Childhood Craniofacial Burkitt's Lymphoma Presenting as Maxillary Swelling: Report of a Case and Review of Literature

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ABSTRACT

Burkitt's lymphoma (BL) is an undifferentiated malignant lymphoma comprising of uniformly primitive lymphoreticular cells. The tumor was seen originally in patients in Africa. African type BL usually occurs in the jaws of young children. In American cases, abdominal involvement predominates. Strong evidence implicats Epstein-Barr virus in the development of BL. BL is found most commonly in childhood, with a peak incidence in African cases at 5 to 8 years old and in American cases at 10 to 12 years old. The disease shows a preference for males in a 2:1 to 4:1 ratio. BL is the most rapidly growing neoplasm requiring immediate diagnosis and treatment; however, it is extremely sensitive to chemotherapy. In this report, a case of BL that was initially misdiagnosed as an acute dental abscess is presented and the role of the dentist in the diagnosis and treatment of these patients is emphasized. (J Dent Child 2006;73:45-50)

KEYWORDS: BURKITT'S LYMPHOMA, MALIGNANT LYMPHOMA, MALIGNANT LYMPHORETICULAR DISORDER, JAW TUMOR, CHILDHOOD CRANIOFACIAL TUMOR

Burkitt's lymphoma (BL) is a high-grade, aggressive subgroup of non-Hodgkin's lymphoma and composed of small, noncleaved, diffuse, undifferentiated, malignant cells of B lymphoid origin.[1-3] The tumor was seen originally in patients in Africa.[4,5] Three subtypes of BL have been identified: (1) African (endemic) Burkitt's lymphoma (eBL); (2) American (sporadic) Burkitt's lymphoma (sBL); and (3) HIV-associated Burkitt's lymphoma (HIV-BL).[6,7] Endemic BL usually occurs in the jaws of young children.[1,4,5,7-11] Its predilection for jaw and other facial bones is the most striking feature of eBL.[7] In sBL cases, abdominal involvement predominates.[1,4,5,8,9]

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Many etiologic theories have been espoused. Historically, the geographic distribution of BL in equatorial Africa coincided with low, hot, humid areas often having high malarial infection rates.[1,5] The theory of infection by an insect-borne virus was postulated. There is strong seroepidemiologic and experimental evidence implicating a human DNA virus called Epstein-Barr virus (EBV) in the development of BL[5]. Cofactors may include chromosomal abnormalities, malarial infection, immune defects, and protein-energy deficits.[3,5]

Although EBV is strongly considered to be a potential etiologic factor of BL, its precise role is not well understood. EBV is an enveloped herpes virus that contains double-stranded linear DNA of 170 to 175 kb in the nucleocapsid. After entering the oropharynx and adjacent structures, this virus preferentially infects B-cells via the C3d complement receptor, CD21. Primary infection during early childhood is mostly asymptomatic, whereas infection during adolescence results in acute infectious mononucleosis in 30% to 50% of cases. Immunodeficiencies may allow viral reactivation and

Table 1. Clinical Staging Classification Suited for Children With Non-Hodgkin's Lymphoma[15]

Stage 1
A single tumor (extranodal) or single anatomic area (nodal), with the exclusion of mediastinum or abdomen
Stage 2
A single tumor (extranodal) with regional lymph node involvement
2 or more nodal areas on the same side of the diaphragm
2 single (extranodal) tumors with or without regional lymph node involvement on the same side of the diaphragm
A resectable primary gastrointestinal tract tumor, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only
Stage 3
2 single tumors (extranodal) on opposite sides of the diaphragm
2 or more nodal areas above and below the diaphragm
All the primary intrathoracic tumors (mediastinal, pleural, thymic)
All extensive primary unresectable intra-abdominal disease
All paraspinal or epidural tumors, regardless of other tumor site (or sites)
Stage 4
Any of the above, with initial involvement of central nervous system or bone marrow or both

the excessive proliferation of EBV-infected B-cells, which may lead to the development of EBV-positive B-lymphoproliferative diseases or lymphomas.[12]

BL cells contain a reciprocal chromosomal translocation, the most frequent of which is an 8q24;14q32 translocation. An association between the chromosome 8 breakpoint and geography has also been shown in BL.[2,3] The overexpression of c-myc oncogene and the functional loss of wild type p53 gene are considered to be possible etiologic factors as well.[12]

