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Retrospective Epidemiological Study of Burkitt's Lymphoma in Israel and Diagnosis by a Conservative Incisional Biopsy

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The clinical features of 74 patients with Burkitt's lymphoma diagnosed at the Hadassah Medical Center in Jerusalem, Israel, are described. The prompt diagnosis of a child with high grade malignant jaw involvement of non-Hodgkin's Burkitt's lymphoma is reported. The use of the open biopsy with special emphasis on the incisional biopsy is discussed in light of the incidental exfoliation of the two primary molar teeth and one permanent successor in this case.

Keywords: Burkitt's lymphoma, Israel, diagnosis

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INTRODUCTION

BURKITT'S LYMPHOMA (BL) is a type of non-Hodgkin's lymphoma (NHL) of monoclonal small, non-cleaved B-cell lymphocytes, which is subclassified as either endemic (African) or non-endemic (American) [1]. This is one of the most rapidly growing paediatric tumours that requires prompt diagnosis before initiation of a specific treatment [2, 3]. Although the clinical features of endemic and non-endemic BL are dissimilar, the characteristics of the tumour cells and prognostic factors are similar [4].

Kinetic studies demonstrated doubling of the tumour's size every 24 h [1, 5]. This extremely rapid growth causes compression and damage to contiguous structures, resulting in symptomatic complaints early in the disease course. Signs of chronic debilitation, such as cachexia, generalised lymphadenopathy, weight loss and anaemia, are not common [1]. The peak incidence was found to be between 4 and 7 years of age, and even earlier in children with jaw involvement. Jaw lesions are the most characteristic and easily recognisable feature of the disease [6], and constitute 50–70% of the patients with the endemic (African) form [6, 7]. In fact, the occurrence of jaw lesions in the endemic form is almost 100% at age 3 years and drops steadily thereafter [8]. In non-endemic regions, the frequency of its occurrence in the jaw is as low as 15–18% [8, 9].

The clinical features of BL in the Middle East [10] differ from those described in the endemic and non-endemic forms. The low median age of BL in the Middle East (7 years) is similar to findings in the African type, while the high incidence of abdominal involvement (76%) and the low incidence of jaw involvement (17%), resembles the American type. Since it is the fastest growing tumour known, it necessitates immediate diagnosis. Open biopsy is rapid and offers reliable diagnosis because it provides viable tissue for histological examination [11, 12], while fine-needle aspiration for cytology is not always adequate for diagnosis [11]. Computerised tomography (CT) can be useful in the staging of the disease [2]. Patients who started chemotherapy promptly after biopsy are long-term survivors [5, 11].

Our purpose is to discuss the aim and extent of the open biopsy in small children, for the final accurate diagnosis of BL with jaw involvement, and to describe 74 patients with BL which were diagnosed at the Hebrew University–Hadassah Medical Center in Jerusalem, Israel, between 1981 and 1994.

CASE REPORT

A 3 year-old girl was brought by her parents to the emergency clinic of the Department of Pediatric Dentistry, The Hebrew University, Hadassah School of Dental Medicine, Jerusalem, suffering from right submandibular and right cheek swellings, and a 2 day history of abdominal pain and constipation. Ten days before admission, she was examined by her paediatrician who sent her for a blood count and referred her to a dentist with a tentative diagnosis of lymphadenopathy due to dental infection. Antibiotic therapy with amoxycillin had been started but no improvement was noticed.

DENTAL EXAMINATION

The child was co-operative with apparent distress. Bilateral submandibular lymph nodes were enlarged. Oral examination revealed large swellings in all four quadrants in the molar

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regions, soft and spongy on palpation, but not tender. They extended bucally and lingually in the mandible and bucally and palatally in the maxilla. The extent of the palatal swellings resulted in a deep midpalatal groove (Fig. 1). The molar teeth were loose and occlusally displaced (supra-eruption), causing premature occlusal contact on biting, that resulted in an anterior open bite (Fig. 2). Pressure application on biting compressed the molar teeth in the apical direction. The tongue showed benign migratory glossitis.

