North American Burkitt's lymphoma presenting with intraoral symptoms

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Abstract

A case is presented in which posterior tooth mobility and pain, bilateral intraoral swelling of the mandible, and anterior open bite following an incident of facial trauma were the presenting symptoms of a 4-year-old, white American male with Burkitt-type malignant lymphoma. Radiographic examination revealed multiple osteolytic lesions in the body of the mandible, with loss of osseous trabecular architecture, and generalized loss of lamina dura in both maxillary and mandibular arches. The patient also had bone marrow involvement at the time of diagnosis. Following the initial course of chemotherapy, the patient experienced a significant resolution of the bilateral mandibular swelling, anterior open bite, tooth mobility, and dental pain. Relapse occurred shortly after remission was achieved, with tumor metastasis to the central nervous system and testes. The tumor remained resistant to further chemotherapeutic treatments and radiation strategems. Because of renal and metabolic complications, Burkitt's lymphoma constitutes an oncologic emergency. If untreated, this rapidly growing tumor is fatal. Early interception and referral of these cases by the examining dentist is crucial.

Introduction

Burkitt's lymphoma (BL) is a rare, extranodal malignant tumor of undifferentiated (small, noncleaved) Blymphocytes occurring predominantly in children; it is worldwide in distribution. The tumor, which originally was described by Dr. Denis Burkitt in 1958 as a jaw sarcoma, involved children in endemic areas of equatorial East Africa (Burkitt 1958). Following early reports of endemic African lymphoma, pathologists reported sporadic cases from Europe and America that were histologically and immunophenotypically indistinguishable from the African tumor (Dorfman 1965; O'Conor 1965). In the United States, the tumor is known as nonendemic or North American Burkitt's lymphoma (NABL).

Although similar histologically, there are numerous epidemiologic, clinical, and cytogenetic differences between cases of Burkitt's lymphoma occurring in endemic areas of equatorial Africa, and the sporadic cases occurring in North America. A summary of these differences is given in the table (see next page). In equatorial Africa, malignant lymphomas account for 50% of all pediatric malignancies. In America, malignant lymphomas account for only 10% of pediatric malignancies, being third in relative frequency after acute leukemias and brain tumors (Young et al. 1986). BL in the United States comprises approximately 1-2% of all childhood tumors, and about one-fifth of childhood non-Hodgkin's lymphomas (Kjeldsberg et al. 1983). In endemic BL, jaw involvement is common, occurring in approximately 60% of cases (Biggar et al. 1979); in nonendemic BL, jaw involvement occurs in only 15-18% of the cases (Ziegler and Magrath 1974; Levine et al. 1982). In the United States, BL most frequently presents as an abdominal mass. However, when the initial presentation involves jaw lesions, the tumor can cause toothache, tooth mobility, tooth displacement, intraoral and extraoral swelling, and perioral paresthesia. Radiographically, the tumor produces generalized destruction of the tooth crypts with loss of lamina dura and loss of trabecular pattern in the mandible and maxilla (Sariban et al. 1984).

Current theory suggests that endemic and nonendemic forms of BL represent the neoplastic coun-

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terparts of closely similar cells, probably cells at adjacent points in the lymphocyte differentiation pathway (Magrath and Sariban 1985). Cytogenetic studies of BL cell lines suggest that a characteristic chromosomal translocation involving the long arms of chromosomes 8 and 14 is implicated in the oncogenetic mechanism generating malignant B-cell tumors (Zech et al. 1976). However, the precise location of the break point on chromosome 8 differs in endemic BL as compared to NABL (Pellicii et al. 1986). Chromosome 8 is the site of the c-myc oncogene, and chromosome 14 is the site of the immunoglobulin heavy chain locus. This unique translocation phenomenon partly may enhance induction of the rapid cell proliferation characteristic of BL tumors (Regezi and Sciubba 1986). Another intriguing difference between endemic and NABL is their association with the Epstein-Barr virus. Ninety-five per cent of all endemic BL tumors carry EBV genomes in their cells, while only 10-15% of NABL tumors carry EBV (Levine et al. 1982). EBV may be implicated directly in the oncogenesis of the endemic form of BL, but, the mechanisms proposed for this remain controversial (Klein 1975; Berger and Bernheim 1985).

