Oral complications in pediatric oncology patients

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Abstract

This study investigated the oral problems occurring in children receiving treatment for malignant disease at a regional oncology center. Forty-three children 2 to 14 years old were followed longitudinally from initial diagnosis for periods ranging from eight to 30 weeks for the development of oral and dental problems. Fifteen children had untreated decay; two required the removal of primary teeth before they began chemotherapy. Three children developed acute dental infections during treatment. Forty (93%) developed oral problems associated with their disease or treatment during the study period. Oral mucosal ulceration was the most frequently encountered problem; it was observed in 28 (65%) patients. In light of the high prevalence of dental and oral problems in these patients, this study emphasizes the need for positive dental involvement, both in pretreatment assessment and in the ongoing care of the pediatric oncology patient. (Pediatr Dent 13:289–95, 1991)

Introduction

Second only to accidents, malignant disease is the most common cause of death in children younger than 15 years old (Lanzkowsky 1983). In the United Kingdom, approximately 1200 new cases are reported annually. Up until the 1960s, the majority of childhood malignancies were considered to be uniformly fatal. Fortunately, considerable advances have been made in recent years in treating such conditions, and the long-term prognosis of these patients has improved vastly. In acute lymphoblastic leukemia, five-year disease-free survival rates of more than 70% have been reported for the most favorable prognostic groups (Hammond 1986).

Complications resulting from cancer, or secondary to cancer treatment, frequently occur in the oral cavity. The reported incidence of such complications in the literature varies considerably, but they appear to be far more common in children (Stafford et al. 1980). Few studies reporting oral complications occurring in pediatric oncology patients have followed children longitudinally and prospectively to investigate the development of orodental complications during cancer therapy (Duffy and Driscoll 1958; Michaud et al. 1977).

Considering these factors, it seemed appropriate to conduct a study designed to investigate the incidence and nature of oral problems occurring in a population of British child cancer patients. Accordingly, a longitudinal study of all children with newly diagnosed malignancies who were treated at a regional pediatric oncology unit was conducted.

Materials and Methods

All patients between 2 and 15 years old admitted to the Yorkshire Regional Pediatric Oncology unit based in Leeds, UK, for the treatment of newly diagnosed malignancies over a nine-month period were included in the study (subject to informed parental consent). The investigator visited the oncology ward weekly, when all patients newly admitted to the unit were seen and consent was obtained. After asking if the child was suffering any oral discomfort, a thorough, systematic examination of the oral and perioral tissues was performed. Patients with a primary tumor located in the head or neck or those being admitted for treatment of recurrence or relapse of previously diagnosed malignancy were excluded.

Extraorally, submental, submandibular, anterior and posterior cervical, and pre- and postauricular lymph nodes were palpated to detect enlargement and/or tenderness. The temporomandibular joints were palpated externally for signs of pain or dysfunction. The perioral skin and the lips also were examined. Intraorally, a full charting of teeth present and their status was made. The presence and site of any gross tooth mobility and tooth/jaw pain also were recorded. Buccal and sulcular mucosa, the tongue, the floor of the mouth, the hard and soft palate, the fauces, and free and attached gingiva were examined systematically for evidence of any abnormality. Details of the child's age, gender, and diagnosis were obtained from hospital records. Admission records were also examined for details of any orofacial problems in the initial series of diagnostic symptoms.

Follow-up screening examinations to detect oral complications were performed in the oncology ward and at the outpatient clinic. Again, the investigator visited each site weekly, and all available patients were reexamined on each occasion.

In addition, forms on which staff were asked to record the nature and location of any oral problems that they observed were provided at both the ward and the outpatient clinic. However, complications reported on these forms only were included in the study results when the presence of the complication was confirmed subsequently at examination by the investigator.

The following criteria were applied in determining the presence of specific complications:

Ulceration — A pathological breech in the continuity of the oral mucosa with exposure of underlying tissues.

Petechiae — Two or more pinpoint hemorrhages visible beneath or within any area of the oral mucosa.

Mucositis and erythema — Inflammation of the oral mucosa, characterized by reddening and pain.

Ecchymosis — Area of black or bluish discoloration of oral mucosa caused by diffuse submucosal extravasation of blood.

Lip cracking — Painful dryness and cracking of lips.

Oral mucosal pallor — Grossly abnormal pallor of all areas of the oral mucosa.

Lymphadenopathy — Enlargement and or tenderness elicited on palpation of two or more nodes in any of the groups listed above.

