%). Less often epistaxis, otalgia and trismus were reported. Displacement of teeth led to dental extraction in 12 patients. A total of 39 maxillary quadrants and 27 mandibular quadrants showed tumour invasion. This indicates a 1.4:1 preference for involvement of the maxilla. The premolar/molar region was the location most frequently affected. In the maxillary cases, the sinuses and the orbits were involved to some degree.

According to Murphy's distribution (Table 4), most cases (89%) involved a secondary location, with only 11% being an isolated oral tumour. Bone marrow and neuro-meningeal involvement was noted initially in 43% and 41% of patients, respectively. Following therapy, 59% of patients achieved complete remission with the planned protocol, while 35% were non-responders and died within a mean of 48 days following admission. Relapse occurred in two patients (one BM, one CNS) after a median of 4 months (range 3–6 months) from diagnosis, and they both died from related treatment toxicity after a second line of therapy. After a follow-up of 45 months (range 9–99 months), 54% were considered long-term survivors, with 100%, 91% and 27%, respectively, for stage II, III and IV; and 50%, 33% and 0%, respectively, for BM+ patients, CNS+ patients and BM-CNS+ patients.

Table 2. Murphy's tumour staging[11]

Stage I	A single tumour (extranodal) or involvement of a single anatomical area (nodal), with the exclusion of the mediastinum and abdomen
Stage II	A single tumour (extranodal) with regional node involvement Two or more nodal areas on the same side of the diaphragm Two single (extranodal) tumours, with or without regional node involvement on the same side of the diaphragm A primary gastrointestinal tract tumour (usually in the ileo-caecal area), with or without involvement of associated mesenteric nodes, that is completely resectable
Stage III	Two single (extranodal) tumours on opposite sites of the diaphragm Two or more nodal areas above and below the diaphragm Any primary intrathoracic tumour Any paraspinal or epidural tumour, whether or not other sites are involved
Stage IV	Any of the above findings with initial involvement of the CNS, bone marrow or both

Discussion

In this first study of the paediatric distribution of NHL in Morocco, it was found that oral Burkitt-type lymphomas account for 8% of total childhood NHL in this country. The age at onset of symptoms ranged from 2 to 15 years with a mean 6.64 years. Like the endemic form, the results suggest that it afflicts younger children between 5 and 7 years[3,8], whereas sporadic BL is associated with slightly older children (10–12 years). The male-to-female ratio was 5.1:1 (31 males, 6 females), which is similar to the

Table 3. Characteristics of patients, oral location, response to chemotherapy and overall survival

