

Leukemia and its Oral Manifestations in Children Younger than 12 Years Referred to Tehran Pediatric Hospitals

Afroz Nakhostin,¹ and Ghasem Meighani^{2,*}

¹Department of Restorative Dentistry, School of Dentistry, Arak University of Medical Sciences, Arak, IR Iran

²Department of Pediatric Dentistry, School of Dentistry, Tehran University of Medical Sciences, Tehran, IR Iran

*Corresponding author: Ghasem Meighani, Department of Pediatric Dentistry, School of Dentistry, Tehran University of Medical Sciences, Tehran, IR Iran. Tel: +98-9121277383, Fax: +98-2188015800, E-mail: mighani@sina.tums.ac.ir

Received 2015 May 16; Revised 2015 December 10; Accepted 2016 January 24.

Abstract

Background: Acute leukemia is a malignant, rapidly progressive disease of the bone marrow and blood that most commonly occurs in children. Abnormalities of blood caused by leukemia and also accumulation of leukemic cells in different parts of the oral cavity cause a wide spectrum of oral manifestations.

Objectives: The current study aimed to estimate the incidence of leukemia among children in Tehran and evaluate oral manifestations of the disease as potential diagnostic markers.

Patients and Methods: In this retrospective cross-sectional study, medical records of children younger than 12 years referred to Mofid hospital, Ali-Asghar hospital and Children's medical center from 1997 to 2011 were retrieved from the hospital archives and evaluated. Records of 100 patients with leukemia were randomly selected for evaluation. The obtained data were transferred to the questionnaires. Data were analyzed using SPSS version 11.5 and Chi-square test.

Results: Of the 3,789 children younger than 12 years referred to the hematology department of Tehran pediatric hospitals from 1997 to 2001, 1,372 had acute leukemia, put of which 94% had acute lymphoblastic leukemia and 5% had acute myeloid leukemia. Boys aged 5 - 10 years made up 69% of the acute leukemia cases. The most common oral manifestation was gingival bleeding and petechiae. The most important disease other than leukemia was anemia in the patients.

Conclusions: The present study highlights the role of dentists to detect oral manifestations of leukemia and their possible role in early diagnosis of patients with the disease.

Keywords: Ecchymosis, Gingival Bleeding, Leukemia, Oral Manifestation, Petechiae

1. Background

Leukemia is a malignant disease affecting hematopoietic tissues. In this condition, white blood cells proliferate abnormally and spread in the peripheral blood. Abnormal leukocytes (blast cells) gradually replace normal bone marrow cells and accumulate in other tissues and organs. Leukemia is classified into 4 subtypes consisting of acute lymphocytic leukemia (ALL), acute myelocytic leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelocytic leukemia (CML) based on cell origin (lymphoid or myeloid) and clinical course (chronic or acute). The survival rate of ALL is 80% in children. At the time of diagnosis, children are most commonly at the age range of 2 - 5 years. Prognosis of disease is much worse in children younger than one year or older than 10 years. ALL most often affects white children and males. However, white boys compared to white girls have a higher chance of recovery and life expectancy. In addition, black girls and boys also have a lower rate of survival. Also, children with primary signs and symptoms of anemia have better survival rates. Early detection and prompt treatment increase the chance

of remission and recovery. Children whose bone marrow seven days after treatment is still not free from immature cells have a poorer prognosis. Also, children with WBCs more than 50,000 per mm³ have a worse prognosis.

The ceased activity of bone marrow, combined with chemotherapy and infiltration of leukemic cells causes a wide array of oral manifestations. The most common manifestations that are usually noticed by dentists include gingival bleeding, petechiae, ecchymosis and lymphadenopathy due to the infiltration of leukemic cells in lymph nodes. Anemia and thrombocytopenia in children result in paleness of oral mucosa, ecchymosis and gingival bleeding. Oral mucosal wounds are also among the common findings in patients with leukemia undergoing chemotherapy. These lesions are significantly large, irregular with a bad odor confined by a pale mucosa. Candidiasis is a common fungal infection in patients with leukemia undergoing chemotherapy. Periodontal disease due to infection is also common. Gingival hypertrophy due to the infiltration of leukemic cells is another common finding in monocytic leukemia (1).

