Review article

Oral manifestations of leukemia as part of early diagnosis

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ABSTRACT

Introduction: The oral cavity can present the first clinical manifestations of leukemia, therefore; it is important to recognize their principal characteristics.

Objective: To identify oral manifestations as the first clinical signs of leukemia.

Methods: This is an integrative review, that gathered data from articles with oral manifestations of leukemia as part of its first clinical features. The were included case reports, case series, clinical research, or reviews with case reports. The variables that were considered relevant: age, sex, sites of the oral lesions, characteristics of the oral lesions, medical history and physical examination, time of evolution, radiographic examination, blood test results, initial diagnosis, differential diagnosis and final diagnosis.

Results: A total of 31 studies were included, with a total of 33 individuals identified. There were 19 (57.57%) males and 14 (42.42%) females. The age range was from 1.6 to 74 years. Acute myeloid leukemia (72.72%) and acute lymphoid leukemia (18.18%) presented more oral manifestations as the first clinical signs of the disease. All individuals with leukemia presented lesions, such as ulcer, erosion, bleeding, ecchymosis, color change of the bluish or pale mucous membranes and areas of tissue necrosis. Hard tissue lesions were less frequent, being 6 (18.18%).

Conclusion: The first clinical manifestations of leukemia can be present in the oral cavity, mainly in acute myeloid leukemia. The principal oral tissues affected were gingival tissue, buccal mucosa and hard and/or soft palate. When hard tissues, such as the maxilla bone or mandible bone were affected, dental mobility was the principal clinical sign.

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Introduction

Leukemia is a component of oncohematological diseases. Healthy blood cells are replaced with modified immature cells in the bone marrow and circulate through the bloodstream. The classification of lymphoid or myeloid leukemia can be
determined by considering the time, whether the leukemia is acute or chronic and the cell type.\textsuperscript{1,2}

The worldwide incidence of leukemia is 437,033 cases, with 30,906 deaths estimated in 2019. The highest prevalence is in males, and acute and chronic leukemia mainly affect the infant/juvenile population and adult population, respectively.\textsuperscript{3}

Given that leukemia is a systemic disease that affects blood components, individuals affected by this disease may present with petechiae, hematomas, ecchymosis and bleeding in different parts of the body, including the mouth, during the physical examination.\textsuperscript{4}

The early identification of this disease allows individuals to start treatment as soon as possible and increases their chances of survival. Therefore, considering that the oral cavity can present the first clinical manifestations of leukemia (MOLs), its recognition from the beginning of the disease is important.\textsuperscript{5−7}

In recent years, few studies have reported oral manifestations as the first clinical signs of leukemia because these manifestations are usually mentioned in clinical case reports that vary from individual to individual and with the type of leukemia.\textsuperscript{8} This integrative review aimed to identify which tissues of the mouth presented the first MOLs and describes the characteristics that allowed the guiding of the diagnosis of leukemia via clinical signs in the mouth as part of the first clinical manifestations of the disease.

Material and methods

This study is an integrative review that gathered data from articles to describe the clinical MOLs in the oral cavity when they were present as the first clinical signs of the disease and those that contributed to guide the final diagnosis.

Structured research was performed by searching the PubMed and Scopus databases using the following terms: “(first OR initial OR early) AND (oral manifestation OR oral sign OR oral lesion) AND (leukemia).”

Articles published in Portuguese, English or Spanish from 2008 to 2020 were included, including case reports, case series, clinical research and reviews that included case reports. The entire publication file had to be available and had to report oral manifestations as the first clinical signs of leukemia. Animal studies, review articles, studies in other languages not mentioned in the inclusion criteria and clinical cases or research articles in which the oral manifestation of leukemia were not part of the first clinical signs of the disease were excluded.

A total of 31 articles fulfilled all the pre-established inclusion criteria. All the information obtained was distributed in a table that contains the variables that were considered relevant: age, sex, sites of the oral lesions, characteristics of the oral lesions, medical history and physical examination, time of evolution, radiographic examination, blood test results, initial diagnosis, differential diagnosis and final diagnosis. \textsuperscript{(Figure 1)}

Results

A total of 31 studies that mentioned oral manifestations as part of the first clinical signs of leukemia were included. All studies included were clinical case reports or literature reviews that included at least one clinical case report with all the previously described variables.