Treatment of both endemic BL and NABL primarily involves chemotherapy. NABL is very sensitive to cytotoxic therapy, and cure is achievable. Patients with only abdominal disease at diagnosis have a 50–75% likelihood of cure with chemotherapy (Anderson et al. 1983; Murphy et al. 1986). In contrast, patients with bone marrow involvement have a poor prognosis, having a prolonged survival of only 10–40% (Magrath et al. 1984; Murphy et al. 1986). Central nervous system (CNS) involvement also confers a poor prognosis. Early relapse after a short remission is associated with resistance to further treatment and carries a poor prognosis; relapse after an initial long remission carries a much more favorable prognosis (Ziegler 1981).

Complicating the initiation of chemotherapy in Burkitt's lymphoma is a syndrome of hyperuricemia, hyperkalemia, and hyperphosphatemia with hypocalcemia (Cohen et al. 1980). It is a consequence of rapid tumor cell proliferation and tumor cell lysis, and has been termed tumor lysis syndrome. It can lead to renal failure and sudden death from hyperkalemia or hypocalcemia. Early management of patients with Burkitt's lymphoma is directed toward controlling preexisting hyperuricemia and/or azotemia, after which chemotherapy is initiated promptly.

This report describes a case in which orodental signs and symptoms were the first manifestations of a widely disseminated malignant Burkitt's lymphoma.

Case Report

On September 28, 1988, a 4-year-old white male presented to the Madigan Army Medical Center emergency room for treatment of trauma to the chin sustained in a fall earlier the same day. The chief complaint on presentation was painful, loose molar teeth. The

Africa (equatorial)	USA	Reference
Very common (10 per 100,000)	Very rare (02 per 100,000)	а
Peak age: 7 years	Peak age: 11 years	d
Distrubution related to climate and geography	Distribution unrelated to climate and geography	b
Nearly always associated with Epstein-Barr Virus DNA in tumor cells (95% of cases)	Uncommonly associated with Epstein-Barr virus DNA in tumor cells (15% of cases)	а
Common sites of initial tumor involvement: jaw, abdomen, retroperitoneum	Common sites of initial tumor involvement: GI tract, abdomen, lymph nodes, bone marrow	С
aw tumors common	Jaw tumors rare	С
50% prolonged survival with chemotherapy, using Cyclophosphamide alone	50% prolonged survival with chemotherapy using Cyclophosphamide, vincristine, and methotrexate	b
Multiple relapses not incompatible with eventual prolonged disease-free survival	Survival uncommon after relapse	d
Chromosome 8 breakpoints: Upstream of c-myc	Chromosome 8 breakpoints: Within c-myc	а

TABLE. Comparison of Burkitt's lymphoma in Artrica and the USA

a. Pizzo and Poplack 1989

b. Magrath and Sariban 1985

c. Levine et al. 1982

d. Ziegler 1981

patient was referred to the Pediatric Dentistry Service to rule out the possibility of mandibular fracture, and to provide follow-up care.

On initial examination, the patient appeared in good general health, with age-appropriate physical and mental development. He was alert, communicative, and cooperative. Vital signs were normal. The past medical history was noncontributory. There was no history of recent foreign travel. The dental history disclosed that before the trauma, there reportedly was no anterior open bite or evidence of loose teeth. The patient admitted no prior experience with painful teeth. The extraoral exam revealed mild lymphadenopathy of the submandibular, jugulodigastric, and cervical lymph nodes. These nodes were freely moveable, firm, and nonpainful. No facial asymmetry, TMJ tenderness, preauricular pain, facial contusion, paresthesias, or painful palpable areas of the head or neck were noted.

The intraoral examination revealed a complete intact primary dentition with marked mobility of all molar teeth. The oral soft tissues were normal in appearance, except for localized areas of mild marginal gingivitis, and mild bilateral swelling of the mandibular and maxillary buccal vestibules. The epithelial attachment associated with the mobile teeth was normal, and periodontal probing revealed no significant pocket formation or hemorrhagic tendencies. A 3-mm anterior open bite was present, with incisal wear facets evident on the maxillary central and lateral incisor teeth, indicating past contact. In ruling out a possible condylar fracture, it was noted that there was no intraoral eccymosis or lateral deviation of the mandible on opening and closing, and no pain associated with functional excursions. Primary second molars were in contact bilaterally in centric occlusion.

The radiographic examination included an orthopantomogram (OPT), maxillary and mandibular occlusal films, periapical films of the four posterior quadrants, and right and left bite-wing films. The OPT (Fig 1) revealed no evidence of a fracture to the condyles, rami, or body of the mandible. Premature root resorption of the lower first and second primary molars, possible congenital absence of permanent tooth buds for all four second premolars, and loss of dental follicles around developing teeth was demonstrated. The OPT also showed a diffuse circular radiolucent area 1.5 cm in diameter in the body of the mandible, inferior to the developing crown of the lower left permanent first molar. The periapical films indicated loss of lamina dura, crestal bone, and trabecular architecture in the bone surrounding the roots of the mobile teeth; this was evident especially in the lower left quadrant (Fig 2).