During the past 25 years, the importance of early detection of leukemia manifestations is increasingly emphasized. Factors such as age, gender, patient's general health status, ethnicity, nutrition, socioeconomic status, signs and symptoms of disease and other conditions associated with leukemia are all important and play a role in treatment outcome. For example, children with Down syndrome have a high prevalence of leukemia and when undergoing chemotherapy, have twice the chance of recovery compared to other children with myeloid leukemia. Infections, genetics, physical and chemical agents or a combination of all are suggested as potential etiologic factors to develop leukemia.

In 1997, Hou et al., in a retrospective study, evaluated the oral manifestations of leukemia and stated that age predilection and prevalence of oral manifestations were closely correlated with the type of leukemia. Fever, lymphadenopathy, laryngeal pain, gingival bleeding, oral ulcers and gingival enlargement were the most common manifestations of leukemia in their study (2).

According to Nikoui and Lalonde, approximately 1000 cancer cases are annually reported among children younger than 14 years in Canada. Leukemia accounts for about 30% of these cases. In their study, they emphasized the role of dentists before, during and after treatment of leukemia (3).

Dentists are responsible for initiating the diagnosis of leukemia in a significant number of acute non-lymphoblastic patients with leukemia since oral lesions are among the common signs or symptoms in undiagnosed patients with acute leukemia (4).

In another study on 50 children with oral manifestations of leukemia, mucosal pallor was the most common presenting oral symptom followed by erythema, ulceration and swelling of the lips, tongue, palate and gingiva. Facial pallor and lymphadenopathy were among the extra-oral manifestations of the disease (5).

In a study by Orbak conducted in Turkey in 1997, mucosal pallor was the most common oral manifestation of leukemia. They also suggested the integration of professional dental follow up and medical follow up of patients with leukemia (6).

Timely diagnosis of leukemia is very important, since in cases of early diagnosis, patients will have a survival rate as high as 80%. By paying attention to the oral manifestations of leukemia, dentists can play an important role in its early diagnosis.

2. Objectives

Since accurate statistics are rarely available in Iran regarding the number of children with leukemia, especially

ALL, the current study aimed to estimate the actual incidence of this disease among children younger than 12 years in Tehran and assess the oral manifestations of their disease. The present study also evaluated the possible causes of leukemia in children and factors such as consanguinity of parents, patients' family history, and correlation of age and gender with the disease.

3. Patients and Methods

In this retrospective cross-sectional study, data were collected using a questionnaire with 14 questions based on a consensus reached in a panel of experts (Table 1).

Medical records of children younger than 12 years referred to three pediatric hospitals in Tehran namely Mofid hospital, children's medical center and Ali-Asghar hospital from 1997 to 2011 were retrieved from the hospital archives and evaluated. Records of 100 patients with leukemia were randomly selected. The questionnaires were filled out based on the data obtained from the medical records of patients with leukemia. Sample size was calculated as 100 using following Equation 1.

$$N = \frac{p \cdot q \left(\frac{u_0}{2}\right)^2}{e^2} \quad (1)$$

Where P is the estimation of patients with leukemia with oral manifestations relative to the total patients with leukemia. Based on the results of preliminary studies P was considered as 0.30, $U_0/2 = 1.96$ and $q = 1 - P = 0.70$ using standard normal distribution and CI = 95%; e was 0.1. Collected data was analyzed using SPSS version 11.5. Chi-square test with 95% CI was used to assess the mean hematocrit (HCT) in children with leukemia below 12 years based on their gender and age.

