Oral Manifestations of Leukemia at the Time of Diagnosis

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Abstract

Introduction: Leukemia is a pathology that consistent with modifications derived from hematopoietic stem cells, which can generate signs and symptoms in the patient’s body. Objective: To verify the oral manifestations of leukemia at the time of diagnosis. Method: A review of the integrative literature was carried out in May and June of 2018 from the PubMed and BIREME databases, using the words registered in the MESH and the DeCS (Health Descriptors), respectively, in English leukemia AND diagnosis AND oral manifestations. We included studies evaluating oral alterations in leukemic patients at the time of diagnosis, published in the bases cited in Portuguese and English, with any study design, except revision of narrative literature and articles published between 1950 to 2018. We excluded articles that did not address the subject of the study, which included individuals other than leukemic patients, with absence of oral manifestations in leukemic patients and articles not found in its full version. Results: Through the search, 353 articles were found, of which 318 were excluded. Thus, 35 articles remained. Conclusion: According to the articles found, the surgeon-dentist has great importance at the time of diagnosis of leukemia, since the first manifestations of this disease occur in the oral cavity, such as gingival bleeding, hyperplasia, gingival swelling, oral ulceration and petechiae. Key words: Leukemia; Diagnosis; Oral Manifestations.

Resumo

Introdução: A leucemia é uma patologia com modificações malignas nas células-tronco hematopoéticas, podendo gerar sinais e sintomas no organismo do paciente. Objetivo: Verificar as manifestações orais de leucemia no momento do diagnóstico. Método: Foi realizada uma revisão de literatura integrativa em maio e junho de 2018, a partir das bases de dados PubMed e BIREME, por meio das palavras cadastradas no MESH e no DeCS (Descritores em Saúde), respectivamente, em inglês leucemia AND diagnosis AND oral manifestations. Foram incluídos estudos avaliando as alterações bucais em pacientes leucêmicos no momento do diagnóstico, publicados nas bases citadas, nas línguas portuguesa e inglesa, com qualquer desenho de estudo, exceto revisão de literatura narrativa e artigos publicados entre 1950 a 2018. Foram excluídos os artigos que não abordem o tema do estudo, que incluíram outros indivíduos, além de pacientes leucêmicos, com ausência de manifestações orais em pacientes leucêmicos, e artigos não encontrados em sua versão completa. Resultados: Foram encontrados 353 artigos; destes, 318 foram excluídos. Assim, restaram 35 artigos. Conclusão: Conforme descrito nos artigos encontrados, o cirurgião-dentista tem grande importância no momento do diagnóstico da leucemia, já que as primeiras manifestações dessa doença ocorrem na cavidade oral, tais como sangramento gingival, hiperplasia, inchaço gengival, ulcerção oral e petequias. Palavras-chave: Leucemia; Diagnóstico; Manifestações Bucais.

Resumen

Introducción: La leucemia es una patología con modificaciones de las células madre hematopoyéticas, las cuales pueden generar signos y síntomas en el organismo del paciente. Objetivo: Verificar las manifestaciones orales de leucemia en el momento del diagnóstico. Métodos: Se realizó una revisión de literatura integrativa en mayo y junio de 2018 a partir de las bases de datos PubMed y BIREME, por medio de las palabras catastradas en el MESH y en el DeCS (Descripores en Salud), respectivamente, en inglés leucemia AND diagnosis AND oral manifestaciones. Se incluyeron los estudios que evaluasen las alteraciones orales en pacientes leucémicos el momento del diagnóstico, publicados en las bases mencionadas en portugués y en Inglés, con cualquier diseño de estudio, excepto la narrativa revisión de la literatura y artículos publicados entre 1950 e 2018. Se excluyeron los artículos que no abordan el tema del estudio, que incluyeran a otros individuos además de pacientes leucémicos, con ausencia de manifestaciones orales en pacientes leucémicos y artículos no encontrados en su versión completa. Resultados: A través de una búsqueda realizada encontraron 353 artículos, de éstos, 318 fueron excluídos. Así, quedaron 35 artículos. Conclusión: Según los artículos encontrados, el cirujano-dentista tiene gran importancia en el momento del diagnóstico de la leucemia, ya que las primeras manifestaciones de esta enfermedad ocurren en la cavidad oral, tales como sangrado gingival, hiperplasia, inchaço gengival, ulceración oral y petequias. Palabras clave: Leucemia; Diagnóstico; Manifestaciones Bucales.

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INTRODUCTION

Leukemia is a hematological disorder characterized by the differentiation and proliferation of malignant leukocytes, which destroy the bone marrow, generating the multiplication of leukemia cells1-7.