In the case reports included in this integrative review, the evaluation and initial diagnosis of leukemia were performed principally by dentists who were the first health professionals to come into contact with the patients. Moreover, the dentists also referred the patients to the hematologist and/or oncologist to perform other analyses to establish the final diagnosis. Table 1 describes the characteristics of the 31 case reports.

A total of 33 individuals were identified in the selected studies: 19 males (57.57%)\textsuperscript{9,10,11−18,19−22} and 14 females (42.42%).\textsuperscript{23−30} The age ranged from 6 to 74 years and only 6 individuals (18.18%) were between 1.6 and 12 years old\textsuperscript{10,19,22,26,31,32}

Among the types of leukemia, oral manifestations were present principally in acute myeloid leukemia (24 individuals [72.72%])\textsuperscript{9,12−14,19,22,23,24,25,30,32} followed by acute lymphoid leukemia (6 individuals [18.18%])\textsuperscript{10,13,20,21,26,31} adult T-cell leukemia/lymphoma (2 individuals [6.06%]) and chronic lymphoid leukemia (1 individual [3.03%]).

First clinical MOL in oral tissues

Oral MOLs as the first clinical signs were more common in soft tissues (27 individuals [81.81%]) than in hard tissues (6 individuals [18.18%]).\textsuperscript{11,19,20,28,31,32} Figure 2 shows the different sites.

Soft tissues

The oral MOLs were in gingival tissue (63.63%)\textsuperscript{9,12,17−19,21,23−25,26,27,30,33−39,15,40} alveolar and jugal mucosa (18.18%)\textsuperscript{14,18,21,22,26,28} and hard or soft palate (18.18%)\textsuperscript{9,11,15,16,27,30} Other regions, such as the floor of the mouth (12.12%),\textsuperscript{13,16,23,38} tongue (9.09%),\textsuperscript{13,33,39} lip (3.03%),\textsuperscript{13} parotid glands (3.03%),\textsuperscript{10} and nasolabial region (3.03%)\textsuperscript{26} were less frequent.

The main lesions found in the soft tissues of the mouth were ulcer, erosion, bleeding, ecchymosis, color change of the bluish or pale mucous membranes, and areas of tissue necrosis. Among the case reports, 13 individuals (39.99%) reported pain as the principal symptom,\textsuperscript{9,13,28,30,31,14,15,17−21,25} which was also principally spontaneous.

Hard tissues

Among the oral MOLs in hard tissues, two cases corresponded to ALL,\textsuperscript{20,31} two cases corresponded to AML\textsuperscript{19,32} one case corresponded to chronic lymphocytic leukemia\textsuperscript{28} and one case corresponded to adult T-cell leukemia/lymphoma.\textsuperscript{13} Dental mobility was the most common clinical condition when hard tissues were affected. Panoramic radiography and computed tomography were used to evaluate the bone structures. The main characteristics of the radiographic images were cortical expansion of the
alveolar bone, osteolytic areas, thickening of the bone surrounding the teeth with mobility and severe vertical bone loss.

**Differential diagnosis of the oral MOLs**

In soft tissues, the differential diagnoses were gingival enlargement during pregnancy, gingival enlargement induced by drugs, squamous cell carcinoma and deep fungal infection, pericoronarite, oral manifestation of HIV, postoperative complications of extraction, candidiasis, necrotizing acute gingivitis, dental cyst eruption and herpetic gingivostomatitis. In addition, when the oral manifestation was in the maxillary bones, the presumptive diagnoses were acute osteomyelitis, osteosarcoma and Ewing sarcoma.

**General clinical signs and symptoms of leukemia**

The general signs and symptoms, in addition to the oral manifestations, were mainly the following: weakness, fatigue, lethargy or tiredness in 11 individuals (45.45%), lymphadenopathies in 8 individuals (36.36%), mucosal pallor in 6 individuals (27.27%), weight loss in 4 individuals (18.18%) and loss of appetite in 5 individuals (18.18%). Adjacent areas, such as the head and neck regions, presented submandibular lymphadenopathy, cervical lymphadenopathy, dysphagia, facial asymmetry and trismus. Other clinical signs and symptoms that were present, but were less frequent, included genital ulcers, vomiting, nausea, diarrhea, dizziness, abdominal swelling, petechiae in the leg and forearm, musculoskeletal pain, increased volume in the pre-sternal region and chills and joint pain.

