Oral Manifestations in Pediatric Patients Receiving Chemotherapy for Acute Lymphoblastic Leukemia.

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The purpose of this study was to determine the prevalence of oral manifestations in pediatric patients with acute lymphoblastic leukemia (ALL) receiving chemotherapy, and to evaluate the significance of independent risk factors (oral health, gender, age, time and type of treatment, and phase of chemotherapy). A cross-sectional study was made in 49 children with ALL between 2 and 14 years of age. To describe oral manifestations, a clinical diagnosis was made and the following criteria were applied: the OHI-S index to describe oral health and the IMPA index to describe periodontal conditions and to differentiate gingivitis from periodontitis. The prevalence of oral manifestations was: gingivitis, 91.84%; caries, 81.63%; mucositis, 38.77%; periodontitis, 16.32%; cheilitis, 18.36%; recurrent herpes, 12.24%; and primary herpetic gingivostomatitis, 2.04%. Other oral manifestations were: dry lips, mucosal pallor, mucosal petechiae, ecchymoses, and induced ulcers. The prevalence of oral candidiasis was 6.12%. It was observed that high risk ALL and poor oral hygiene were important risk factors for the development of candidiasis and gingivitis. The type of leukemia, gender, and phase of chemotherapy were apparently associated with the presence of candidiasis, gingivitis, and periodontitis, and they could be considered risk factors for the development of oral manifestations.

Keywords: *acute lymphoblastic leukemia, chemotherapy,children.*
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INTRODUCTION

Cancer is the leading cause of disease-related fatalities for children between 1 and 14 years.[1,2] The incidence is greatest in the first year of life, with a second peak at 2 to 5 years of age. Boys are more often affected than girls. Leukemia is a malignancy with disseminated proliferation of immature or blast cells of the bone marrow, which replace the normal marrow elements and tend to accumulate in various tissues of the body.

Leukemias are classified according to cellular morphology and immunophenotype (B-cell and T-cell cases), maturity of malignant cells, gene alterations (specific chromosomal changes), and speed of onset of symptoms.[3-5]

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy, accounting for three fourths (75%) of all newly diagnosed leukemias and one fourth (25%) of all cancers in childhood, with a peak incidence at 4 years of age.[6] The most common signs and symptoms are anorexia, irritability, lethargy, anemia, bleeding, petechiae, fever, lymphadenopathy, splenomegaly, hepatomegaly, bone pain, and arthralgia.[7]

According to prognostic factors, only high-risk cases are treated aggressively, and less-toxic therapy, is reserved for standard risk cases. Age and leukocyte count continue to be used for risk classification; according to the National Cancer Institute, leukocyte count less than 50 x 10^9/ L is the minimal criteria for standard risk ALL (60% to 70% of all B-cell precursor cases). With a long-term, event-free survival probability of 70% to 85%, the remaining 30% to 40% would have higher risk disease and survival probability of 50% to

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60%.[8] Morphologic examination and cytochemical staining of blast cells are usually sufficient to distinguish ALL from acute myeloid leukemia.[8]

Patients with ALL receive various treatments for their disease, including chemotheraphy, radiation, surgery, and bone marrow and stem cell transplants. These therapies for childhood malignant conditions have improved long-term survival; however, they often cause severe side effects in the oral cavity and adjacent structures.[1,9-13]

The oral cavity is at risk for complications that vary from mucosal lesions and infections to exacerbations of pre-existing dental disease. An increased incidence of numerous oral problems such as generalized ulcers; spontaneous bleeding of mucosa and gingivae; coated tongue; limited mouth opening; foul odor; oral infections (mucositis, candidiasis, herpes simplex, varicella/zoster, and cytomegalovirus); shallow papillae; differences in salivary flow rate and pH; Numb Chin syndrome; mucosal pallor; swallowing and chewing difficulties; ulceration and edematous areas; erythema; trigeminal nerve neuropathy; reticular lesions; ecchymoses; neuropathy; xerostomia; reddened, tender, and painful mucosa; gingival pain and hemorrhage have been reported.[3, 5, 10-16]

Oral complications that frequently occur during therapy cause severe discomfort that interferes with proper nutrition and may delay completion of cancer therapy; the initial appearance of these intraoral complications in children with ALL is gingival inflammation due to bacterial plaque.[5,10-16] Oral complications depend on the type of treatment applied, buccal mucosal condition, chemotherapeutic agents, and dose and time of administration of these agents.[10-16] Studies have found that 60% to 69% of patients with ALL present oral complications, and only 38% of them present symptoms. However, 85% of patients under cancer treatment with elevated doses of mucotoxic chemotherapy develop oral complications, mainly in young children.[14]

This study aimed to evaluate the prevalence of oral manifestations in pediatric patients with ALL during chemotherapy, and to evaluate the significance of independent risk factors (oral health, gender, age, time and type of treatment, and phase of chemotherapy).