According to Silva et al.8, leukemia represents one-third of all childhood cancers, and 75% of pediatric patients suffer acute lymphoblastic leukemia, which can originate in the B or T cells.

The causes of this disease are unknown and uncertain, although it is associated with radiation exposure, chromosomal anomalies, chemical lesions, and viral infections and may be caused by a combination of environmental and genetic factors2,9.

Leukemias are classified according to their clinical course (acute or chronic) and histogenetic origin (lymphoid or myeloid). Chronic leukemia tends to show relatively high leukocyte concentrations and its evolution is slower, while acute leukemia presents with more rapid progression2,5,10-12.

The alterations are associated with the compromise to the hematopoietic system, generating systemic signs and symptoms in the patient, such as fatigue and dyspnea, besides alterations in the oral cavity, with gingival swelling, petechiae, bruising, spontaneous bleeding/hemorrhage, ulcers, lichen planus, hyperplasia, erythema multiforme, lupus erythematosus, pemphigus vulgaris, and mucositis13-24.

The current study thus aims to investigate the oral manifestations of leukemia at the time of diagnosis and thus contribute to knowledge through the detection of alterations in the mouth that indicate diseases than dental problems. The study also aims to verify the age with the highest rate of involvement of the oral cavity as well as the dentist’s role at the time of diagnosis.

METHOD

This study is an integrative literature review on the oral manifestations of leukemia at the time of diagnosis. We consulted the PubMed (MEDLINE) and Virtual Health Library (BIREME) databases. The review was conducted in May and June 2018 using a search strategy that addressed MeSH and entry terms in PubMed and the keywords registered in DeCS in BIREME.

The search strategy was the following: in PubMed via MeSH and entry terms - “Leukemia”[MeSH] OR “Leukemia” OR “Leucocythaemia” OR “Leucocythaemias” OR “Leucocytosis” OR “Leucocytosis” AND “Oral Manifestations”[Mesh] OR “Manifestation, Oral” OR “Manifestation” AND “Diagnosis”[MeSH] OR “Diagnoses” OR “Diagnoses and Examinations” OR “Examinations and Diagnoses” OR “Antemortem Diagnosis” OR “Antemortem Diagnoses” OR “Diagnoses, Antemortem” OR “Diagnosis, Antemortem”. The search in BIREME used the words registered in DeCS: “leukemia” AND “diagnosis” AND “oral manifestations”. The search was expanded to “leukemia” AND “diagnosis” AND “oral manifestation”; the term “oral manifestation” is not registered in DeCS.

Inclusion criteria were: studies reporting oral manifestations in leukemia patients at the time of diagnosis; published in Portuguese and English in the above-mentioned databases; any study design except narrative literature review; and published from 1950 to 2018. Exclusion criteria were: articles that did not address the study theme; that included individuals other than leukemia patients; that did not report oral manifestations in leukemia patients; and that were not found in full text format, even after requesting them for purchase/acquisition.

The studies were analyzed by two independent researchers based on the titles and abstracts, according to the inclusion and exclusion criteria. After the articles were included, they were submitted to an analysis of the full text according to the eligibility criteria. The extracted data were related to oral manifestations, patients’ age, and the dentist’s role in the leukemia diagnosis.

RESULTS

The search yielded 353 articles, selected via the inclusion and exclusion criteria. A total of 35 articles were included. Chart 1 provides details on the included studies.

DISCUSSION

Clinical manifestations of patients with chronic leukemia are related to the decrease in the production of blood cells, which can lead to anemia, neutropenia, and thrombocytopenia3,17.

The oral alterations most frequently reported in the literature in leukemia cases confirm the review’s findings and are reported in different studies, such as gingival bleeding3,16,18-24; gingival swelling3,11,23,25,26; oral ulcers2,5,13,15,25,27-30; petechiae2,5,27,28,31,32; and hyperplasia5,10,21,27,29,31,33,34.

The review also verified pain in the maxillary and/or mandibular region3,18,20,32,33.