**Results of laboratory tests that led to the presumptive diagnosis of oral MOLs**

The blood count was the main blood test requested to help support the presumptive diagnosis of an oral MOL. Thrombocytopenia was present in 22 cases (59.09%), anemia was present in 23 cases (63.63%) and leukocytosis was present in 19 cases (45.45%). Leukopenia was present in 5 cases (22.72%).

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**Figure 1 – Flow diagram of the studies included in the integrative review.**
### Table 1 – Principal characteristics of individuals with oral manifestations as first clinical signs of leukemia.

| Authors/Years          | Gender/Age   | Site of oral lesions             | Time of evolution | Radiographic exam                                                                 | Test blood results                                                                 | Biological reference range                                                                 | Initial diagnosis | Established differential diagnosis | Final diagnosis (Medical specialist) |
|------------------------|--------------|----------------------------------|-------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------|-----------------------------------|------------------------------------|
| Madhu Singh Rathe, et al., 2018 | M/52         | Generalized gingival enlargement | 3 months          | Panoramic radiography revealed slight to moderate generalized horizontal bone loss (non-significant for the leukemic diagnosis). | Erythrocyte count 2.6 M (Low), leucocyte count 198,800 (High), neutrophils 0.3%, platelet count 30 (Low), blast cells 95%. | Erythrocyte count 3.5 - 5.50 M/µl, leucocyte count 4,000 - 12,000/µl, neutrophils 75%, platelets 150 - 450 x 10^9/µl, blast cells 0%. | Leukemia          | None                              | Acute myeloid leukemia               |
| Hwa Suk Chae, et al., 2017 | M/12         | Bilateral parotid and submandibular glands | 2 days           | Panoramic radiograph showed no significant findings.                              | White blood cells (x 10^7/µL) 16.24, (x 10^6 red blood cells/µL) 3.88, hemoglobin (g/dL) 11.2, hematocrit (%) 31.0, platelets (x 10^9/µL) 16.24. | White blood cells (x 10^7/µL) 4.8 - 10.8, red blood cells (x 10^6) 4.6 - 6.2, hemoglobin (g/dL) 13.0 - 18.0, hematocrit (%) 40.0 - 50.0, platelets (x 10^9/µL) 130 - 400. | None              | Not mentioned                      | Acute leukemia/sialadenitis            |
| Dalirans Z, et al., 2015 | M/45         | From the right second molar to the left second molar in the mandibular and maxillary bones and hard palate | 4 months          | The panoramic radiograph: generalized rarefaction of jaw bones, but the inferior alveolar canal was unclear. Thinning of the inferior cortex of the mandible and destruction of the posterior region of the right cortex. Ocular radiograph: the resorption of the cortical border of the anterior mandible. Periapical radiograph: lamina dura was unclear and indistinct. | White blood cells 53,900/µL, red blood cell 5.3 M/µL, platelet count 319,000/µL; alkaline phosphate 1,530 U/L. | Not mentioned                              | Leukemia or lymphoma | None                              | Adult T-cell leukemia/lymphoma       |
| Guan G, Firth N, 2015  | M/49         | Palatal gingiva of the maxillary central incisors | 2 years          | Panoramic and periapical radiographs showed no significant findings.               | Hemoglobin (63 g/L), hematocrit (0.39), platelet count (23.10^9/µL) and leucocytes (0.57x10^9/µL). | Hemoglobin 130 – 175 g/L, hematocrit 40 – 52, platelets 150 – 400 10^9/µL, leucocytes 4 – 11 10^9/L. | Leukemia          | None                              | Acute myeloid leukemia               |
| Hasan S, Khan NI, Reddy LB, 2015 | F/18         | Generalized gingival enlargement | 1 month           | Panoramic radiography showed no significant findings.                              | Hemoglobin 7.4 g, red blood cell 1.23 million cu mm, platelets 60,000 cu mm, white blood cells 812,000/cu mm, neutrophils % 5, lymphocytes % 2. | Hemoglobin 11 - 13 g, red blood cells 3.5 - 5.5 million cu mm, platelets 150,000 - 450,000 cu mm, white blood cells 4,000 - 11,000 cu mm, neutrophils % 40 - 70, lymphocytes % 20 - 40. | None              | Acute myeloid leukemia               |
| Babu SP, et al., 2004  | F/43         | Generalized gingival enlargement | 2 months          | Panoramic radiography showed no significant findings.                              | Platelets: 11,000 150,000 – 400,000, red blood cells: 1.56 x 10^11, white blood cells: 197,600, neutrophils: 1%, blast cells: 90%. | Platelets: 150,000 - 400,000, red blood cells: 4.6 - 6.5, white blood cells: 4,000 - 10,000, neutrophils: 45 - 65, lymphocytes: 20 - 40, blast cells: 0. | Leukemia          | None                              | Acute myeloid leukemia               |
| Martini V, et al., 2013 | M/52         | Mouth floor, labial mucosa and tongue | 2 years           | None                                                                               | Normal                                                                            | Not mentioned                              | Leukemia          | None                              | Acute lymphoblastic leukemia (mature Natural Killer) |
| Gowda TM, et al., 2013 | F/28         | Generalized gingival enlargement | 2 months          | None                                                                               | White blood cells (cells/cu mm) 48,400, red blood cells (cells/cu mm) 2.810^6, hemoglobin (g/dL) 8.4, hematocrit (%) 25.1, platelets (cells/cu mm) 0.46 lacs, neutrophils (%) 6. | White blood cells (cells/cu mm) 4,800 - 10,500, red blood cells (cells/cu mm) 4.6 - 6.2x10^6, hemoglobin (g/dL) 14 - 18, hematocrit (%) 42 - 52, platelets (cells/cu mm) 1.4 - 4.4 lacs, neutrophils (%) 50 - 70. | Pregnancy gingival enlargement | None                              | Acute myeloid leukemia               |
| Silva BA, et al., 2012  | F/10         | The left-nasolabial region        | Not mentioned     | Occipital radiograph with no signs of abnormality.                                  | Anemia, leukopenia and thrombocytopenia (there were no reference values), white blood cells 1.5 x 10^9/µL, red blood cells 3.6 x 10^11/µL, platelets 6.3 x 10^11/µL, hemoglobin 107.0 g/L, hematocrit 0.30. | Not mentioned                              | Hematopoietic malignancy | None                              | Chronic lymphocytic leukemia        |
| Suarez-Cuenca JA, et al., 2009 | M/24         | Right lower third molar region   | 2 days            | None                                                                               | Coagulation disorder                                                                  | Postoperative complication of tooth extraction | Not mentioned                              | Acute myeloid leukemia (sub-type M3) |