Intra-oral and lateral oblique radiographs showed large radiolucencies with irregular borders surrounding the second primary molars and loss of the lamina dura. The growing tissue in the bifurcation area caused alteration in the position and possibly in the shape of the developing tooth buds of both premolars. The primary mandibular molars were displaced occlusally, and the mandibular first molars were displaced towards the upper border of the mandible (Figs 3 and 4).

Following these findings, differential diagnosis of lymphoma or eosinophilic granuloma was suggested. The girl was referred the same day to the paediatric oncology unit at the Hadassah University Hospital for further evaluation and treatment. The following day, under general anaesthesia, an open biopsy from the right mandibular lesion was performed. It is important to note that during the biopsy procedure, an incidental pressure with a periostal elevator on the base of the lesion, resulted in an unexpected exfoliation of the entire tumorous mass.

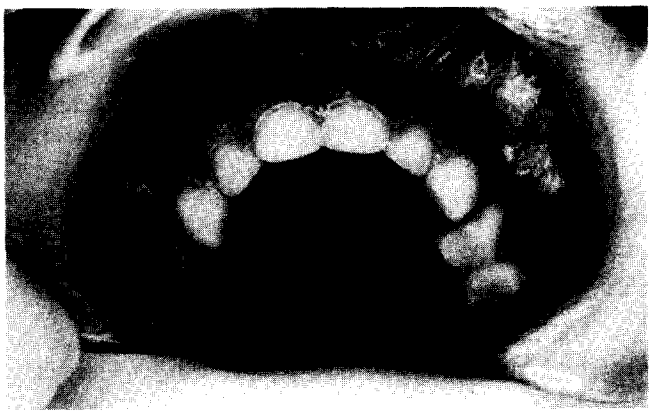

Fig. 1. Bilateral maxillary Burkitt's tumour, showing the bulging of both sides of the alveolus creating a deep groove in the midline of the palate.

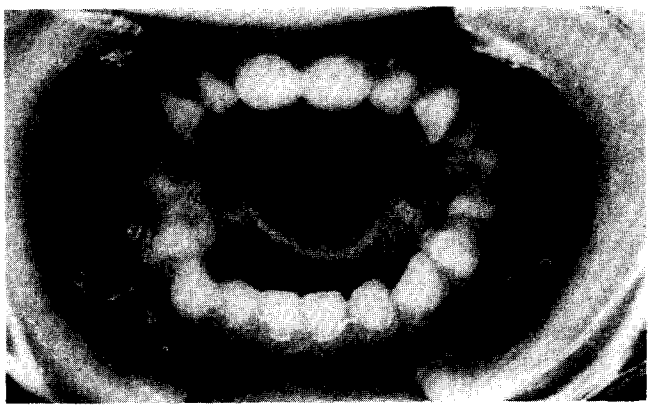

Fig. 2. Bilateral mandibular expansion of Burkitt's tumour appearing in the buccal and lingual areas. Note the supra-eruption of the second primary molars creating a prominent anterior open bite. The tongue has a benign migratory glossitis.

Fig. 3. Radiograph of mandibular primary molars in Burkitt's lymphoma. Note loss of lamina dura of teeth and germinating follicles with alteration in their position (arrow to second premolar tooth bud).

Fig. 4. Lateral-oblique radiograph of the child with Burkitt's lymphoma, showing the displacement of the first permanent molar by the tumour towards the upper border of the mandible.

PAEDIATRIC ONCOLOGY EVALUATION

In addition to the dental findings, physical examination revealed bilateral cervical lymphadenopathy, right lower lobe athelectasis and a right abdominal mass. CT showed para-aortic, mesenteric and pelvic lymphadenopathy and portal and retroperitoneal masses. Laboratory evaluation disclosed a mild anaemia and lactate dehydrogenase (LDH) of 13453 units. The mandibular biopsy specimen revealed high grade malignant lymphoma, small non-cleaved cells of Burkitt's type, with a prominent starry sky appearance. A bone marrow aspirate and biopsy showed no evidence of malignancy. A lumbar puncture did not show any malignant cells in the cerebrospinal fluid. Twenty-four hour urine collection for catecholamines was normal for the child's age. Following hydration, alkalinisation and allopurinol therapy, the child was treated with chemotherapy. The protocol delivered consisted of intravenous vincristine, cyclophosphamide, methotrexate and intrathecal Ara-c and methotrexate alternating with intravenous Ara-c, ifosfamide, etoposide and intrathecal methotrexate. A computerised tomography scan per-