Other manifestations were reported, including mobility of the lower front teeth3; lymphadenopathy1,23,31,32; and tenderness on palpation of bilateral submandibular lymph nodes7.
Chart 1. Description of eligible articles

<table>
<thead>
<tr>
<th>References</th>
<th>Patient assessment procedures</th>
<th>Oral manifestations</th>
<th>Patients’ age</th>
<th>Dentist’s approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alessandriní et al. (2012)</td>
<td>Intraoral tests, CT, complete blood count, immunohistochemistry, biopsy, and extraoral tests</td>
<td>Swelling in upper left vestibule, painful firm mass on palpation, with smooth, elastic consistency</td>
<td>74 years</td>
<td>---</td>
</tr>
<tr>
<td>Anil et al. (1996)</td>
<td>Intraoral and extraoral tests, blood test, and biopsy</td>
<td>Gingival enlargement and difficulty chewing</td>
<td>34 years</td>
<td>After performing intra and extraoral tests and ordering blood tests, which came back normal, the dentist performed a gingivectomy and sent sample for biopsy, suspecting leukemia</td>
</tr>
<tr>
<td>Appel and Miggantz (1988)</td>
<td>Intraoral tests, x-ray, biopsy of inter-molar papilla, bone marrow biopsy, and laboratory tests</td>
<td>Pain in right mandibular region, reddish-purple alveolar mucosa, erythema, papillae and gingiva with purulent appearance. Right lower molar showed advanced periodontal destruction and subgingival calculus. Generalized horizontal bone loss, caries in third lower right molar, subgingival calculus, and periodontal pocket of 8 to 10 mm</td>
<td>59 years</td>
<td>Dentist performed first treatment for patient, then referred to periodontist, who ordered biopsy of the buccal papilla between lower left teeth and first and second molars. Patient was then referred to hospital for treatment with oncologist</td>
</tr>
<tr>
<td>Aronovich and Connolly (2008)</td>
<td>Complete blood count, clinical tests, biopsy, histopathology, and intraoral tests</td>
<td>Pain in left posterior region, pain and gingival bleeding, edema on the left around lower maxilla, trismus, and localized erythema</td>
<td>18 years</td>
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</tr>
<tr>
<td>Babu et al. (2014)</td>
<td>Extraoral and intraoral tests and complete blood count</td>
<td>Bleeding and gingival swelling, deep bilateral submandibular cervical lymphadenopathpy; erythematous gingiva, dental plaque and calculus, generalized enlargement of maxilla and mandibular gingiva with buccolingual involvement</td>
<td>43 years</td>
<td>After ordering extraoral, systemic, and intraoral tests and complete blood count, dentist instructed patient to use a soft toothbrush and perform mouthwash with chlorhexidine (0.2%) 3 times a day and referred immediately to cancer center</td>
</tr>
<tr>
<td>Boddu et al. (2017)</td>
<td>Extraoral and intraoral tests, CT, and biopsy</td>
<td>Gingival pain and oral lesions, sublingual ulcers</td>
<td>62 years</td>
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<tr>
<td>Brenneis, Mattson and Commers (1988)</td>
<td>Clinical and blood tests</td>
<td>Cyanotic gingiva with hyperplasia, bilateral cervical lymphadenopathy, enlarged and erythematous tonsillar tissue</td>
<td>43 years</td>
<td>Dentist ordered blood tests, since patient presented typical signs of leukemia</td>
</tr>
<tr>
<td>Bressman et al. (1982)</td>
<td>Clinical tests, x-ray, hematomatological assessment, physical tests, and bone marrow aspiration</td>
<td>Gingival pain and bleeding in right maxilla in premolar region, fibrotic marginal gingiva, teeth with extensive restorations and bone loss</td>
<td>36 years</td>
<td>Patient referred to regular physician with a special request for hematomatological assessment</td>
</tr>
<tr>
<td>Cale, Freedman, and Lumerman (1988)</td>
<td>Extraoral and intraoral tests</td>
<td>Hemorrhagic bullae on the anterior dorsum of tongue and spontaneous gingival bleeding</td>
<td>45 years</td>
<td>Upon receiving patient, dentist treated first with vitamin C and amoxicillin, without ordering any tests</td>
</tr>
<tr>
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<tr>
<td>Chavan et al. (2010)</td>
<td>Intraoral clinical tests and blood tests</td>
<td>Painful swelling and gingival bleeding, altered color of gingiva and marginal papillae, gingival ulceration, bruising on the mucosa of hard and soft palate</td>
<td>35 years</td>
<td>Dentist ordered a hematological assessment due to the severity and extent of the gingival alterations. After diagnosis, referred to an oncologist</td>
</tr>
<tr>
<td>Chung et al. (2011)</td>
<td>Physical tests, complete blood count, intraoral test, x-ray, CT, and biopsy</td>
<td>Pain in posterior right mandible and mobility of lower front teeth</td>
<td>35 years</td>
<td>Dentist took a complete history, including oral history, and requested hospital admission for systemic assessment of the patient</td>
</tr>
<tr>
<td>Claus and Denver (1954)</td>
<td>Laboratory and physical tests</td>
<td>--</td>
<td>37 years</td>
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</tr>
<tr>
<td>Cooper, Loewen, and Shore (2000)</td>
<td>Intraoral tests, x-ray, blood tests, and biopsy</td>
<td>Hyperplasia and gingival bleeding</td>
<td>35 years</td>
<td>--</td>
</tr>
<tr>
<td>Dean, Ferguson, and Marvan (2003)</td>
<td>Extraoral and intraoral tests, complete blood count, and x-ray</td>