**Note:** The table includes data from various publications with different diagnostic criteria and methodologies, providing insights into the hematological and radiographic findings associated with oral manifestations as initial clinical signs of leukemia.
| Authors-Year | Gender/Age (years) | Site of oral lesions | Time of evolution | Radiographic exam | Test blood results | Biological reference range | Initial diagnosis | Established differential diagnosis | Final diagnosis (Medical specialist) |
|--------------|------------------|---------------------|------------------|------------------|------------------|--------------------------|----------------|---------------------------------|----------------------------------|
| M. Misirlioglu, MZ Adisen, S. Yilmaz 2015 | M/30 | Generalized gingival enlargement | 10 days | It was not mentioned what kind of radiograph was made. It revealed no significant changes. | White blood cells: 35,000/mm³, platelet: 30,000/mm³ and red blood cells: 2.7 million/mm³. | Not mentioned | Acute leukemia | None | Human immunodeficiency virus (HIV) | Acute myeloid leukemia (sub-type 4) |
| Zacharias Vourexa- kis, 2015 | M/30 | Hard palate and the floor of the mouth (promyelocytic) | 3 days | None | 5 platelets/mL, 1.1 leukocytes/µL and 22% hematocrit | Not mentioned | Leukemia | None | None | Acute myeloid leukemia |
| Mohammed Tag- Adeen, et al., 2018 | F/49 | Middle of the soft palate | 1 month | The head and neck computed tomography revealed mild bilateral cervical and axillary lymphadenopathy with left maxillary sinus effusion. | Red blood cells: 4.4 \( \times 10^12/\text{L} \), platelets: 274 \( \times 10^9/\text{L} \), leukocytes: 8.3 \( \times 10^9/\text{L} \) | Red blood cells: 3.8 \( \pm 4.9 \times 10^12/\text{L} \), platelets: 158 \( \pm 348 \times 10^9/\text{L} \), leukocytes: 3.3 \( \pm 8.6 \times 10^9/\text{L} \) (40% were abnormal) | Candidiasis | Malignant lesion | None | Adult T-cell Leukemia/Lymphoma |
| Chowdhri K, et al., 2018 | M/40 | Generalized gingival enlargement involving the buccal, palatal and lingual region | 2 months | The panoramic radiograph revealed generalized horizontal bone loss. | White blood cell count: \( \times 10^9/\text{L} \) 44.78, red blood cells: \( \times 10^12/\text{L} \) 1.47 4.00 - 6.00, hemoglobin (g/dL) 4.9 13.5 - 17.5, hematocrit (%) 14.5, platelet: \( \times 10^11/\text{L} \) 65 | White blood cell count: \( \times 10^9/\text{L} \) 4.00 - 11.00, red blood cells: \( \times 10^12/\text{L} \) 4.00 - 6.00, hemoglobin (g/dL) 5 - 17.5, hematocrit (%) 42 - 52, platelet: \( \times 10^11/\text{L} \) 150 - 450 | Acute leukemia | Acute manifestation of systemic disease | None | Acute monocytic leukemia (sub-type M5b) |
| M. Alessandrinia et al., 2012 | F/74 | The upper left vestibule next to the left upper incisor and upper left secondary premolar | Not mentioned | Computed tomography confirmed a tissue-like mass, \( 3.2 \times 0.7 \times 0.3 \text{ cm} \) located in the left vestibule of the maxillary bone. | White blood cell count of 0.5, hemoglobin 103, platelet count 31, red blood cell count 3.31, hematocrit 0.3, neutrophil count 0.1 | White blood cell count 74.4 1.3 0.5 - 11 100/µL, hemoglobin 130 - 180 g/L, platelet count 150 - 400 10^9/µL, red blood cell count 4.50 - 6.00 10^12/µL, hematocrit 0.40 - 0.52 L/L, neutrophil count 1.7 - 7.5 10^9/L | Squamous cell carcinoma, deep fungal infections | Leukemia | Chronic lymphocytic leukemia |
| A. Chatzipantelis, F. A. Atkin, 2018 | M/50 | Gingiva adjacent to the upper right first molar and buccal right mandibular buccal sulcus | 1 week | The panoramic radiograph had no significant findings. | White blood cell count 0.5, hemoglobin 103, platelet count 31, red blood cell count 3.31, hematocrit 0.3, neutrophil count 0.1 | White blood cell count 74.4 1.3 0.5 - 11 100/µL, hemoglobin 130 - 180 g/L, platelet count 150 - 400 10^9/µL, red blood cell count 4.50 - 6.00 10^12/µL, hematocrit 0.40 - 0.52 L/L, neutrophil count 1.7 - 7.5 10^9/L | Acute leukemia | None | Acute myeloid leukemia |