Severe gingivitis/gingival enlargement — The method of Löe (1967) was used to evaluate gingivitis. Patients exhibiting marked redness and edema of the gingiva with a tendency toward spontaneous bleeding and scoring code 3, using Löe's criteria, were considered to have severe gingivitis

Herpes simplex infection — Oral or perioral localized or generalized ulceration, severe gingivostomatitis, or "cold sore" like lesions of the lips or perioral skin, and when a rising titer of serum antibodies to herpes simplex virus over a 10-day period was demonstrated, or where herpes simplex virus was isolated from viral culture of swabs of the lesions.

Candidiasis — White plaque like lesions which could be removed by gentle swabbing with cotton wool to reveal erythematous and/or bleeding mucosa beneath, and where such lesions covered at least 10% of the oral mucosal surface, and where the presence of candidal hyphe was demonstrated by direct gram staining of smears taken from the lesions.

Sore throat — The patient complained of a sore throat with or without clinical signs of pathology.

Coated tongue — A white or brown plaque coating the dorsum of the tongue where a diagnosis of candidiasis had not been confirmed.

Once the field study was complete, the medical records of each patient were scrutinized for details of any further oral problems.

A full record also was made of all chemotherapeutic agents used. The drugs used, dosage, and the dates of administration all were determined from each patient's drug record chart.

Results

Forty-three children, 25 males and 18 females, between 2 and 15 years old, were included in the study group. Their mean age was 7 years and 3 months, with more than half being younger than 5 years old. The age distribution of individuals in the study group is shown in the figure. Except for six Asians and one Black, the

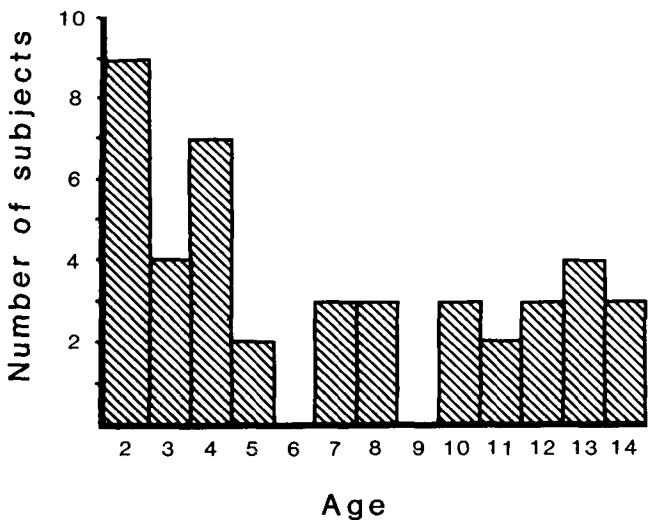

Figure. *Age distribution of subjects in the study group.*

subjects were Caucasians. The various types of malignancy and the number of subjects suffering from each type are shown in Table 1 (see next page). The most common diagnosis was acute lymphoblastic leukemia (ALL), which accounted for almost half the study group.

Fifteen children were found to have untreated dental caries at their initial dental screening; two children required dental extractions before chemotherapy. Other oral problems present at the time of admission, as recorded in the admitting medical officers' notes, are shown in Table 2 (see next page). The most common finding was lymphadenopathy of submandibular, auricular, or cervical nodes.

Forty (93%) of the children in the study group developed oral problems at some stage after their admission to the unit. During treatment, three patients developed dental infections, and eight patients developed severe gingivitis . Two patients with acute myeloblastic leukemia (AML) experienced marked gingival enlargement. In all cases, the absolute neutrophil count was 0.6×10^9/

Table 1. Distribution of children by age and type of malignancy in the study group

Type of Malignancy	Numbers of Children by age (years)													
	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
Acute lymphoblastic leukemia	4	3	5	1	-	1	2	-	1	1	-	2	-	20
Rhabdomyosarcoma	-	-	-	-	-	-	-	-	-	1	1	1	2	5
Acute myeloblastic leukemia	2	-	-	-	-	-	1	-	-	-	-	-	-	3
Non-Hodgkins lymphoma	-	-	-	-	-	2	-	-	-	-	1	-	-	3
Ewings sarcoma	-	-	-	-	-	-	-	-	1	-	-	1	-	2
Neuroblastoma	-	-	2	-	-	-	-	-	-	-	-	-	-	2
Osteosarcoma	-	-	-	-	-	-	-	-	1	-	-	-	1	2
Wilm's Tumor	1	-	-	1	-	-	-	-	-	-	-	-	-	2
Astrocytoma	1	-	-	-	-	-	-	-	-	-	-	-	-	1
Chronic myeloblastic leukemia	-	1	-	-	-	-	-	-	-	-	-	-	-	1
Hepatoblastoma	1	-	-	-	-	-	-	-	-	-	-	-	-	1
Hodgkins lymphoma	-	-	-	-	-	-	-	-	-	-	1	-	-	1
Totals	9	4	7	2	0	3	3	0	3	2	3	4	3	43