MATERIALS AND METHODS

A cross-sectional study was done in the Pediatric Oncohematology Department of the Hospital Central "Dr. Ignacio Morones Prieto," San Luis Potosi, México. The study included 49 patients having a diagnosis of ALL. Inclusion criteria were as follows: medical diagnosis of ALL, any gender, and age between 2 and 14 years. Patients with other medical problems, patients in radiotherapy and patients receiving bone marrow transplants were excluded. The study was explained to the legal caregiver, and informed consent was obtained. Previous to the study, the main examiner carried out a clinical calibration. The diagnosis of oral manifestations was made by the main examiner and another pediatric dentist to assess interexaminer agreement. Ten full-arch tooth blocks were examined. Studies were completed to assess the reproducibility of recording indexes, and kappa values were calculated,[17] which were 0.80. Oral health and periodontal conditions were diagnosed for each patient. To describe the changes, the following diagnostic criteria were applied: OHI-S Index to describe oral health (0 = good, 1 = fair, and 2 = poor) and IMPA index to describe gingivitis or periodontitis.

For the statistical analysis, means ± standard deviations, frequencies, and percentages were calculated for all variables. The potential effect of independent risk factors was controlled with the use of a Mantel Haenszel X^2 test. The JMP IN v. 4.0.1 statistical program was used to analyze the data.[18]

RESULTS

The population sample of 49 patients included 23 females (47%) and 26 males (53.6%) whose ages ranged from 2 to 14 years, with mean age of 7.34±3.3. The time in chemotherapy of patients with ALL varied from 2 to 96 months (mean, 18 months). All patients were treated according to chemotherapy protocol for all risk groups (The Pediatric Nordic Society of Pediatric Hematology and Oncology 1992-2000 ALL Protocol),[9] which consisted of continuous treatment and was divided according the 3 phases of therapy: Remission induction (weeks 0–7) consisted of Vincristine, Doxorubicina, Prednisone, L-asparaginase and Methotrexate, Consolidation-Intensification (weeks 7–14) consisted in high doses of Methotrexate, Dexamethasone, Arabinosid of Cytosine, Cytarabine, Cyclophosphamide and the Maintenance phase (week 14 to year 3) consisted of Methotrexate, 6-Mercaptopurine, Cyclophosphamide, Cytarabine, or a combination of therapy: Prednisone, Vincristine and Arabinosid of Cytosine.

Forty-four patients (90%) presented higher frequency of B-cell ALL and the other 5 patients (10%) presented T-cell ALL. The risk of ALL was divided into 2 groups: standard risk, 28 patients (57%) and high risk, 21 patients (43%).With respect to phase of treatment, 36 patients (73.47%) were in Maintenance, 8 (16.33%) were in Remission Induction, and 5 (10.20%) were in Consolidation- Induction. Of the total patients observed with ALL in 3 phases of chemotherapy during the study, 7 relapsed.

The mouth of each patient was evaluated by the main examiner for oral manifestations of the hard and soft tissues and other findings. The oral hygiene was found to be good for 6 patients (12.2%), fair for 16 patients (32.65%), and poor for 27 patients (55.10%). Gingivitis was the most common manifestation, involving 45 patients (91.84%), of which 22.44% presented papular gingivitis, 44.89% marginal gingivitis, and 24.52% gingivitis on attached gingivae; caries was found in 40 (81.63%) and mucositis in 19 patients (38.77%) (Table 1). Other findings were dry lips, 93.80%; mucosal pallor, 71.42%; and mucosal ecchymoses and petechiae, 36.73% and 34.70%, respectively (Table 2).

We also evaluated the possible influence of some risk factors for the development of oral manifestations in this group of patients. Table 3 shows the risk of leukemia (standard and

Table 1. Frequency of oral manifestations

Oral Manifestations	Frequency (n)	Frequency (%)
Candidiasis	3	6.12
Recurrent herpes	6	12.24
Cheilitis	8	18.36
Gingivitis		
Absent	4	8.16
Papillary	11	22.44
Marginal	22	44.89
Attached	12	24.51
Periodontitis	8	16.32
Mucositis	19	38.77
Caries	40	81.63