| Shimizu R, et al., 2017 | M/12 | The right maxillary molar and the second primary molar | 1 month | The panoramic: diffuse opacification in the right maxillary sinus cavity, non-contrast computed tomography showing osteolastic lesions of the anterior and posterior walls of the maxillary sinus and thickening of the surrounding bone and soft tissue of the right maxilla were observed. | Mild leukopenia and high serum alkaline phosphatase | Not mentioned | Osteosarcoma of the right maxilla | Osteogenic sarcoma, Ewing’s sarcoma, and hematologic malignancy or metastatic malignancies | None | Acute myeloid leukemia (sub-type M6a) |
| Zhang Y, et al., 2010 | F/9 | Right facial asymmetry, the maxillary region clearly protruding outward. | 2 weeks | A contrast computed tomography scan of the maxillae demonstrated a homogeneous mass located in the right maxillary fossa extending backward into the infratemporal fossa without bone destruction. | White blood cell count of 3.16 \( \times 10^9/\text{L} \), a platelet count of 272 \( \times 10^9/\text{L} \), and hemoglobin and red blood cell count of 107 g/L and 3.87 \( \times 10^12/\text{L} \) | Not mentioned | Leukemia infiltration | None | Acute lymphoid leukemia (High-risk B-cells) |
| Mattheos K. et al., 2010 | F/70 | The alveolar socket of the extracted left mandibular first premolar | 20 days | The radiographic examination of the mandible did not show any bone damage. | Not mentioned | Not mentioned | Myeloid sarcoma (biopsy) | None | Acute myeloid leukemia |
| Chung SW, et al., 2011 | M/35 | The lower anterior and left posterior teeth | 4 months | A panoramic radiograph revealed an osteolytic lesion on the left mandibular body and ascending ramus area with severe vertical bone loss on the lower left posterior mandible. The computed tomography showed an osteolytic lesion on the entire left half of the mandible. | Red blood cells: 3.93 \( \times 10^12/\text{L} \), but normal white blood cell count (10.39 \( \times 10^9/\text{L} \), platelet count (661 \( \times 10^9/\text{L} \)) | Not mentioned | Hematologic malignancy | Acute osteomyelitis of the mandible, osteosarcoma | Acute lymphoid leukemia (Burkitt type) |
| Authors/Year                                      | Gender/Age (years) | Site of oral lesions                        | Time of evolution | Radiographic exam                                                                 | Test blood results                                                                 | Biological reference range                              | Initial diagnosis                                         | Established differential diagnosis                      | Final diagnosis (Medical specialist)                      |
|-------------------------------------------------|--------------------|---------------------------------------------|-------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------|----------------------------------------------------------|-----------------------------------------------------------|----------------------------------------------------------|
| Sharon Aronovich, Thomas W. Connolly, 2008      | M18                | Mandibular left third molar                 | 1 week            | A panoramic radiograph showed a 30° mesial tilt of the mandibular left third molar with minor ovoid radiolucencies mesial to roots of the mandibular left third molar and the mandibular right third molar. These radiographic findings were deemed inconclusive. | Blood count showed 44% lymphoblasts with profound neutropenia and severe thrombocytopenia (17,000 platelets/mm3). | Not mentioned                                               | Pericoronitis with occlusal trauma                         | None                                                      | Acute lymphoblastic leukemia                             |
| Sepulveda E, et al., 2012                       | M/6                | Gingiva and hard palate                    | 2 weeks           | None                                                                                | Hemoglobin 7.2 (g/dL), hematocrit 20 (%), white blood cells 26,600 (cells/ml), neutrophil absolute count 1,500 (cells/ml), lymphocyte absolute count 14,900 (cells/ml), platelets 20,000 (cells/ml). | Not mentioned                                               | Leukemia                                                   | Complication of hemorrhage after tooth extraction          | Acute myeloid leukemia (sub-type M3)                      |