The most common oral signs of BL may include hyperplastic gingiva, mobile teeth, buccolingual displacement of vital dental elements, and swelling of the jaw. Premature eruption of permanent molars is often an early sign of a tumor. Sometimes dental or jaw pain and paresthesia is present.[5,11,13] Cervical lymphadenopathy enlargement is very rare in eBL.[7]

Radiologic features of this osteolytic lesion aid in diagnosis. An early sign of involvement in the jaw is the loss or disruption of the lamina dura around developing or erupting teeth. Tooth follicles may be enlarged, the cortex surrounding the tooth crypts may be destroyed, and teeth and tooth buds may be displaced by the enlarging tumor mass. Small radiolucent foci around the dental elements eventually coalesce to form large radiolucent defects in the jaw, which give the impression of "teeth floating in air". In the maxilla, the outline of the maxillary sinus may be blurred. Root resorption is usually not a factor, although invasion of the dental pulp by tumor has been observed.[5,10,11]

Several laboratory findings are consistently abnormal in BL patients. Serum lactic dehydrogenase (LDH) is elevated to a level corresponding to the extent of tumor dissemination.[5,14] Serum uric acid is elevated as an index of tumor necrosis. Increased activity of SGOT, alkaline phosphatase, and the immunoglobulins has been reported. Anemia and leukocytosis are common. In addition, the erythrocyte sedimentation rate (ESR) and blood urea nitrogen (BUN) may be elevated.[5]

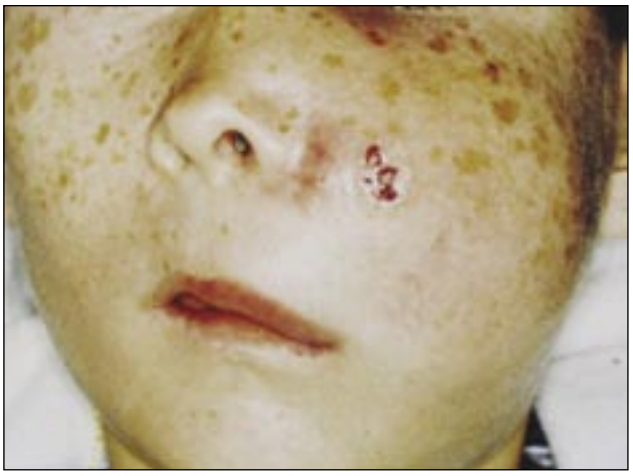

Figure 1. Patient shown on day of admission.

The disease stage appears to be a more important prognostic factor in African cases.[1] Different staging systems have been used for BL.[6] One system, as enumerated by Murphy,[15] is presented in Table 1.

BL is one of the fastest-growing neoplasms requiring immediate diagnosis and treatment.[1,5,7,11] The recognized treatment of choice for BL is chemotherapy, due to the disseminated nature of the disease and the phenomenal drug sensitivity of rapidly replicating BL tumor cells.[5] BL is one of the first human malignancies shown to be curable by chemotherapy alone.[12]

In this report, a case of BL that was initially misdiagnosed as an acute dental abscess is presented and the role of the dentist in the diagnosis and treatment of these patients is emphasized.

CASE REPORT

An 11-year-old Caucasian boy was referred to the Oral and Maxillofacial Surgery Department of the Dental Faculty of the University of Gazi, Ankara, Turkey, with a chief complaint of left facial swelling. The patient had continuous pain in the left upper molar region in spite of the administration of analgesics.

His history revealed that 6 weeks prior to his first visit to the authors' department, he was admitted to a dental practitioner with a complaint of mildly painful left facial swelling. He was told that the cause of this swelling was an acute infection of odontogenic origin, and he was treated with cefazolin sodium for 5 days. There was no improvement over the next 5 days; moreover, his facial swelling was quite remarkable. The child was admitted to another dental practitioner who referred him to a district hospital. The patient then was referred to the authors' department.

The child's past medical history was negative. He was well-nourished and well-developed. He complained, however, of headache, poor appetite, and listlessness. He was suffering from pruritus of the left maxillary area. It was thought that this may be due to the numbness of the stretched swelling area.