4. Results

Out of the 3,789 children younger than 12 years referred to the hematology departments of Tehran pediatric hospitals from 1997 to 2001, 1,372 had acute leukemia of which, 94% had ALL and 5% had AML. Of these patients, 69% were boys and 31% were girls. In terms of age range, 41% were 1-5 years, 42% 5-10 (highest frequency) and 17% were older than 10 years. The majority of mothers (48%) and fathers (54%) had educational level below high school diploma. Only 8% of the subjects had a family history of leukemia. In 100% of patients, the primary diagnosis of leukemia had been made by the physician. In 6% of cases, oral manifestations had helped the diagnosis. In total, 22% of subjects had first-degree consanguineous parents.

Table 1. The Questionnaire Used in the Study

Questions	Answer Choices
Is there anyone with leukemia in the family or close relatives?	Yes/No
How the leukemia was primarily diagnosed?	By a physician/By a dentist
What were the oral symptoms of leukemia?	Gingival bleeding/ petechiae/ ecchymosis/ fungal lesions/ mucosal changes
Did oral symptoms help the diagnosis of leukemia?	Yes/No
What was the relationship of parents?	First-degree relatives/Second-degree relatives/ Non-consanguineous
Number of children in the family?	1/2/3/4/5 or more
Does the patient have a disease other than leukemia?	Mental retardation/ physical disability/ systemic diseases/ anemia/ gingival bleeding/ cervical lymphadenopathy
Had the patient received complete vaccination?	Yes/No
What is the patient's hematocrit?	
What is the type of leukemia?	ALL/AML/CML/CLL

Out of the 2,150 patients referred to the hematology department of Ali-Asghar hospital, 757 cases; of 971 patients referred to the hematology department of children's medical center, 369 cases and of 668 patients referred to the hematology department of Mofid hospital, 246 had leukemia. Thus, 36% of aforementioned children younger than 12 years had leukemia and assuming 95% CI, the incidence of leukemia in children younger than 12 is 34.7% to 37.7% in this population.

The most common oral manifestations were gingival bleeding, petechiae, ecchymosis, oral mucosal changes and fungal lesions (Table 2). Also, the most common systemic disease after leukemia was anemia with the prevalence of 22.8% in boys and 22.6% in girls (Table 2).

In general, the most common oral manifestation in 41.4% of ALL patients was gingival bleeding. The most common systemic disease other than leukemia was anemia followed by cervical lymphadenopathy. The highest incidence of leukemia was in children aged 1 - 10 years which indicates that by increased age, incidence of ALL decreases. Table 3 shows the relative frequency of oral symptoms and history of other conditions based on the patients' age group. The mean HCT in 94 ALL subjects was 33.4. This rate was 34.54 in the remaining five patients with AML which was below the normal range in both groups (Table 4).

Totally, 95% of families of children with leukemia had at least two children and vaccination was complete in 99% of the patients. The most common oral manifestation in boys was gingival bleeding (43.3%). In girls, the prevalence of gingival bleeding, petechiae and ecchymosis were almost the same.

There was a significant correlation between the age of children and development of leukemia. No correlation was found between consanguinity of parents and

Table 2. Relative Frequency of Oral Symptoms and History of Other Conditions Based on Patients' Gender

Symptoms	Male	Female	Total
Oral Symptoms/Complications			
Gingival bleeding	46.3	27.3	39.7
Petechiae	22.0	22.7	22.2
Ecchymosis	17.1	22.7	19.0
Oral mucosal changes	12.2	18.2	14.3
Fungal lesions	2.4	9.1	4.8
Total	100.0	100.0	
Other Diseases			
Not mentioned	65.2	63.7	64.8
Systemic disease	2.5	2.4	2.5
Anemia	22.8	22.6	22.8
Gingival bleeding	1.4	0.813	
Cervical lymphadenopathy	8.0	10.5	8.8
Total	100.0	100.0	100.0

development of leukemia in their children. Complete vaccination had no correlation with the incidence of leukemia. Family history was not correlated with the incidence of leukemia either. A significant association was found between leukemia and anemia and the prevalence of leukemia was significantly higher in boys. The results of the Chi-square test for the hypotheses of the study and the P-values are shown in Table 5.