Patient	Gender	Age	Duration of symptoms	Facial bones	Other structures	BM or NM	Staging	Response to therapy	Survival (months from diagnosis)
1	M	12	1 month	R mand	Kidney, spleen	BM	IV	NR	<1
2	M	6	10 days	L mand	Pleural effusion, mesentery	BM	IV	CR	41+
3	M	3	2 months	B max	Mediastinum	BM NM	IV	NR	<1
4	M	4	1 month	B max B mand	Mesentery	BM	IV	CR	44+
5	F	9	2 months	L max	Pancreas		III	CR	50+
6	M	3	2 months	B max R mand	Pleural effusion, humerus	BM NM	IV	NR	<1
7	M	15	2 months	R mand	Mesentery, paraspinal	BM NM	IV	NR	<2
8	M	5	15 days	B max	Kidney	NM	IV	NR	<1
9	M	3	20 days	B max	Mesentery, kidney		III	CR	32+
10	M	7	2 months	R mand	Mesentery, mediastinum		III	CR	61+
11	M	13	2 months	B max L mand	Pancreas, liver, pleural effusion	NM	IV	R-NM	9
12	M	3	1 month	L max	Kidney		III	R-BM	4
13	M	6	1 month	B max			II	CR	89+
14	M	7	1 month	B max B mand	Mesentery, liver kidney, pancreas	NM	IV	CR	39+
15	M	6	40 days	L max L mand		NM	IV	CR	99+
16	M	13	1 month	L max	Nasopharynx	BM NM	IV	NR	<2
17	M	8	40 days	B mand	Mesentery	BM	IV	NR	<2
18	M	6	2 months	L mand	Liver		III	CR	99+
19	M	3	1 month	L max	Kidney		III	CR	82+
20	M	7	40 days	R max			II	CR	96+
21	M	4	25 days	B mand	Mesentery	NM	IV	NR	<1
22	M	7	1 month	B max	Kidney, liver, pleural effusion	BM	IV	NR	<1
23	M	3	2 months	R max	Kidney, liver, mesentery		III	CR	32+
24	M	11	20 Days	L mand	Liver, mediastinum, mesentery		III	CR	30+
25	M	4	20 days	B max	Mesentery		III	CR	30+
26	F	8	1 month	B max B mand	Kidneys, pleural effusion	BM	IV	CR	25+
27	F	3	2 months	B max		BM NM	IV	NR	<1
28	M	3	1 month	B max	Kidney, mesentery, testicle	BM NM	IV	NR	<1
29	F	3	1 month	L max	Kidney, mesentery, ovary	BM	IV	NR	<1
30	M	4	2 months	L mand	Sphenoid	BM NM	IV	NR	4
31	M	3	1 month	B mand B max	Kidney, liver, pancreas, mesentery	BM	IV	CR	12+
32	M	2	1 month	L mand	Kidney, pancreas, testicle		III	CR	13+
33	M	4	2 months	R mand R max	Pterygoid, infratemporal fossa	NM	IV	NR	5
34	F	8	2 months	R mand			II	CR	12+
35	M	5	2 months	L mand L max	Tibia, humerus, sternum		III	CR	9+
36	M	14	2 months	L max	Kidney, pancreas, intracranial	BM NM	IV	NR	<1
37	F	13	2 months	R max			II	CR	9+

M, male; F, female; R, right; L, left; B, bilateral; max, maxilla; mand, mandibula; BM, bone marrow involvement; NM, neuro-meningeal involvement; R-NM, relapse with neuro-meningeal involvement; R-BM, relapse with bone marrow involvement; CR, complete response; R, relapse; NR, no response.

gender distribution ratio for African and American patients[8,14].

In general, the clinical features of the disease depend on the location of the primary lesion. The signs of oral BL include a combination of oral masses, jaw expansion and mobile teeth, accompanied by characteristic radiographic features of jaw rarefaction and poorly circumscribed lytic lesions[18,24]. In the present study, pain and displacement of teeth were the most common chief complaints followed by swelling and sensory disturbances. Jaw and facial bone involvement closely resembled that reported in African BL[3,8], and was dissimilar to the pattern of jaw involvement in American BL[17]. Additionally, the maxilla appears to be involved at a higher rate than the mandible (1:4.1), which is

Table 4. Distribution of patients according to Murphy tumour staging

Stage	Total no. of patients	% Patients in given stage	Deaths	% Survivors
II	4	11	0	100
III	11	30	1	91
IV	22	59	16	27
Total	37	100	17	54