| Freeti Chawla Arora, et al., 2020               | F/18               | Several ulcers on the tip of the tongue, buccal mucosa and gingiva; mild enlargement of interdental gingiva in maxillary and mandibular anterior teeth | One week | None                                                                                 | Hemoglobin 7.8 g%, high leukocyte count 34,900 mm3 and low platelet count 25,000 mm3 | Not mentioned                                               | Aphthous stomatitis and HIV-associated oral ulcers       | None                                                      | Acute myeloid leukemia                                   |
| Mahnaz Fatahzadeh and A. Michael Krakow, 2008   | M/26               | Generalized gingival enlargement            | One month         | None                                                                                | Hemoglobin level (5 g %), leukocyte count 65,000 mm3, platelet count 25,000 mm3 and red blood cell count 1.69 million mm3 | Not mentioned                                               | Gingival enlargement induced by drugs                     | Gingival enlargement due to leukemia                      | Acute myeloid leukemia                                   |
| Acute myeloid leukemia                          |                     |                                             |                   |                                                     |                                                     |                                                              |                                                          |                                                          |                                                          |
| Y-W Fu, H-Z Xu, 2017                           | F/27               | Generalized gingival enlargement            | 3 months          | None                                                                                | Blood cell count of 9.68 9 x 10^9/L, with a hemoglobin count of 64.0 g/L and a platelet count of 17 9 10^9/L. | Not mentioned                                               | Gingival enlargement in pregnancy                         | none                                                      | Acute myeloid leukemia (monocytic lineage)               |
| Hyun-Chang Lim, Chang-Sung Kim, 2014            | F/56               | Generalized gingival enlargement            | 20 days           | Panoramic radiograph revealed generalized horizontal bone loss that was most prominent in the anterior maxillary region. | White blood count: 112,000 cells/ml, platelets 15,000 cells/ml, hemoglobin: 6.6 g/dL. | Not mentioned                                               | Manifestation of underlying systemic disease              | None                                                      | Acute myeloid leukemia (sub-type M4)                      |
| F/49                                            | Generalized gingival enlargement          | 3 weeks                                      | Panoramic radiograph and computed tomography revealed severe periodontal destruction. | White blood count: (71.52 x 10^3/μL), decreased red blood cell (2.14 ± 10^4/μL) and platelet (83 ± 10^4/μL) counts, white blood count of 38.01 x 10^3/μL and decreased red blood cell (1.66 ± 10^3/μL) and platelet (20 ± 10^4/μL) counts. | Not mentioned                                               | Complications and abscess after tooth extraction          | None                                                      | Acute myeloid leukemia (sub-type M4)                      |
| Srinivas Rao Ponnam, et al., 2014               | F/45               | Gingival enlargement in the anterior region of the upper jaw and | 1 month           | Panoramic radiograph opacification of the left maxillary sinus and presence of root stumps in relation to 21st, 22nd and 23rd teeth | Not mentioned                                               | Metastatic tumor of unknown origin                         | Small round cell tumor (after biopsy)                     | Acute myeloid leukemia                                   |                                                          |