Table 3. Relative Frequency of Oral Symptoms and History of Other Conditions Based on Patients' Age Group

Symptoms	1 - 5 Years	5 - 10 Years	Over 10 Years	Total
Oral Symptoms/Complications				
Gingival bleeding	64.9	32	33.2	39.7
Petechiae	15.6	32	16.7	22.2
Ecchymosis	21.9	16.0	16.7	19
Oral mucosal changes	12.5	16.0	16.7	14.3
Fungal lesions	3.12	4.0	16.7	4.8
Total	100.0	100.0	100.0	100.0
Other Diseases				
Not mentioned	64.4	64.3	66.2	64.8
Systemic disease	1.2	3.0	4.4	2.5
Anemia	22.6	22.6	23.5	22.8
Gingival bleeding	1.8	1.2	-	1.3
Cervical lymphadenopathy	9.8	8.9	5.9	8.8
Total	100.0	100.0	100.0	100.0

Table 4. The Mean and Standard Deviation of Hematocrit in Patients

Type of Leukemia	Mean	Mode	Median	Standard Deviation	Number
ALL	33.04	34.00	33.50	6.03	94
AML	34.54	25.50	34.00	8.54	5
Total	33.17	34.00	33.60	6.12	100

5. Discussion

Children rarely develop cancer but leukemia is the most common cancer among them; therefore, the highest cancer-related morbidity and mortality in children is due to leukemia (1). Leukemia-related morbidity and mortality is decreasing in many countries. In the United States, the prognosis of this condition has greatly improved and, at present, annual rate of leukemia-related morbidity and mortality is about 20,400 individuals which have decreased by 42% compared to the previous rate. The majority of conducted studies emphasize the role of dentists in early detection of this disease.

The current study evaluated children with ALL and AML. AML has the highest incidence in adults with 10,000 new cases annually in the United States and affects all age groups. ALL is the most common form of leukemia in children with 3000 new cases per year in the United States. Approximately there are 140,000 patients with leukemia in the US and there are 20,400 annual cases of death due to this disease. A total of 25,700 new cases of leukemia are de-

tected and registered every year in the US alone. The prognosis of this disease has greatly improved during the recent years and the life expectancy of patients has reached five years which shows a 3-fold increase (42%) compared to 38 years ago. There are 3000 to 4000 new cases of ALL per year, two-third of which are in children. That is why ALL is largely considered childhood leukemia (7).

A wide array of oral manifestations is reported in patients with leukemia. The most common manifestations usually noticed by dentists include gingival bleeding, petechiae, ecchymosis and lymphadenopathy. Severe gingival bleeding may be treated with local treatments with no need for platelet transfusion. Elimination of stimuli and pressure with fingers may be helpful. Oral mucosal wounds are also among the common findings in patients with leukemia undergoing chemotherapy. These lesions are significantly large, irregular and with a bad odor confined by a pale mucosa. In these cases, prevention of infection, minimizing the risk of bacteremia and pain relief by administration of systemic and topical antibiotics, chlorhexidine mouthwash and diphenhydramine are recommended. Candidiasis is a fungal infection commonly found in patients with leukemia undergoing chemotherapy. Periodontal disease due to infection is a common finding as well. Thus, hopeless teeth and sources of infection have to be eliminated before the initiation of chemotherapy.

The present study provided accurate statistics regarding the incidence of leukemia among children below 12 years in Tehran and evaluated their oral manifestations.

Table 5. The Results of Chi-square Test for the Hypotheses of the Study^a

Null Hypothesis	Highest Frequency	P Value	Result
Equal number of large and small families for leukemia patients	Large families, n = 89	0.001	Refuted
Not receiving adequate vaccination may result in development of leukemia	Complete vaccination, n = 93	0.000	Refuted
Frequency of different oral complications is similar in patients with leukemia	Mostly had gingival bleeding	0.000	Refuted
Leukemia increases the risk of other blood-borne conditions	Anemia	0.000	Refuted
Number of patients with leukemia in different age groups younger than 12 is equal	1-5 years and 5-10 years, n = 40 each	0.001	Refuted
Equal number of male and female patients with leukemia	Males, n = 66	0.000	Refuted
Equal frequency of different levels of education of mothers of patients with leukemia	Below high school diploma, n = 43	0.00	Refuted
Equal frequency of different levels of education of fathers of patients with leukemia	Below high school diploma, n = 50	0.00	Refuted
Equal number of parents of patients with leukemia with and without consanguinity	Non-consanguineous, n = 65	0.000	Refuted
Noticing oral complications does not help early diagnosis of leukemia	Not mentioning oral complication in the records of 89 patients	0.000	Refuted
Positive history of leukemia in the family or relatives affects the occurrence of this disease in children	No history, n = 87	0.000	Refuted