<td>Pain, gingival and mucosal ulcers, petechiae</td>
<td>22 years</td>
<td>Medicated the patient and referred to a specialist</td>
</tr>
<tr>
<td>Demirer et al. (2007)</td>
<td>Clinical tests, x-ray, complete blood count, and bone marrow biopsy</td>
<td>Gingival hyperplasia, erythematous areas on gingiva</td>
<td>17 years</td>
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</tr>
<tr>
<td>Fatahzadeh and Krakow (2008)</td>
<td>Clinical tests, x-ray, intra and extraoral tests, complete blood count, bone marrow biopsy and peripheral blood test, smear test</td>
<td>Intermittent pain, generalized gingival bleeding, swollen and erythematous gingiva, plaque, tartar, submandibular lymphadenopathy</td>
<td>26 years</td>
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</tr>
<tr>
<td>Guan and Firth (2015)</td>
<td>Extraoral and intraoral tests, blood tests</td>
<td>Spontaneous gingival bleeding</td>
<td>49 years</td>
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<tr>
<td>Gordon, O'Neal, and Woodyard (1985)</td>
<td>Clinical tests, urine test, complete blood count, serum glutamic oxaloacetic transaminase</td>
<td>Pale oral mucosa, firm, non-transcendent gingiva with normal physiological contours</td>
<td>42 years</td>
<td>After dentist treated the periodontitis with radicular scraping and smoothing, patient underwent periodontal surgery. One month after surgery, patient returned with symptoms of respiratory infection, was medicated, and blood tests were ordered. With the results, patient was referred to hospital</td>
</tr>
<tr>
<td>Gowda et al. (2013)</td>
<td>Extraoral, intraoral, and laboratory tests</td>
<td>Gingival swelling, pain, and bleeding, bilateral submandibular lymphadenopathy, localized necrosis and desquamation involving interdental papilla, and discoloration of marginal gingiva</td>
<td>28 years</td>
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<tr>
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<tr>
<td>Katz and Peretz (2002)</td>
<td>Extraoral and intraoral tests, panoramic radiograph, blood tests</td>
<td>Trismus, tenderness on palpation of submandibular nodules bilaterally</td>
<td>6 years</td>
<td>After initial assessment of patient, dentist ordered blood tests due to patient’s debilitated state</td>
</tr>
<tr>
<td>Keene, Hussman, and Bruner (1972)</td>
<td>Radiographs and intraoral tests</td>
<td>Gingival hyperplasia, pain, diffuse erythema, generalized bone loss, gingival bleeding</td>
<td>54 years</td>
<td>Dentist ordered a complete blood count before performing periodontal treatment</td>
</tr>
<tr>
<td>Komeno et al. (2015)</td>
<td>Intra and extraoral tests and blood tests</td>
<td>Oral and esophageal candidiasis</td>
<td>47 years</td>
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</tr>
<tr>
<td>Menezes and Rao (2012)</td>
<td>Intraoral tests, laboratory tests, complete blood count, and bone marrow biopsy</td>
<td>Pain, swelling, and bleeding of maxillary and mandibular gingiva, enlarged and edematous gingiva, gingival necrosis at the margins of teeth</td>
<td>34 years</td>
<td>Dentist ordered routine blood workup that revealed alteration suggestive of leukemia</td>
</tr>
<tr>
<td>Pogrel (1978)</td>
<td>Clinical tests, radiographs, and biopsy</td>
<td>Severe hypertrophy on incisal mandible, purplish hypertrophic area, bleeding, mobility of lower incisors, and gingival lesion</td>
<td>32 years</td>
<td>Dentist performed a biopsy of the hypertrophic region of the incisal mandible</td>
</tr>
<tr>
<td>Ratre et al. (2018)</td>
<td>Intra and extraoral tests and blood tests</td>
<td>Swollen gingiva and difficulty eating</td>
<td>51 years</td>
<td>--</td>
</tr>
<tr>
<td>Reenesh, Munishwar and Rath (2012)</td>
<td>Physical, intraoral, and blood tests</td>
<td>Gingival pain and bleeding, bluish gingiva with bruising</td>
<td>32 years</td>
<td>--</td>
</tr>
<tr>
<td>Shimizu et al. (2017)</td>
<td>Physical, intraoral, and blood tests and CT</td>
<td>Severe edema in right vestibular area. Enlarged right maxillary sinus on CT</td>
<td>12 years</td>
<td>--</td>
</tr>
<tr>
<td>Sepúlveda et al. (2012)</td>
<td>Intraoral and blood tests</td>
<td>Hyperplasia and gingival bleeding, petechiae and bruising, lymphadenopathies</td>
<td>6 years</td>
<td>--</td>
</tr>
<tr>
<td>Sharma and Bhalla (2011)</td>
<td>Intra and extraoral tests and blood tests</td>
<td>Painful herpetiform lesions on extraoral region adjacent to redness on lower lip, ulcers covered with whitish spots. Loss of normal contours and dotted gingiva</td>
<td>16 years</td>
<td>--</td>
</tr>
<tr>
<td>Shen et al. (2018)</td>
<td>Intra and extraoral tests</td>
<td>Gingival swelling, chronic periodontitis, and epulis</td>
<td>41 years</td>
<td>--</td>
</tr>
<tr>
<td>Silva et al. (2008)</td>
<td>Physical tests, biopsy of genital ulcer, ancillary tests, complete blood count, cytogenetics, and immunophenotyping</td>
<td>Multiple, recurrent, difficult-to-heal oral ulcers and gingivitis</td>
<td>10 years and six months</td>
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</tbody>
</table>
Aronovich and Connolly\(^1\) report an inflammatory condition that occurs in impacted or partially erupted teeth, known as pericoronitis. This manifestation normally occurs in third molars at the time of eruption, where bacterial plaque and food remnants adhere below the gingiva, providing a substrate and medium for infection.