Table 2. Oral problems, other than tooth related, present at diagnosis

Problem	No. of Patients
Head and neck lymphadenopathy	4
Lip cracking	3
Oral mucosal ulcers	3
Herpes simplex infection	2
Oral mucosal petechiae	2
Dry mouth	1
Sore throat	1
Oral mucosal pallor	1

L or less. Four episodes of pericoronitis occurred in three patients. In all cases, the pericoronitis was associated with partially erupted second permanent molars.

Ulcerations and erosions of the oral mucosa were the most frequent oral problem to occur during chemotherapy. Ulceration was observed on 43 occasions in 28 (65%) of the subjects. This tended to appear 5–10 days following the start of chemotherapy, and occurred with approximately equal frequency during both induction and intensification chemotherapy. In almost all cases, the patient involved had a low neutrophil count (<0.5 x 10^9/L).

The ulcers usually lasted 5–10 days, healing once the patient's neutrophil count improved. The areas of ulceration were generally painful and varied in size from just a few millimeters to several centimeters in diameter, with buccal and sulcular mucosa being the most common site of such ulceration. In two cases, areas of oral ulceration subsequently became secondarily infected with *Candida albicans*.

Erythema and mucositis of the oral mucosa also were observed frequently; 13 patients were affected. These were most commonly observed on the fauces and in the pharynx and resembled the appearance of a sore throat. In some cases they were associated with areas of ulceration.

Many patients exhibited signs of thrombocytopenia Oral punctate petechiae were a frequent finding, especially on buccal mucosa. These tended to occur when the platelet count was below 50 x 10^9/L. However in one patient, petechiae were observed on several occasions when the platelet count was in excess of 250 x 10^9/L. Two patients developed significant intraoral ecchymoses. In both cases, the platelet count was below 20 x 10^9/L. Spontaneous oral bleeding was encountered in nine children and was invariably associated with platelet counts of less than 20 x 10^9/L. The gingiva was the most common site of such bleeding.

A significant proportion of subjects suffered complications related to infections. Acute pseudomembranous candidiasis occurred in five patients, while six patients developed herpes simplex virus (HSV) infections. All cases of HSV infection were seen in patients with ALL. In one patient, severe orofacial necrosis developed. This patient died despite aggressive systemic antiviral and antimicrobial therapy.

Cracking of the lips, sometimes accompanied by bleeding, was a frequent finding in patients receiving chemotherapy. This was especially common during or following a febrile episode, although no association with any particular drug was evident.

Table 3. Oral problems observed during study

Problem	*No. of patients affected*	*No. of occasions problem observed*
Oral mucosal ulcers	28	43
Oral mucosal petechiae	18	29
Lip cracking	15	27
Mucositis and erythema	13	24
Head and neck lymphadenopathy	15	16
Oral bleeding	9	12
Severe gingivitis	8	11
Sore throat	9	10
Oral mucosal pallor	8	10
Coated tongue	7	7
Herpes simplex infection	6	6
Candidiasis	5	5
Cushingoid facies	5	5
Pericoronitis	3	4
Jaw pains	3	3
Toothache — no apparent cause	3	3
Angular chelitis	3	3
Dental infection	3	3
Extrinsic staining of the teeth	2	2
Dry mouth	2	2
Ecchymoses	2	2

A complete list of the nature and frequency of oral problems recorded in the study is given in Table 3 (see next page). As the table indicates, the same problem was observed in some patients on more than one occasion, although it should be noted that in some instances, this represented a persistent lesion or complication seen and recorded at several successive examinations.

The number of examinations performed on each subject by the investigator ranged from three to 16, with a mean of 7.8 examinations per child. All patients were followed for at least two months from initial diagnosis. The maximum period of follow up was seven months.

The retrospective review of treatment records revealed only two oral problems that had not been seen and recorded by the investigator during the study period. One complication was oral bleeding; the other was lymphadenopathy. Neither episode was included in the final data. Although impossible to quantify, this finding supported the impression that the study design kept missed diagnoses to a minimum.