Table 2. Frequency of other oral findings

Oral Findings	Frequency (n)	Frequency (%)
Dry lips	46	93.80
Pale tissue	35	71.42
Enamel Hypoplasia	15	29.61
Petechiae (mucosal)	17	34.70
Ecchymoses	18	36.73
Induced ulcers	17	34.70
Coated tongue	3	6.12
Self-induced injury	1	2.04

high) as a risk factor for the development of oral manifestations; the patients with ALL of standard risk had a probability of 95.24% of developing gingivitis and 52.38% of developing mucositis, whereas high-risk patients had a 14.29% probability of developing candidiasis, 89.28% gingivitis, and 28.57% of developing mucositis. In both groups a high probability of developing gingivitis was observed. The *P* value was significant for development of candidiasis ($P = 0.03$). According to the immunophenotype of leukemia as a risk factor for the development of oral manifestations, we observed that patients having B-cell ALL had a probability of 6.82%, 90.70%, and 38.64% of developing candidiasis, gingivitis, and mucositis, respectively. Patients with T-cell ALL had a probability of developing gingivitis of 100% and of mucositis 40%. The *P* value was not significant; nevertheless, it is important to note the high frequency of developing these complications (Table 4). Gender as a risk factor for development of oral manifestations is noted in Table 5, in which the probabilities of patients developing candidiasis, gingivitis, and mucositis in males were 7.69%, 88.46%, and 34.62%, respectively, and in females 4.35%, 95.65%, and 43.48%, respectively. The *P* value was not significant. Table 6 shows phases of treatment as a risk factor for developing oral manifestations, in which patients in the induction phase had a risk of 50% for developing mucositis, 20% in maintenance, and 38.89% in consolidation. The *P* value was not significant. Hygiene as a risk factor for developing candidiasis, gingivitis, and mucositis is shown in Table 7, in which, depending on the degree of hygiene evident, the risk of developing gingivitis was 81.25% for good hygiene, 88.33% for fair hygiene, and 100% for poor hygiene ($P = 0.01$).

Table 3. Risk of leukemia as a risk factor for development of oral manifestations (according to prognostic factors, therapeutically relevant risk groups and of the presence of Philadelphia chromosome)

Risk	Candidiasis	Gingivitis	Mucositis
Standard	0.00%	95.24%	52.36%
High	14.29%	89.28%	28.57%
P	0.03	0.31	0.09

Mantel-Haenszel X^2

Table 4. Immunophenotype of leukemia as a risk factor for development of oral manifestations

Type of ALL	Candidiasis	Gingivitis	Mucositis
B-cell	6.82%	90.70%	38.64%
T-cell	0.00%	100.00%	40.00%
P	0.54	0.44	0.95

Mantel-Haenszel X^2

Table 5. Gender as a risk factor for development of oral manifestations

Gender	Candidiasis	Gingivitis	Mucositis
Male	7.69%	88.46%	34.62%
Female	4.35%	95.65%	43.48%
P	0.62	0.62	0.55

Mantel-Haenszel X^2

Table 6. Phases of treatment of leukemia as risk factors for development of oral manifestations

Phase of Treatment	Candidiasis	Gingivitis	Mucositis
Remission induction	0.00%	100.00%	50.00%
Consolidation-intensification	0.00%	100.00%	20.00%
Maintenance	8.33%	89.00%	39.89%
P	0.56	0.63	0.55

Mantel-Haenszel X^2

Table 7. Oral hygiene as a risk factor for development of oral manifestations

Hygiene	Candidiasis	Gingivitis	Mucositis
Good	0.00%	81.25%	25.00%
Fair	6.25%	883.33%	33.33%
Poor	7.41%	100.00%	48.15%
P	0.79	0.01	0.3

Mantel-Haenszel X^2

DISCUSSION

This study evaluated oral manifestations in pediatric patients receiving chemotherapy for ALL, in which these manifestations were found to be frequent. As for the most common oral manifestations, our group of patients had a prevalence

of gingivitis of 91.84% and of mucositis, 38.77%. These results are similar to those reported by Lopez (2005)[14] and El- Housseiny (2007).[19] The prevalence of candidiasis in our population was 6.12%, which was low compared with other studies;[1,10,11,20] this could be due to the levels of immunosuppression, degree of oral hygiene, or change in the administration of chemotherapy. Other manifestations were cheilitis, 18.36%; periodontitis, 16.32%; recurrent herpes, 12.24%; and primary herpetic gingivostomatitis, 2.04%, whose prevalence had not been reported in the literature.

A common factor in the development of caries, gingivitis, periodontitis, and candidiasis in children with ALL was poor oral hygiene, a situation that could aggravate the conditions already established. Similar to what has been described in the literature, there were no statistically significant differences by age or gender in the development of oral manifestations, but our group had a higher risk of developing oral manifestations, depending on the high risk of ALL, phase of treatment, type of leukemia, and degree of oral hygiene.