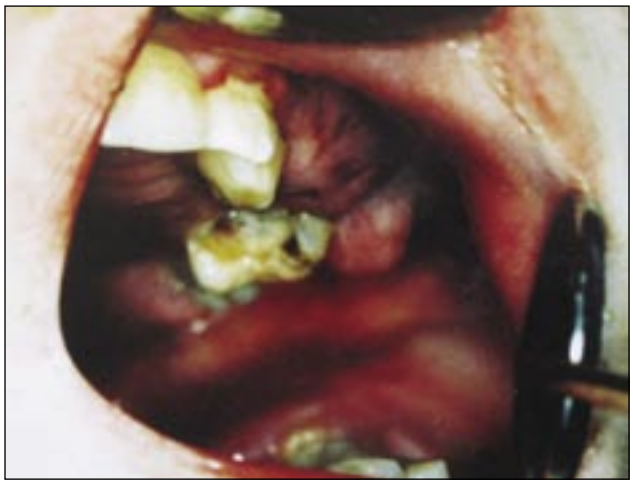

Figure 2. Intraoral appearance at initial examination.

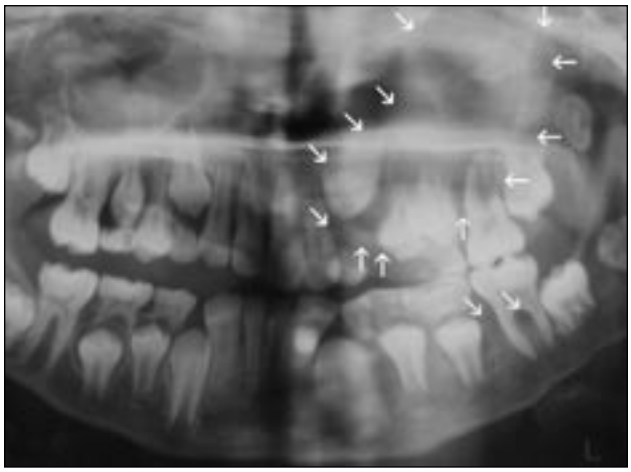

Figure 3. Panoramic radiograph at initial examination.

Extraoral examination revealed swelling and tenderness in the left maxillary region. The skin overlying the lesion area was ulcerated and hyperemic. Due to the swelling, the left corner of the mouth transposed in a downward direction and the tip of the nose pointed toward to the right side. The left sulcus nasolabialis was not clear (Figure 1). Left submandibular lymphadenopathy was noted. A nonfluctuant, firm node 2 cm in size was palpated in this region. Trismus was present. Vital signs were as follows:

1. pulse was 100 beats/minute (normal=80-120 beats/minute);
2. respiratory rate was 24 breaths/minute (normal=15-20 breaths/minute);
3. blood pressure was 120/70 mmHg (normal=125/80 mm Hg); and
4. weight was 30 kg.

Intraoral examination showed a firm, nonfluctuant mass both in the buccal sulcus of the left maxilla and in the posterior of the left lower first molar. The swelling extended from the left upper lateral incisor area to the left permanent first molar area in the maxilla and from the left lower primary second molar to the retromolar area. The soft tissue in that region had become swollen and boggy (Figure 2). The overlying mucosa looked normal, with no ulceration or erythema. The left upper and lower first molars were grossly mobile (grade 2) and tender to percussion. Both the upper left deciduous canine and second molar and lower left deciduous first and second molars were mobile (grade 3). The upper left deciduous first molar was absent, and the second molar was carious. The patient's oral hygiene was poor and visible plaque was present on the tooth surfaces. The gingiva was pale, pink, and swollen with areas of spontaneous bleeding.

Panoramic radiographs showed diffuse loss of the crestal alveolar bone around the upper and lower first molar on the left side and displacement of the germs of the unerupted left upper and lower third molars, indicating possible infiltration of these structures. The outline of the left maxillary sinus was blurred (Figure 3). A computed tomogram (CT) showed a large mass of left maxillary sinus origin with total

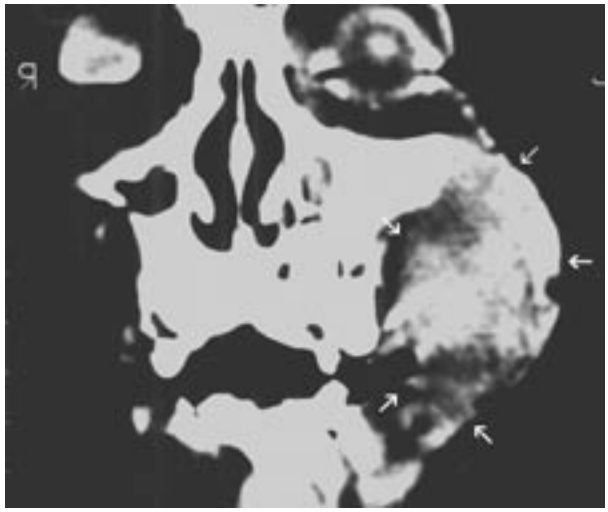

Figure 4.