**Table 1 (continued)**
Discussion

The diagnosis of leukemia is based initially on clinical signs and symptoms that allow for the initial diagnosis of the disease. However, the definitive diagnosis is made by different complementary tests, such as karyotyping, flow cytometry and bone marrow biopsy. Early diagnosis allows the individual to start antineoplastic treatment as soon as possible, thus increasing the chance of survival and improving the prognosis.

Before the diagnosis of leukemia, individuals can present with fatigue, fever, adenomegaly, hepatosplenomegaly, persistent or recurrent infections, hematomas, pallor, petechiae and unexpected bleeding from the skin and mucous membranes, including the oral mucosa. These symptoms and clinical signs may be similar and appear in other systemic diseases, thus hindering an early diagnosis. In the current review, the oral MOLs were the main complaint during examination, however, fatigue, lethargy or tiredness, lymphadenopathies, pallor, weight loss and loss of appetite were also reported, as well as the presence of dysphagia, facial asymmetry and trismus.

In this review, among the different types of leukemia with oral manifestations as the first clinical signs, acute leukemia was the most common, particularly acute myeloid leukemia; this finding is similar to that of previous studies. The first oral MOLs include gingival bleeding, gingival hyperplasia, ulcers and petechiae. When oral MOLs are present, it is easier for patients to identify these clinical signs because of the visibility of the mouth, compared to other body structures. All cases that were included in this review reported oral lesions as the main complaint, which was the principal reason for visiting dentists before being referred to specialists in the field of oncohematology for the final diagnosis of leukemia.

Oral MOLs can be found mainly in the gingiva, lips, hard and/or soft palate and tongue. In all case reports in this review, the clinical signs of leukemia in the mouth affected mainly the soft tissues. The gingival tissue had the highest manifestation among the types of leukemia and the mouth floor, parotid, tongue and nasolabial region had the lowest manifestations. Some cases reported spontaneous pain at the time of the complaint and this was one of the main reasons for seeking dental care.

In this review, it was identified that bone structures, such as the maxilla and/or mandible, had the principal features of areas with increased volume, rapid growth and dental mobility without apparent cause as part of the first clinical signs of leukemia. These characteristics led to the suspicion of malignant bone lesions, thus necessitating evaluation by imaging exams.