^aLevel of significance $P < 0.05$.

Age, gender, patient's family history, consanguinity of parents, vaccination chart, level of education of parents and other systemic diseases were among other factors evaluated in this study.

Katz and Peretz reported a case of trismus that resulted in a diagnosis of ALL. Trismus was most probably due to the infiltration of leukemic cells in the deep portion of contracting facial muscles. They highlighted the importance of physical and laboratory examinations ordered by dentists and their independent judgment even in the cases referred by other physicians (8).

Baliga et al. discussed oral mucosal lesions in ALL patients. During head and neck examinations, they found lymphadenopathy to be the most common finding suggestive of leukemia. Gingival bleeding and oral mucosal pallor were among other common oral manifestations. Oral mucosal ulcers, uncontrolled herpes, candidiasis and pseudomonas infection were among the side effects of chemotherapy observed in patients (9). Their study results were in consistent with those of the current study in terms of initial oral manifestations of the disease. However, oral side effects of chemotherapy were not evaluated in the current study.

Infection due to the suppression of bone marrow and the immune system, impaired healing responses, and poor oral hygiene were reported in another study on 77 patients with ALL (10).

Review of literature reveals that leukemia is associated

with a high incidence of oral complications at the time of diagnosis and during the course of treatment. Oral manifestations of leukemia can be categorized into three groups. Primary lesions are caused by the infiltration of malignant cells into the oral structures such as gingiva and bone. Secondary lesions include symptoms of anemia, higher bleeding tendency and greater susceptibility to infections and are due to myelophthitic character of the disease. Tertiary lesions develop as the result of chemotherapy (11). The present study reported primary and secondary lesions. Another study is recommended to evaluate and report the tertiary lesions in children with leukemia in Tehran.

Shubich in a study discussed oral manifestations related to leukemia and its treatment. According to him, certain anti-leukemic drugs can show severe oral toxicity in the form of pain, or development of superficial white, red-bordered patches in the gingiva, labial mucosa, palate and pharynx, as well as other locations (12).

The present study was not able to collect data regarding the oral manifestations of chemotherapy in the under-study patients since such data had not been recorded in their medical files. It is required to perform further studies on larger sample sizes to evaluate both pre- and post-treatment oral manifestations in leukemic children with leukemia in Tehran as well as other cities of Iran.

In another study, maxillary unilateral swelling and pain in the buccal vestibule were reported in a 12-year-old

girl as the first diagnostic symptom of ALL relapse (13). Pericoronitis (14) and numb chin syndrome (15) are also reported as the primary manifestations of ALL. Gingival hypertrophy in another study was noticed as an unusual feature of precursor T-cell lymphoblastic leukemia (16). Sepulveda et al., in a case report, discussed a six-year-old boy with persistent and severe bleeding following a tooth extraction and generalized gingival enlargement over a short period of time that lead to the diagnosis of acute myeloid leukemia (17).

The present study, as well as the aforementioned ones, emphasizes the role of dentists in providing an opportunity for timely diagnosis, early referral, and proper treatment of an underlying leukemia by having adequate knowledge about the early oral signs and symptoms of this disease.

Acknowledgments

Authors wish to thank Dr. Ahmad Reza Shamsari, department of community oral health, Tehran University of Medical Sciences, for assistance with methodology and comments that greatly improved the manuscript.

Footnotes

Authors' Contribution: Study concept and design: Ghasem Meighani; analysis and interpretation of data and Statistical analysis: Ahmad Reza Shamsari.; drafting the manuscript: Afroz Nakhostin.