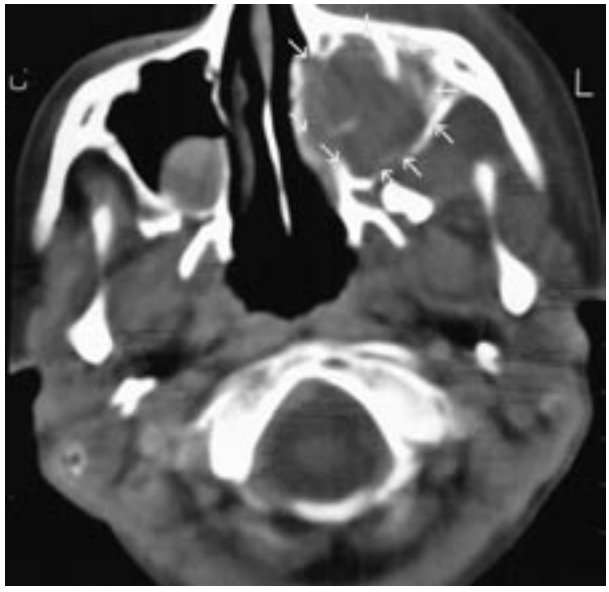

Figure 5.

Figures 4 and 5. Computed tomography scans reveal a large mass of left maxillary sinus origin.

obliteration and bony destruction of the medial part of the sinus. The maxillary antrum was infiltrated with tumor, but the left orbit was intact (Figures 4 and 5).

Acute dental abscess and dentigerous cyst were included in the differential diagnosis. Aspiration of the lesion was nonproductive. To determine the definite diagnosis, a biopsy was performed. Histopathological examinations revealed a neoplastic lesion that arranged in a diffuse, sheet-like pattern and invaded skeletal muscle. The neoplastic cells were uniform in size and shape. The nuclei were round and noncleaved with several prominent nucleoli. The thin rim of cytoplasm was deeply basophilic. Mitoses and interspersed histiocytes with engulfed nuclear debris and scattered tangible body macrophages were also observed (Figure 6). The cytoplasm of cells showed pyroninophili with Methyl green pyronin, and immunohistochemical stainings revealed diffuse anti-CD 45 (leucocyte common antigen) and focal anti-CD 20 (B-cell phenotype; Figure 7) positivity in neoplastic cells. This data was consistent with the diagnosis of BL. The patient was then referred to the Pediatric Department.

The results of hematologic studies were as follows:

1. Hemoglobin was 12.8 g/dl (normal=10.9-14.4 g/dl).
2. White blood cell count was 14,000 cells/mcl (normal=4,500-10,000 cells/mcl) with 64% neutrophils, 12% lymphocytes, and 24% atypical lymphocytes.

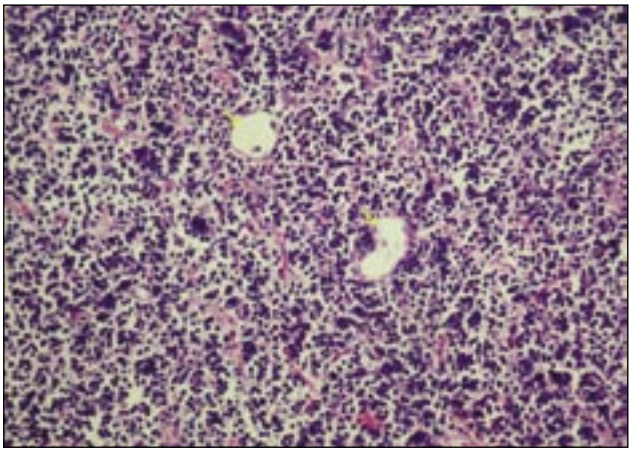

Figure 6. Sheets of neoplastic lymphocytes and scattered tingible body macrophages (arrow; Hematoxylin and Eosin X200).