Discussion

The high prevalence of untreated dental caries in the group of children studied emphasizes the need for dental involvement in the pretreatment assessment of pediatric oncology patients. Because infection during neutropenia is the most common cause of death in oncology patients, all efforts should be made to minimize this risk. Chronic infections of the dental pulp and the periodontal tissues may become a source of significant systemic infection during periods of myelosuppression (Peterson and Overholser 1981; Greenberg et al. 1982; Peterson and Sonis 1982)

In this study, admission records indicated that 13 children (30%) had oral signs suggesting malignancy at diagnosis. Significantly, 12 of these children subsequently were found to have acute leukemia; 10 had ALL. None of those with solid tumors had any oral manifestations of the disease at diagnosis.

The observation of specific oral signs at diagnosis in a significant proportion of patients with ALL has been reported in previous studies (Lynch and Ship 1967a; Curtis 1971). As in previous reports, lymphadenopathy, mucosal ulcerations, and petechiae were frequent observations (Table 4, see next page). However other studies have reported gingival inflammation and/or enlargement (Lynch and Ship 1967a), and oral bleeding (Lynch and Ship 1967a; Curtis 1971; Stafford et al. 1980), neither of which was recorded as present at diagnosis in this study.

The incidence of acute dental infections during chemotherapy in this study was similar to that found by previous investigators (Sonis et al. 1978; Sonis and Sonis 1979). This emphasizes the need for continued dental vigilance during treatment and for close association between the oncology and dental teams.

Of the children included, 40 (93%) had at least one oral or perioral problem during the study. Most previous studies have reported the proportion of patients suffering such oral complications to be much lower (Table 5, see page 294). Only once before has such a high incidence of oral problems been reported (Sonis and Sonis 1979). Even more striking was the finding that all 23 patients with acute leukemia developed oral complications, indicating a much higher incidence of these problems in children with acute leukemia than has been demonstrated previously (Duffy and Driscoll 1958).

The incidence of candidiasis was lower than that reported in previous, similar studies (Tables 4 and 5). In their longitudinal study of 77 patients with acute leukemia, Michaud et al. (1977) reported candidiasis occurring in nearly 30% of children with acute leukemia. Scully and MacFarlane (1983) elicited a positive history of candidal infection in 18.2% of their group of pediatric

Table 4. Nature and incidence of oral problems observed during treatment in the study group compared with previous studies of pediatric oncology patients

Oral problem	*Number of patients affected (%)*			
	Present study (N = 43)	*Sonis, Sonis and Lieberman (1978) (N = 93)[r]*	*Sonis and Sonis (1979) (N = 49)[a]*	*Scully and MacFarlane (1983) (N = 44)[b]*
Mucosal ulcers	28 (65)	17 (18)	32 (65)	17 (39)
Lip cracking	15 (35)	-	17 (35)	-
Lymphadenopathy	15 (35)	2 (2)	3 (6)	-
Mucositis/erythema	13 (30)	-	4 (8)	-
Oral bleeding	9 (21)	1 (1)	-	-
Severe gingivitis	8 (19)	4 (4)	-	-
Herpes simplex	6 (14)	-	-	12 (27)
Candidiasis	5 (12)	2 (2)	2 (4)	8 (18)
Dry mouth	2 (5)	10 (11)	5 (10)	-
Dental infection	4 (9)	4 (4)	3 (6)	-
Total number affected	40 (93)	36 (39)	45 (92)	27 (61)

Note: Figures given are number of patients affected. Percentages given in parentheses are included only to assist comparison.

a — patients only examined on one occasion; b — prevalence of oral problems determined by retrospective questioning of patients and parents; r — retrospective analysis of hospital records; N — number of patients studied

oncology patients. Other studies have reported a low incidence of such infection in pediatric oncology patients (Sonis et al. 1978; Sonis and Sonis 1979), but these findings must be interpreted with some caution. In one study, data were obtained retrospectively from hospital record cards, and in the other, patients were examined on one occasion only. The relative infrequency of candidal infection in the present study may be a result of the intensive oral hygiene measures employed by the children, particularly the routine use of chlorhexidine gluconate and antifungal (nystatin) mouthwashes.

The incidence of mucosal ulceration and inflammation in this study is much higher than in most previous comparable reports. Only one other study found a similarly high occurrence (Sonis and Sonis 1979). Of those with ALL, 15 (75%) developed oral ulcers. This may reflect the use of more aggressive chemotherapeutic regimens in treating childhood malignancy during recent years. This also may suggest that the retrospective or cross-sectional types of studies conducted in the past may have allowed a significant proportion of complications to remain undetected.