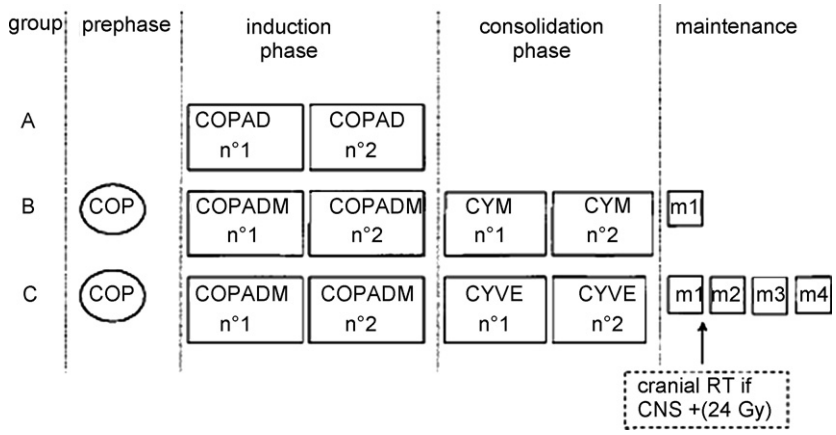

Fig. 1. LMB protocol schedule 12.COP: cyclophosphamide, vincristine, prednisone, methotrexate intrathecal + hydrocortisone; COPAD: cyclophosphamide, vincristine, prednisone, adriamycine, leucovorin; COPADM: cyclophosphamide, vincristine, prednisone, adriamycine, leucovorin, methotrexate intrathecal + hydrocortisone (grp C: +cytarabine); CYM: cytarabine, high-dose methotrexate, methotrexate intrathecal + hydrocortisone, cytarabine intrathecal + hydrocortisone, leucovorin; CYVE: high-dose cytarabine, etoposide; m: maintenance chemotherapy; m1: vincristine, high-dose methotrexate, leucovorin, prednisone, cyclophosphamide, adriamycine, methotrexate intrathecal + hydrocortisone (grp C: +cytarabine); m3: similar to m1 but without high-dose methotrexate and intrathecal; m2 or m4: cytarabine, etoposide.

consistent with previous reports in endemic areas[22].

In addition to oral and maxillofacial location, most of our patients presented a more disseminated disease (>89%), including abdominal, bone marrow and/or CNS involvement. Although the abdominal and bone marrow involvement resembled more closely the American form[14,23], bone lesions and CNS invasion, which are less often encountered in the sporadic form[16,18], are more similar to the findings of African BL[8].

The role of EBV in the development of BL of all types is well established[21], but this infection appears to be a more significant cofactor in endemic areas (95%)[10]. Testing for the presence of EBV was not done in the present series because of the lack of availability of special techniques. The finding of 88% EBV-associated cases with greater incidence of abdominal tumours and infrequent jaw involvement in Algeria[9] suggests a new histopathological subtype of BL in North African countries that remains to be elucidated. The variable incidence rate of EBV and existence of variant translocations or different breakpoint locations give support for the existence of several molecular subtypes of BL throughout the world[6].

Intensive combination chemotherapy is the treatment of choice for childhood BL; radiotherapy is limited to CNS prophylaxis[2,15]. Currently, patients with BL at the authors' institution receive chemotherapy according to the French LMB protocol for an African setting[7]. This treatment is based on intravenous cyclophosphamide, vincristine, prednisone, high-dose méthotrexate, cytarabine, doxorubicin and etoposide[12]. Results of multicentre studies using this type of protocol showed a ≥90% 5-year event-free survival with localized childhood B-cell lymphoma (Burkitt and large B-cell) or L3ALL, and slightly inferior event-free survival rates in patients with CNS involvement[12,13]. The 54% overall survival rate in the present study may be due to the greater number of patients at advanced stages at diagnosis (89% were stage III and IV) with CNS involvement in 38% of patients. CNS disease at onset in children is associated with a worse outcome[16]. These findings must be considered with caution because of the small number of patients and toxicity-related deaths. Such morbidity (metabolic disorders, febrile neutropenia and mucositis) may compromise the use of such intensive protocols in less privileged countries[12]. In view of this, determining optimal therapy that is equally or less toxic remains an important challenge. Delineation of clinical and biological features specific to this geographical area can help in prognosis improvement and prediction of treatment failure.

It is concluded from this series that clinical aspects of these cases may represent a form of BL that is distinct from the well-described endemic and sporadic subtypes. Future investigations are needed to attain a better understanding of the behaviour of BL in North Africa. Chemotherapy is the mainstay of treatment, but patients at advanced stages continue to have a dismal outcome. Continuing refinements in therapy are required to improve prognosis, specifically in advanced disease.

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