Funding/Support: This study was financially supported by Tehran University of Medical Sciences.

References

1. Uj CH. Childhood Leukemias. 1 ed. Cambridge: Cambridge University Press; 1999.
2. Hou GL, Huang JS, Tsai CC. Analysis of oral manifestations of leukemia: a retrospective study. *Oral Dis.* 1997;**3**(1):31-8. [PubMed: 9456644].
3. Nikoui M, Lalonde B. [Oro-dental manifestations of leukemia in children]. *J Can Dent Assoc.* 1996;**62**(5):443-6. [PubMed: 8640581] 449-50.
4. Stafford R, Sonis S, Lockhart P, Sonis A. Oral pathoses as diagnostic indicators in leukemia. *Oral Surg Oral Med Oral Pathol.* 1980;**50**(2):134-9. [PubMed: 6967202].
5. Theodoropoulos-Papadimitriou K, Donta AN, Kosmidei EB. [Incidence of oral manifestations in children with acute leukemia]. *Odontostomatol Proodos.* 1989;**43**(4):357-63. [PubMed: 2518062].
6. Orbak R, Orbak Z. Oral condition of patients with leukemia and lymphoma. *J Nihon Univ Sch Dent.* 1997;**39**(2):67-70. [PubMed: 9293702].
7. Dean JA, Avery DR, McDonald RE. McDonald and Avery's Dentistry for the Child and Adolescent. Netherlands: Mosby/Elsevier; 2010.
8. Katz J, Peretz B. Trismus in a 6 year old child: a manifestation of leukemia?. *J Clin Pediatr Dent.* 2002;**26**(4):337-9. [PubMed: 12175125].
9. Baliga AM, Brave VR, Vyas HA. Oral mucosal lesions in patients with acute leukemias and related disorders due to cytotoxic therapy. *J Indian Soc Pedod Prev Dent.* 1995;**13**(1):25-9. [PubMed: 9522736].
10. Michaud M, Baehner RL, Bixler D, Kafrawy AH. Oral manifestations of acute leukemia in children. *J Am Dent Assoc.* 1977;**95**(6):1145-50. [PubMed: 271678].
11. Vinckier F, Declercq D. [Oral manifestations in leukemic children and their diagnostic value]. *Acta Stomatol Belg.* 1989;**86**(3):219-26. [PubMed: 2519179].
12. Shubich I. [Acute leukemia: oral manifestations and treatment]. *Pract Odontol.* 1990;**11**(9):21-2-6-7. [PubMed: 2151940].
13. Fallahinejad Ghajari M, Moshref M, Taghipour E. Maxilla unilateral swelling as the first diagnostic symptom of acute lymphoblastic leukemia relapse: a case report. *J Dent (Tehran).* 2011;**8**(1):44-7. [PubMed: 21998807].
14. Aronovich S, Connolly TW. Pericoronitis as an initial manifestation of acute lymphoblastic leukemia: a case report. *J Oral Maxillofac Surg.* 2008;**66**(4):804-8. doi: 10.1016/j.joms.2006.10.062. [PubMed: 18355610].
15. Hiraki A, Nakamura S, Abe K, Takenoshita Y, Horinouchi Y, Shinohara M, et al. Numb chin syndrome as an initial symptom of acute lymphocytic leukemia: report of three cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1997;**83**(5):555-61. [PubMed: 9159815].
16. Premalata CS, Madhumati DS, Lakshmidivi V, Pradeep R, Appaji L, Mukherjee G. Gum hypertrophy - an unusual presenting feature in a case of precursor T-cell acute lymphoblastic leukemia. *Turk J Haematol.* 2008;**25**(4):201-4. [PubMed: 27264925].
17. Sepulveda E, Brethauer U, Fernandez E, Cortes G, Mardones C. Oral manifestations as first clinical sign of acute myeloid leukemia: report of a case. *Pediatr Dent.* 2012;**34**(5):418-21. [PubMed: 23211920].