The apparent relationship between the administration of methotrexate and oral ulceration and mucositis was in agreement with the findings of other studies (White 1970). Not all patients who received methotrexate developed ulceration, and those who did develop ulceration did not suffer oral mucosal reactions on every occasion they received the drug. Dosages that produced severe oral reactions in some patients caused no problems in others of the same age with the same malignancy. These phenomena have been described before (Bottomley et al. 1977; Dreizen 1978) and demonstrate the multifactorial etiology of such complications and the highly variable patient susceptibility to them.

As shown in other studies, manifestations of defective hemostasis occurred in many patients. It was, however, noteworthy that oral mucosal petechiae were seen repeatedly in one patient with a platelet count consistently above 250 x 10^9/L. Such occurrences have been reported before (Lynch and Ship 1967b) and it is clear that although thrombocytopenia may be the most obvious cause of such findings, qualitative differences in platelets (Stafford et al. 1980) or defects of other components of the clotting mechanism (Firkin and Moore 1960) also may be associated with hemorrhagic tendencies.

Severe gingivitis and gingival enlargement were seen less frequently in this group of patients than might have been expected from previous studies. Duffy and Driscoll (1958), for example, found that 53% of patients with leukemia had a nonspecific gingivitis, and 45% had hypertrophic gingivitis.

The frequent observation of dry and cracked lips compares closely with the 35% incidence of the same problem seen by Sonis and Sonis (1979). Lip cracking tended to occur in those patients who had suffered a febrile episode, but possibly was aggravated by the dry, air conditioned ward.

Herpes simplex infection is a frequent complication in patients with hematological and lymphoreticular malignancy (Aston et al. 1972). Herpes simplex virus infections often follow an atypical course in immunocompromised patients; this occurred in one patient in the present study. Large, necrotic perioral

ulcerations due to herpes simplex infection in immunocompromised patients have been described by several authors (Muller et al. 1972; Logan et al. 1971). The term "chronic cutaneous herpes simplex" has been used to describe this type of lesion (Logan et al. 1971).

Three patients developed painful pericoronitis; in all cases, partially erupted second permanent molars were involved. Dreizen (1978) has reported the same problem occurring in association with partially erupted third permanent molars in adults.

Although some chemotherapeutic agents are known to reduce salivary flow, the low incidence of xerostomia in this study seems to indicate that in the absence of irradiation to the perioral region, dry mouth is not a common complaint in pediatric oncology patients.

Table 5. Nature and incidence of oral problems observed during treatment in patients with acute lymphoblastic leukemia compared with previous studies of patients with acute lymphoblastic leukemia

Oral problem	*Number of patients affected (%)*			
	Present study (N = 20)	*Duffy and Driscoll (1958) (N = 38)*	*Michaud et al. (1977) (N = 63)*	*Scully and MacFarlane (1983) (N = 22)[c]*
Mucosal ulcers	15 (75)	15 (39)	23 (37)	10 (45)
Petechiae/ecchymoses	10 (50)	14 (37)	39 (62)	-
Lip cracking	10 (50)	-	[a]	-
Lymphadenopathy	8 (40)	15 (39)	20 (32)	-
Mucositis/erythema	6 (30)	-	17 (27)	-
Herpes simplex	6 (30)	-	5 (8)	8 (36)
Oral bleeding	5 (25)	16 (42)	11 (17)	-
Mucosal pallor	4 (20)	-	7 (11)	-
Severe gingivitis	2 (10)	20 (53)	3 (5)	-
Candidiasis	2 (10)	-	16 (25)	7 (32)
Cushingoid facies	2 (10)	-	13 (21)	-
Tooth/jaw pains	2 (10)	1 (3)	1 (2)	-
Total number affected	20(100)	30 (79)	[b]	[b]

Note: Figures given are number of patients affected. Percentages given in parentheses are included only to assist comparison.

a — observed, but frequency not reported; b — total number of patients affected not reported; c — prevalence of oral problems determined by retrospective questioning of patients and parents; N — number of patients studied

Children seem particularly susceptible to the stomatotoxic effects of chemotherapy, and therefore warrant special attention in preventing and treating these problems. In view of the significant existing dental disease at diagnosis and the subsequent very high incidence of complications in and around the oral cavity, it is clear that the dentist has a very important role in the initial assessment and ongoing care of the pediatric oncology patient.

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Chocolate milk myth

Myth: The cocoa in chocolate-flavored milk interferes with the body's ability to absorb calcium.

Reality: Although toxalate, found in cocoa, can bind to calcium and render the mineral unusable in the body, the amount of oxalate in chocolate-flavored milk is not enough to interfere significantly with calcium absorption. A study of chocolate milk, whole milk, and yogurt found that calcium from all was absorbed equally. (Reported in *Tufts University Diet & Nutrition Letter*).