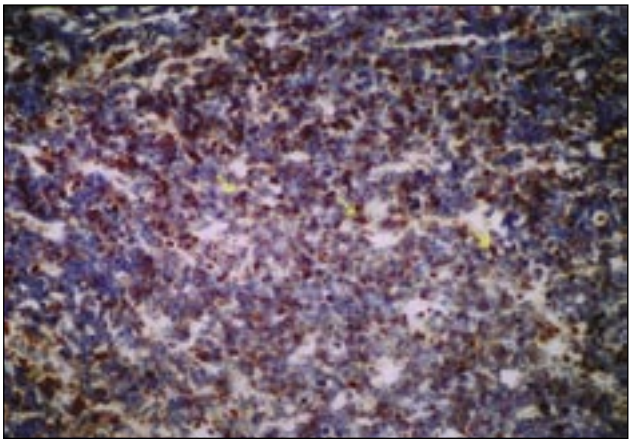

Figure 7. CD 20 positive stained lymphocytes (X100, ABC).

3. Serum LDH was 1,435 IU/L (normal for 2-12 years old=110-295 IU/L).
4. BUN was 13 mg/dL (normal=5-18 mg/dL).
5. EBV IgM and IgG were negative, indicating recent or active infection with EBV.
6. Cerebrospinal fluid examination revealed no abnormality.
7. Bone marrow samples were negative for tumor.
8. The abdominal scan was within normal limits.
9. The chest radiograph and bone scan were negative for any pathology.
10. The tumor was stage 2, according to the Murphy Classification, but considered in the risk group of the NHL BFM-95 chemotherapy protocol because of the close localization of the tumor to the central nervous system (CNS).

Chemotherapeutic induction consisted of intravenous methotrexate, vincristine, VP-16, cytosine arabinoside, ifosfamide, cyclophosphamide, dexamethasone, doxorubicine and intrathecal methotrexate, and prednisolone.

After 3 courses of chemotherapy, the submandibular lymphadenopathy had resolved and the oral swelling was greatly diminished. The patient was clinically free of disease, but fever and aphthous stomatitis were observed in that time and filgrastim (Neupogen, Roche, Switzerland), thienamycin (Tienam, Merk Sharp and Dohme, Turkey), teicoplanin (Targocid, Aventis Pharma, Italy), nystatin (Mycostatin, Bristol-Myers Squibb, Turkey) were administered. The patient's temperature was normal the next day, and 7 days later aphthous stomatitis was resolved. Three more cycles of chemotherapy were administered, resulting in a total of 6 cycles. The radiographs of the teeth and jaws were normal. MRI just after completion of chemotherapy showed complete resolution of the lesion (Figure 8). At the 36-month follow-up, no recurrence was observed.

DISCUSSION

Endemic BL is a malignant lymphoreticular disorder usually occurring in the jaws of young children. Sporadic BL differs in its mode of occurrence, frequently presenting with abdominal disease and involvement of cervical lymph nodes and bone marrow at an early stage.[8] BL is also one of the more common lymphomas complicating the clinical course of HIV infection.[9]

A number of clinical and biological differences between eBL and sBL have been reported.[9,10] One of the most striking of those is the presence of Epstein-Barr virus (EBV) DNA in more than 90% of eBLs, but in only 10% of sBLs.[9-11] The virus is latent in the tumor cells and its role is unclear.[9,12] Endemic BL usually occurs in the jaws of young children[8-10,11] and it involves (in descending order) the: (1) gastrointestinal tract; (2) CNS; and (3) orbit. The pattern of distribution of sBL is different. It frequently involves the gastrointestinal tract and, less frequently, lymph nodes, bones, and bone marrow.[9] The peak incidence of eBL is at age 5 to 8 years,[9,16] whereas it is 10 to 12 years with sBL.[5,11] In epidemic regions, BL