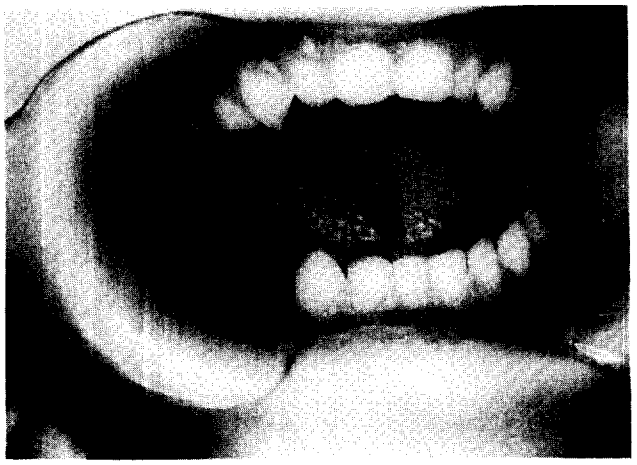

Fig. 5. Twenty months after termination of therapy. Note the complete regression of the tumour in the buccal and lingual right mandibular region. Also note the missing primary molars due to their inclusion in the biopsy specimen.

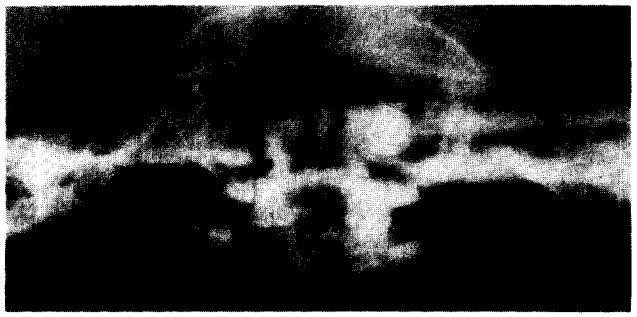

Fig. 6. Panoramic radiograph of the girl aged 5 years with BL 20 months after termination of therapy. Note the normal bone density, the reformed crypt of the right premolar, and the normal position of the right first permanent molar.

formed after two cycles of chemotherapy showed resolution of the disease in the jaws and in the abdomen. During chemotherapy the patient developed recurrent episodes of fever and neutropenia, staphylococcal sepsis, pneumocystis carinii infection and recurrent left lower lobe pneumonias. The child continues to do well 25 months after diagnosis. After the successful therapeutic recovery and the clinical regression of the tumour mass (Fig. 5), the bone density increased, the trabecular pattern returned to normal, and the premolar crypt also reformed with complete disappearance of the rarifications (Fig. 6).

EPIDEMIOLOGICAL AND DEMOGRAPHIC FEATURES OF BL IN THE ISRAELI REGION

74 cases of BL which were diagnosed at the Hebrew University-Hadassah Medical Center in Jerusalem, Israel, between 1981 and 1994 were evaluated retrospectively. The Hadassah Medical Center in Jerusalem is a 1000 bed University teaching hospital, one of the largest in the Middle East, which constitutes a referral centre for approximately one million citizens, including those from the Gaza Strip and the West Bank. The diagnosis of BL was made according to the criteria recommended by the NIH [13]. The age, at the time of presentation, ranged from 2 to 61 years. 47 cases (64%) were in the first decade, and 16 cases (22%) in the second decade. The peak incidence is in the 3–5 year age group with a median age of 5 years (Fig. 7).