A provisional differential diagnosis pending further testing was formulated to include: prepubertal localized juvenile periodontitis; hypoparathyroidism;



Fig 1. Orthopantomogram taken at initial presentation. There is generalized loss of lamina dura, crestal bone, and trabecular architecture in the mandible and maxilla.



Fig 2. Periapical radiograph taken at initial presentation demonstrating loss of lamina dura and premature resorption of primary molar root.

hypophosphatasia; and histiocytosis-X. The patient was scheduled to return to the clinic in the following week for a complete blood count, urinalysis, and blood chemistry profile.

The patient returned the following week with the prior symptoms of painful mobile teeth unresolved. The open bite persisted unchanged, with occlusion on second primary molars only. No significant change in the mobility of the posterior teeth was evident. The patient had been unable to eat solid foods during the intervening week. Some moderate expansion of the mandibular lateral alveolus was noted. The patient was referred to the pediatric service for medical evaluation and blood studies, to rule out metabolic, endocrine, and neoplastic disease.

Standard laboratory studies were within normal limits except for a low hemoglobin. A long bone radiographic series was read as normal; no osteolytic lesions were recognizable. Because of the inconclusive findings of the medical examination, the patient was referred to the oral and maxillofacial surgery service for a biopsy of alveolar bone tissue underlying one or more of the mobile primary molars. The differential diagnosis was revised to include: histiocytosis-X; lymphoma; central giant cell tumor; and leukemic infiltrate.

The following day the patient was taken to the operating room and under general anesthesia, the upper and lower right second primary molars were removed. Underlying soft tissue was curetted and submitted to the pathology service for tissue examination.

The hematoxlyn and eosin stained touch preparations demonstrated a diffuse and monotonous proliferation of immature undifferentiated lymphoid cells infiltrating bone and fibrous connective tissue (Figs 3-5). The cells, in general, were uniform in size and had large round to oval nuclei, one to four small nucleoli, and a sparse amount of amphophilic cytoplasm. Mitotic figures were frequent, as was individual cell karyorrhexis. Nuclear debris was abundant and was ingested in large, irregular macrophages. These cells had abundant, clear, and vacuolated cytoplasm and small orthochromatic nuclei. The characteristic macrophages were found scattered throughout the closely packed lymphoid cells, producing the characteristic "starry-sky" pattern (Fig 3). An unusual finding in one tissue section was the presence of odontogenic epithelium, with characteristic palisading, polarized columnar cells surrounded by tumor (Fig 5). Immunohistochemical marker studies identified a B-cell lymphoma with IgM kappa light chain phenotype. The microscopic diagnosis was consistent with malignant lymphoma, small noncleaved cell, Burkitt's type, also known as Burkitt's lymphoma.

Following pathologic identification of a malignant process in the biopsy specimen, pediatric oncology consultation was obtained. A detailed evaluation was undertaken to identify other areas of tumor involvement. At that time, generalized lymphadenopathy, hepatosplenomegaly, and bilateral kidney enlargement were noted. Significantly abnormal laboratory studies included hematocrit 29.6%, hemoglobin 10.3 gm/dl (N = 11.5–14 gm/dl), BUN 36 mg/dl (N = 10-20 gm/dl), creatinine 1.9 mg/dl (N = 0.2–0.8 mg/dl), and uric acid 13.4 (N <7 mg/dl). A diagnostic lumbar puncture revealed normal cerebrospinal fluid without malignant cells. A bone marrow aspirate and biopsy showed that B-lymphoblasts had almost completely replaced the normal marrow.

A chest X ray was normal. Computer tomographic scan of the abdomen showed marked bilateral renal enlargement. A technetium bone scan showed abnormal radionuclide uptake in the proximal left humerus, the maxilla, and the distal right femur (Fig 6, see next page). A gallium scan showed similar findings.