Within these risk factors it is important to include the administration of certain drugs concurrent with the chemotherapy, such as methotrexate and prednisone, that have the potential of influencing the appearance of oral lesions; such is the case with the mucositis and candidiasis that developed in our study population within 3 to 7 days of administration.[21,22] Although our patients took other drugs for the control of opportunistic infections during the 3 phases of chemotherapy, there was no relationship with the presence of oral manifestations.

Another underlying, frequently occurring problem is the absence of inflammatory symptoms, resulting in a preliminary diagnosis of a more complicated infection. Such a situation can be dangerous to young patients undergoing chemotherapy, wherein the reduction of immune defenses favors the establishment of life-threatening septicemic and hemorrhagic infections.[20] It was demonstrated that a protocol of preventive oral and dental care, jointly with the chemotherapy, reduces the incidence of oral complications. Therefore, the attendance of a pediatric dentist in the initial phases when the disease is pronounced is of great importance. Only meticulous observation allows a clinical diagnosis of the dento-periodontal alterations of the oral cavity resulting from both the disease process and the chemotherapy.[23] During each phase of treatment it is necessary to consider the medical condition of the patient and the availability of the family, whose presence is generally positive; parents are usually receptive to all information and motivations about how the disease affects the health of their child.

Finally, multidisciplinary care, including pediatric dentistry, is important in patients with ALL, because during the initial period of treatment, the effects of the disease and the chemotherapeutic drugs can cause severe oral complications. Ideally, all dental care should be completed before cancer therapy is initiated.[23] When that is not feasible, temporary restorations can be placed, and definitive treatment can be delayed until the patient´s hematological status is stable. Priority should be given to infections, extractions, periodontal care, and sources of tissue irritation.[24] Only conservative, emergency dental care should be provided during immunosuppression and only after consultation with the medical team regarding platelet and antibiotic therapy. For the management of oral complications related to chemotherapy, efforts are directed to reduce the influence of secondary factors on mucositis; monitoring of the oral cavity allows for timely diagnosis and treatment of fungal, viral, and bacterial infections. For oral bleeding, treatment should consist of local approaches such as pressure packs and systemic measures such as platelet transfusions. Fluoride rinses and gels are highly recommended for caries prevention.[25,26]

The American Academy of Pediatric Dentistry recognizes that the pediatric dental professional plays an important role in the diagnosis, prevention, stabilization and treatment of oral and dental problems that can compromise the child´s quality of life before, during and after chemotherapy; therefore, early and radical dental intervention, including aggressive oral hygiene measures, reduces the risk for oral and associated systemic complications.[23] In the present study we included contemporary recommendations for management of the pediatric cancer patient in the dental setting. Before the initiation of cancer therapy we identified and stabilized or eliminated existing potential sources of infection, local irritants, and irregular surfaces that may complicate the cancer therapy, and to educate the patient and caretakers about the importance of optimal care in order to minimize oral problems during and after treatment. We included a preventive protocol that consider a medical history review: Information about the underlying disease, time of diagnosis, treatment modalities the patient has received since the diagnosis and complications; dental history review: includes information such as oral hygiene, habits, diet, treatment symptomatology and previous dental treatments, trauma and preventive practices, and dental care during inmunosuppression periods.

The goal is to maintain optimal oral health during cancer therapy, to manage any oral side effects that may develop as a consequence of the cancer therapy, such as mucositis, oral mucosal infection, oral bleeding, dental sensitivity pain and xerostomia. Close monitoring of the oral cavity, allows for timely diagnosis and treatment of fungal, viral, and bacterial infections, the palliation of symptoms and efforts to reduce the influence of secondary factors and to educate the patient and caretaker about the importance of optimal care in order to minimize oral problems/discomfort during treatment.[9,11,23,27]

Further studies are needed to determine prospectively the role of the risk factors described herein, as well as to establish specific protocols of treatment for each of the phases of chemotherapy according to the risk of disease, type of leukemia, and phase of treatment.

CONCLUSIONS

In patients with ALL receiving chemotherapy, we found that gingivitis was the most frequent complication, with 91.84% of the cases; caries, 81.63%; mucositis, 38.77%;

periodontitis, 16.32%; cheilitis, 18.36%; recurrent herpes, 12.24%; and primary herpetic gingivostomatitis, 2.04%. Other oral manifestations were dry lips, mucosal pallor, mucosal petechiae, ecchymoses, and aphthous ulcers. The prevalence of oral candidiasis was 6.12%. For the analysis of the risk factors in this study, it was observed that high risk ALL (according to prognostic factors, therapeutically relevant risk groups, and to the presence of Philadelphia chromosome) and poor oral hygiene were important risk factors for the development of candidiasis and gingivitis. The type of leukemia, gender, and phase of chemotherapy were apparently associated with the presence of candidiasis, gingivitis, and periodontitis, and they could be considered risk factors for the development of oral manifestations.

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