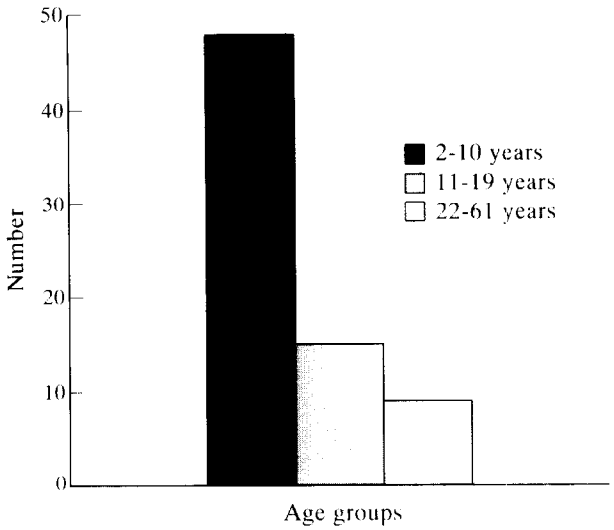

Fig. 7. Age distribution in 74 patients with Burkitt's lymphoma in Israel.

The disease shows a preference for males in a 3:1 ratio (56:18). Except for one patient, all others were born in the Middle East. 42 (57%) patients were of Arabic origin, while the remaining 32 (43%) patients were Jewish, of which 19 (26%) were of Sephardic origin, and 13 (17%) of Ashkenazi origin.

The predominant primary tumour sites were the abdomen in 56 (76%) patients, head, neck and maxillofacial region in 14 (19%) patients, 2 patients presented with mediastinal primary site, and one in the spinal cord and in one case (that of a 17-year-old girl) in the ovary. There was no apparent predilection to any ethnic group.

DISCUSSION

Being the fastest growing human tumour, BL has the potential to reach a prodigious size in a matter of days [14]. Patients, therefore, often present in an emergency situation, and definitive diagnosis and treatment must be acomplished within 24–48 h of admission [14]. When the age of the patient and the site, namely the jaws, are considered, the clinical differential diagnosis should include, in addition to BL, Ewing's sarcoma, neuroblastoma, eosinophilic granuloma and rhabdomyosarcoma.

There is no doubt if lymphoma is suspected, based on clinical appearance and on radiographic examination, that open biopsy should be carried out in order to obtain a quick and reliable diagnosis, since it provides viable tissue for histological examination [11, 15]. The goal should be immediate chemotherapy for almost every patient with this rapidly growing tumour [15].

The intention in this case was to perform an incisional biopsy. During surgical intervention, after the reflection of a mucoperiostal flap, incidental pressure with a periostal elevator on the base of the tumour resulted in an unexpected exfoliation of the entire tumour mass. Both primary molars and one permanent successor were included in this specimen. This phenomenon of unexpected enucleation of the entire tumoral mass, might be associated and related to the odonto-

genesis hypothesis [9], and the multicentric infiltration of the jaws and dental pulp by the tumoral cells [9, 16, 17], or by the release of an osteoclastic activating factor by the lymphoid cells [18].

The prompt diagnosis of the child in the present case as having high grade malignant lymphoma (Burkitt's type) led to immediate treatment by chemotherapy. Today, 20 months after termination of therapy, the girl has a 75–95% chance of a permanent cure [2, 4, 15, 19].

Using the most effective modern regimens to achieve complete remission, the use of open biopsy in children should be restricted to incisional biopsy only and not to surgical debulking. In so doing, fundamental treatment advances in the management of Burkitt's lymphoma will be transferred completely to the patient without accompanying restrictions. In our series, the predilection of the disease in males and the higher incidence in the abdomen and the head and neck, is in accordance with the findings in both the African and the American types. Similar features to those described in our study, namely, the predilection in males and the frequent abdominal presentations, were previously reported by groups from Israel [20], Iraq [21] and Lebanon [10].

Although the tumour is predominantly a childhood affliction in Africa, it may occur at any age in non-African countries [6]. Like the endemic (African) form, our results suggest that it afflicts younger children with a median age of 5 years, while the median age in the American form is 12. In two studies on BL in the Middle East: Israel [22] and Lebanon [10], the median age was 7 years. The common abdominal presentation in 76% of the patients in the present study is similar to the American form, while it presents in only 30% of patients with the African form. The most frequent site of presentation in the African form is the jaw. Head and neck childhood BL was studied retrospectively between 1976 and 1988 in one hospital in Israel [22], and this comprises 38.8% of the total of 80 children examined. However, this number includes 61% of children presenting with a primary tumour in another site.

In conclusion, our study delineates some of the distinctive features of BL in the Middle East that are similar and different to those previously described in the African and the non-African forms.

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