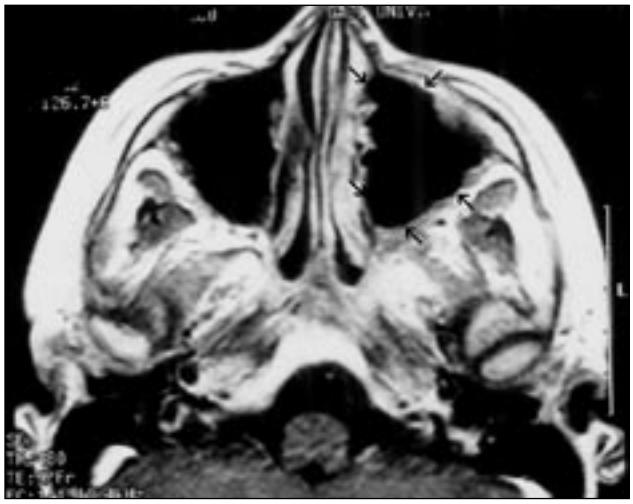

Figure 8. MRI taken after completion of treatment shows complete resolution of the lesion

accounts for about 50% of all childhood cancers.[9] BL has a male-to-female ratio of 2:1 to 4:1.[1,9] In this report, the case of an 11-year-old male is presented.

Cervical lymphadenopathy enlargement, which is very rare in eBL,[5] is more common in sBL.[5,7] In this case, the extraoral examination revealed submandibular lymphadenopathy. BL is a frequently seen form of childhood malignant tumor in Turkey. It is reported that the epidemiological features, clinical presentation, and course of Turkish Butkitt's lymphoma are in a form between eBL and sBL.[2,3] Although the case presented here is an e BL, the submandibular lymphadenopathy was noted. The authors think that this finding may be stemming from the features of BL in Turkish population.

BL's jaw tumors are commonly confused with such lesions as an acute dental abscess, osteomyelitis, ossifying fibroma, embryonal rhabdomyosarcoma, osteosarcoma, dentigerous cyst, retinoblastoma, mucoepidermoid carcinoma, eosinophilic granuloma, neuroblastoma, and fibrous dysplasia.[5,11] With the error in clinical diagnosis approaching 48% in some studies, the importance of histologic diagnosis is evident.[5] Sariban et al,[10] who reviewed 16 patients, reported that 14 of them were initially evaluated by the dental practitioners and 10 were misdiagnosed as tooth infection. In this case, BL had been initially confused with acute dental abscess by the dental practitioners.

Jaw involvement is far more frequent in BL than with other lymphomas.[16] Among the jaws, the maxilla appears to be involved at a higher rate than the mandible.[5] In the current case, the lesion was located in the left maxillary and mandibular regions.

Radiographic findings of the involved jaw include discrete foci of alveolar bone destruction, premature tooth eruption, destruction of dental crypts, loss of lamina dura, and widening of the periodontal ligament.[10,11,13,14] Similar findings were observed in this case.

The prognosis improves with younger age at diagnosis, minimal tumor burden, and rapid initiation of chemotherapy, demonstrating the importance of early diagnosis and treatment. Prolonged survival is predicted by site and extent of the tumor, with bone marrow and CNS involvement being an indication of a poor prognosis.[5] Patients with HIV-BL have a much poorer prognosis.[9] BL is extremely sensitive to chemotherapy.[8] Patients with limited or localized disease (stages 1 and 2) are cured in 90% to 100% of cases with intensive chemotherapy. Unlike other lymphomas, radiation therapy does not improve the results.[9,16] This patient had a complete remission after 6 courses of chemotherapy.

Because the BL frequently involves the jaws at an early stage, the need for dentists to have an adequate knowledge of the early changes in the oral cavity is crucial.[11] BL is also one of the fastest-growing neoplasms, with a cell doubling time of 24 hours.[1,6,7,11,16] Because of this high growth fraction of the tumor, little time should elapse between diagnosis and treatment. Thus, staging needs to be accomplished immediately.[9]

Relapse of disease occurs within 8 months of starting treatment or it does not occur at all.[9] In the current case, although 36 months had passed, no relapse was observed.

The clinical course of BL in untreated patients is progressive, with rapid wide dissemination followed by death.[7] Patients in whom the bone marrow or CNS is involved have a poor prognosis.[11]

Dentists must be suspicious when faced with a child patient presenting with unexplained hypermobility of teeth, displacement of tooth buds, and loss or disruption of the lamina dura around developing or erupting teeth. The radiological appearance of teeth as "floating in air" is another worrisome sign. Facial swellings should be given serious attention, and jaw tumors should be considered in clinical differentiation. Early recognition, diagnosis, and treatment will improve patient prognosis.

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