Sepúlveda et al.\(^{23}\) report that leukemia is a neoplasia that occurs most frequently in children under 15 years of age. Meanwhile, Brenneise et al.\(^{24}\) report that the highest prevalence of acute lymphocytic leukemia is in children 15 years of age, while chronic lymphocytic leukemia predominates in patients over 60 years of age.

Oral lesions are often the first sign or symptom of leukemia, leading patients to seek dental care in the belief that they have a local rather than systemic problem. The dentist thus plays a crucial role in the patient’s initial workup, assisting with the diagnosis and prognosis\(^2,8\). Patient education and an emphasis on prevention and improvements in routine oral hygiene are some of the relevant attitudes\(^{10,13,22}\).

The dentist’s assessment consists basically of performing intraoral and extraoral tests. Dentists thus use various tools to assist them, such as biopsy of suggestive areas or bone marrow.

Intraoral and extraoral tests are reported in most of the articles, while biopsy, a simple, safe, and less invasive alternative, was only reported by a few studies\(^{1,2,19,20,23,25,31,33}\). However, the articles did not appear to follow a set parameter for patient assessment. No criteria were reported, nor did the articles specify how the physical, extraoral, or intraoral assessment was performed in the reported cases.

As for imaging tests, periapical and panoramic radiography did not reveal any abnormality according to some authors\(^7,10,22\), while other authors showed bone loss using radiography\(^20,23,27,33,34\).

In addition to performing proper initial care for the patient, the dentist should thus be alert not only to the manifestations, but also to the patient’s follow-up, being aware of the different systemic diseases versus more benign conditions.

Any invasive dental procedures in these patients should be performed with caution due to the high risk of hemorrhage and infection.

The studies were limited in their designs, since virtually all were case reports. We found no observational study with a larger sample of patients. There was thus a relative shortage of consistent information. There were also constant publications involving reports on the same disease and approached in similar ways.

**CONCLUSION**

Based on the above, leukemia tends to present its first manifestations in the oral cavity, and the most frequent alterations are gingival bleeding, hyperplasia, gingival...
swelling, oral ulcers, and petechiae. Age with the highest incidence of leukemia and oral manifestations was 32 to 37 years. Dentists play a crucial role in rapid and early diagnosis of the disease, since they are the first health professionals patients turn to when they experience alterations in the oral cavity. The dentist is thus the first health professional to see the signs and symptoms of leukemia and can order tests to confirm the suspicion of a possible alteration, thus allowing a rapid and early diagnosis and favoring better prognosis for patients. In the multidisciplinary oncology team, the dentist contributes to the medical team before, during, and after medical treatment.

**CONTRIBUTIONS**

All the authors contributed equally to all phases of the study.

**CONFLICT OF INTEREST:**

None.

**REFERENCES**