Complementary imaging examinations, such as panoramic radiography and computed tomography, are essential to evaluate bone structures in greater detail. For this reason, when radiography revealed the characteristics of malignant bone lesions, the patients were referred immediately to specialists in hematology/oncology.

Other dentists used the radiographs to guide the incisal biopsy, which was also useful for early referral to a
specialist.28,31 Dentists can perform a biopsy if the patient agrees with the procedure. Among all the case reports of this review, one patient refused biopsy. Nevertheless, because of the malignant characteristics, the patient was immediately referred to a specialist.11 Therefore, malignant characteristics in radiography, with clinical signs and symptoms that are suspected of being oral MOLs, need to be immediately referred to a specialist in hematology/oncology, regardless of whether an oral biopsy needs to be performed.

Bone alterations as oral MOLs are rare, however, when present, they can provoke facial asymmetry, which can be the main reason for seeking dental care.31 Some bone alterations were also present in children.19,31 Therefore, bone alterations can also appear in patients who are still undergoing bone development.

The literature mentioned that children and adolescents with leukemia, who are undergoing bone development and bone maturation, respectively, had bone areas with osteotropic characteristics that can promote the local invasion of malignant cells into bone structures, thus provoking their destruction.47,48

Moreover, hypercalcemia was found in adult patients with bone MOLs.11,36 One of the clinical reports in this review mentioned that hypercalcemia was associated with the ectopic production of the parathyroid hormone protein, in addition to a severe increase in alkaline phosphatase levels.42 Oral manifestations in bone structures as the first clinical signs of leukemia are considered extremely rare, however, after chemotherapy, the bone lesions can regress and the follow-up can be performed via radiography examination.11,19,20,28,31

The diagnosis of leukemia can be challenging and complex, particularly when the oral MOLs have characteristics similar to those of other systemic diseases and specific oral diseases. In this review, 11 cases of oral MOLs were initially confused with other lesions that presented clinical signs and symptoms that are identical to those of some oral diseases.14,15,35,36,19–21,25,27,28,32,33

For example, a case report included in this review mentioned pericoronitis as an initial diagnosis, which is characterized by inflammation, pain, trismus and sometimes, infection associated with the periodontitis eruption of the third molar tooth.21 The oral MOL in this case presented characteristics that initially mimicked the oral MOL. Therefore, the referral to the hematologist was delayed. Another case report in which the final diagnosis was leukemia had pregnancy gingivitis or hyperplasia as the first diagnosis.25 Some pregnant patients with relative frequency may present with changes in the gingival tissue, such as gingivitis. Therefore, considering that the patient was pregnant, the initial diagnosis coincided with the clinical condition of the patient.

Complementary tests, such as the complete blood count, were essential in establishing the initial diagnosis based on the first oral MOL. In this review, a blood count was requested for all patients and this approach allowed for the immediate

**Figure 2 – Site of first clinical signs of leukemia in oral cavity.**

![Figure 2 – Site of first clinical signs of leukemia in oral cavity.](image-url)
referral to specialists in hematology/oncology. The main alterations were leukocytosis, thrombocytopenia, anemia and the presence of blasts in the blood count, which was essential and useful, not only in diagnosing leukemia, but also in evaluating the prognosis and guiding the treatment of the patient. An early diagnosis of leukemia corresponds to a high chance of survival.

This integrative review included data from patients of different ages and therefore, we did not analyze the data by age group. This was a limitation because there is a possibility of finding specific first clinical signs of leukemia in the oral cavity of children, young people and the elderly.

Conclusions

Leukemia may present with oral manifestations as part of its first clinical signs. Acute leukemia was the type with the most oral manifestations, particularly acute myeloid leukemia. The anatomical structures most affected in the oral cavity were the gingival tissue, jugal mucosa and hard or soft palate. When oral MOLs were present in hard tissues, such as the maxilla or mandible, dental mobility was the main clinical characteristic. The main complementary test to help formulate the initial diagnosis of leukemia and referral to specialists, such as a hematologist and/or oncologist, was the complete blood count, which can identify leukocytosis, anemia, and thrombocytopenia.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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