Before chemotherapy was initiated, measures were instituted to reduce uric acid and improve renal function. Chemotherapy then was begun according to Children's Cancer Study Group Protocol 503, using

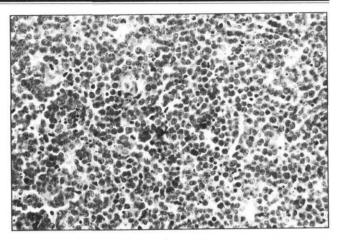


Fig 3. Typical "starry-sky" pattern of Burkitt's lymphoma. The tumor is characterized by dense monotonous proliferation of undifferentiated B-lymphocytes many demonstrating mitotic activity. Interspersed in the B-cell tumor mass are numerous large pale-staining histiocytes containing cellular debris. (H&E stain, 400X mag., B-5 fixative)

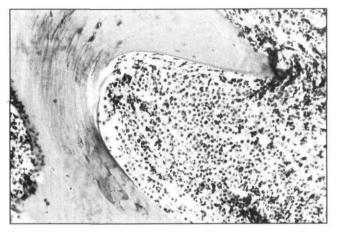


Fig 4. Bone trabecula resorption with replacement by Blymphocytic tumor mass. (H&E stain, 200X mag., B-5 fixative)

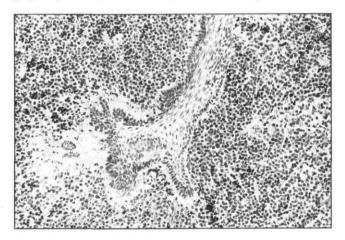


Fig 5. Odontogenic epithelium surrounded by tumor mass. Note the palisading arrangement of the polarized columnar cells. Specimen was curetted from the alveolus of the lower 2nd deciduous molar extraction site. (H&E stain, 200X mag., B-5 fixative)

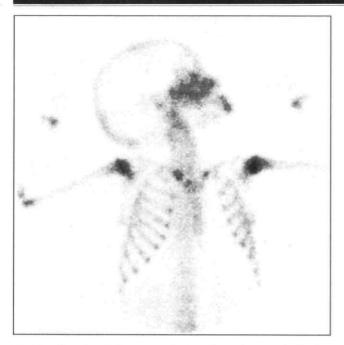


Fig6. Technetium 98 bone scan before chemotherapy, indicating probable tumor activity in the left humerus and maxilla.

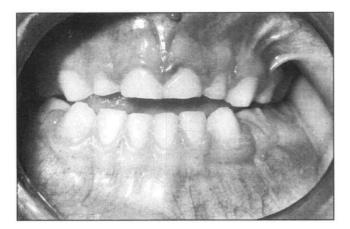


Fig 7. An anterior open bite created by hypereruption of primary molars secondary to the expansile proliferative tumor mass within the basal and alveolar bone of the mandible and maxilla.

cyclophosphamide, vincristine, prednisone, and intrathecal ARA-C initially (Anderson et al. 1983). At this time, the patient had developed marked bilateral bony expansion of the mandible, with an increase in anterior open bite (Fig 7). Also, soft tissue edema increased in the lower face and submental region (Fig 8). At three days postinduction chemotherapy, a dramatic reduction in both the bilateral mandibular expansion and generalized facial edema occurred (Fig 9). Five days after chemotherapy was begun, the hypereruption of the primary molars persisted, maintaining the anterior open bite; however, tooth mobility had decreased. There was only mild regression of the intraoral man-



Fig 8. Patient one day before initiation of chemotherapy. There is marked bilateral bony expansion of the mandible and generalized soft tissue edema in the lower face area and submetal region.



Fig 9. Patient three days after induction chemotherapy. There is marked reduction in both bilateral mandibular expansion and facial edema.

neoplasm, with a potential doubling time of 24 hr and a growth fraction of nearly 100% (Regezi and Sciubba 1989). If untreated, this tumor invariably is fatal. Because of its growth rate and associated metabolic consequences, BL constitutes an oncologic emergency. Metabolic imbalances are particularly severe in patients with Burkitt's lymphoma, as a consequence of rapid tumor cell proliferation and lysis, and may lead to renal failure and sudden death from hyperkalemia or hypocalcemia (Cohen et al. 1980). Early intervention with a remission induction chemotherapy regimen is

dibular swelling. At 36 days following initiation of chemotherapy, an OPT (Fig 10, see next page) showed improved trabecular pattern in the mandible, better alignment of the developing follicles of the lower second molars, and a closed anterior occlusion. The diffuse radiolucency inferior to the developing lower permanent first molar had not resolved. The patient was considered to be in remission since bone marrow aspirate, abdominal computerized tomography scan, technetium bone scan, and gallium scan showed no evidence of disease. Patient care was transferred to Loma Linda University Medical Center, CA, for social reasons.

At three months postdiagnosis, relapse occurred in the CNS and testes. Further efforts to control the spread of the tumor by chemotherapy and radiation strategems were unsuccessful. The patient died 10 months after initial diagnosis.

Discussion

Burkitt's lymphoma has the highest proliferation rate of any human

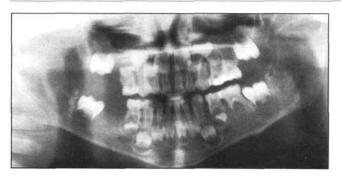


Fig 10. Orthopantomogram taken 37 days after induction chemotherapy. The patient is in remission. There is evidence of improved trabeculation and some resolution of lytic bone lesions.

critical for assuring a reasonable probability of longterm survival.

Sariban and associates (1984) reviewed 100 cases of NABL and found 16 with jaw lesions at presentation. Of these, 14 first were evaluated by a dentist. Adults most frequently presented with toothache and perioral numbness, and children with toothache, loose teeth, and intraoral and extraoral swelling. Of these cases, 10 were treated initially by dentists for presumed dental infection with antibiotic therapy and/or dental extractions. Significant delays in cancer therapy resulted. The incidence of jaw lesions on presentation has been estimated to be 12% (Levine 1982). This suggests that dentists may have the opportunity to play an important role in the early recognition of NABL patients presenting with oral symptoms.

The most important diagnostic aids besides biopsy in differentiating early BL from gingival and odontogenic infection are intraoral and panoral radiographs (Baden and Carter 1987). The loss of lamina dura in the posterior quadrants is one of the most consistent radiographic findings associated with early stage BL (Nzeh 1987). A panoral view often will reveal diffuse osteolytic lesions in the body of the mandible or maxilla. Accordingly, lymphoma always must be included in the differential diagnosis when a young patient presents with clinical findings of generalized loss of lamina dura with resulting tooth mobility, associated pain, and swelling. BL then can be differentiated from other oral and systemic disease entities with similar presentation by histopathologic examination of one or more of the osteolytic lesions. Alveolar bone biopsies of young patients ideally are performed in an operating room with general anesthesia. The biopsy specimen should not be fixed, but placed in 0.9% sterile saline and immediately transferred to the pathology laboratory for histopathologic examination. Cytological, histochemical, and immunological cell marker studies needed to confirm the diagnosis require a variety of special tissue preparation techniques. Therefore, the pathology service should be consulted before a biopsy to determine the requirements for a representative and adequate specimen, and to order specific studies.

Clinical diagnosis of this case centered on a variety of intraoral findings inconsistent with the chief complaint of trauma to the chin. Most notable of the early signs was hypermobility of all posterior teeth. Diffuse neoplastic osteolysis in areas of the alveolar process caused by the B-cell tumor mass resulted in loss of supporting alveolar cortical bone and its associated bundle bone. The hypereruption of posterior teeth is related to the expansile nature of the B-cell tumor mass. The same physiologic pressure causing the lateral expansion of the jaws also may cause the teeth to hypererupt. This phenomenon of disarticulated or "floating teeth" can be explained by the replacement of supporting bone by tumor with an intact epithelial attachment at the dentogingival junction (Staalman and Aarts 1984). The osteolytic nature of the neoplasm also may account for the unusual resorption pattern seen on roots of teeth embedded in the tumor mass. Following tumor ablation therapy, loose teeth generally return to stability with the regeneration of alveolar bone and the periodontal ligament (Hupp et al. 1982).

In the case presented, the patient responded favorably to remission induction chemotherapy. Yet, within three months of remission, relapse occurred, with metastasis of the tumor to the CNS and testes. Cases such as this, with early relapse following a short period of remission, tend to respond poorly to further chemotherapy treatment. New treatment modalities that may improve the survival of Burkitt's lymphoma patients are being investigated. Murphy et al. (1985) suggests that future trends will involve marrowtransplant rescue, either allogeneic or autologous, with marrow treated in vitro to remove tumor cells. However, better means to control CNS involvement need to precede this development.

A review of the literature shows that the majority of American Burkitt's lymphoma cases presenting with jaw involvement are seen initially by dentists for treatment of oral and dental symptoms (Sariban et al. 1984). Dentists treating children must always suspect lymphoma when there is unexplained tooth mobility, tooth pain, jaw swelling, or numbness of the chin. Prompt referral for medical evaluation and biopsy can be lifesaving.

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Dental school applicants

The number of applicants to dental schools has stayed the same or is increasing slightly, says the American Association of Dental Schools. This observation is based on last year's figures.

Also, the number of students taking the Dental Admission Test (DAT) last October was up 3.9 percent, the first increase of any sort in years. The number of DAT takers has always been the most reliable harbinger of changes in the size of the applicant pool.