

Review article

Oral manifestations of leukemia as part of early diagnosis



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ARTICLE INFO

Article history:

Received 20 January 2021

Accepted 6 August 2021

Available online 22 November 2021

Keywords:

Leukemia

Diagnosis

Oral

Mouth

Oral manifestations

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

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<https://doi.org/10.1016/j.htct.2021.08.006>

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determined by considering the time, whether the leukemia is acute or chronic and the cell type.^{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.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.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.^{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.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. (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%)^{9,10,11–18,19–22} and 14 females (42.42%).^{23–30} The age ranged from 6 to 74 years and only 6 individuals (18.18%) were between 1.6 and 12 years old.^{10,19,22,26,31,32}

Among the types of leukemia, oral manifestations were present principally in acute myeloid leukemia (24 individuals [72.72%]),^{9,12,14–19,22,23,24,25,30,32} followed by acute lymphoid leukemia (6 individuals [18.18%]),^{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 those in hard tissues (6 individuals [18.18%]).^{11,19,20,28,31,32} Figure 2 shows the different sites.

Soft tissues

The oral MOLs were in gingival tissue (63.63%)^{9,12,17–19,21,23–25,26,27,30,33–39,15,40} alveolar and jugal mucosa (18.18%)^{14,18,21,22,26,28} and hard or soft palate (18.18%).^{9,11,15,16,27,30} Other regions, such as the floor of the mouth (12.12%),^{13,16,23,38} tongue (9.09%),^{13,33,39} lip (3.03%),¹³ parotid glands (3.03%),¹⁰ and nasolabial region (3.03%),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,^{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,^{20,31} two cases corresponded to AML,^{19,32} one case corresponded to chronic lymphocytic leukemia²⁸ and one case corresponded to adult T-cell leukemia/lymphoma.¹¹ 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

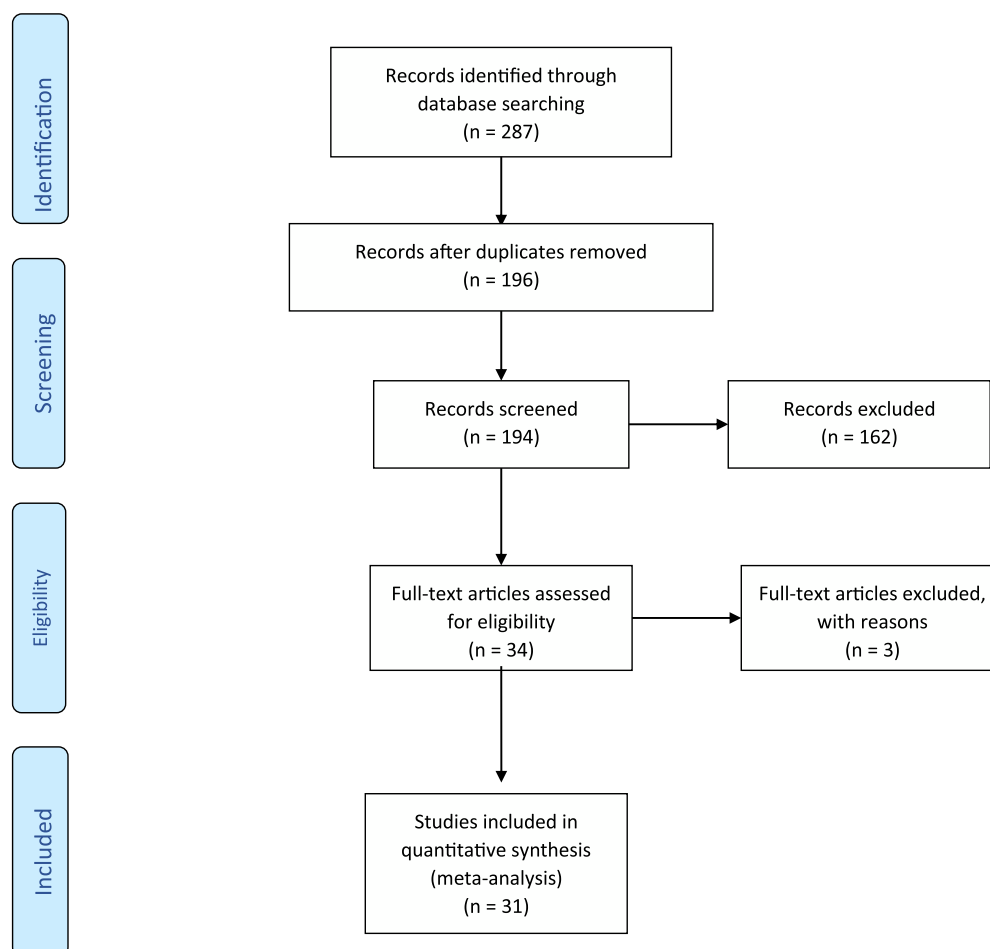


Figure 1 – Flow diagram of the studies included in the integrative review.

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,^{25,35} gingival enlargement induced by drugs,⁴¹ squamous cell carcinoma and deep fungal infection,²⁸ pericoronaritis,²¹ oral manifestation of HIV,^{15,33} postoperative complications of extraction,^{14,36} candidiasis,²⁷ necrotizing acute gingivitis,⁴⁰ dental cyst eruption³² and herpetic gingivostomatitis.³⁴ In addition, when the oral manifestation was in the maxillary bones, the presumptive diagnoses were acute osteomyelitis,²⁰ osteosarcoma^{19,20} and Ewing sarcoma.¹⁹

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%);^{9,12,15,17,18,20,23,26,30,36} lymphadenopathies in 8 individuals (36.36%);^{9,14,15,17,22,25–27}

mucosal pallor in 6 individuals (27.27%);^{12,14,15,22,26} weight loss in 4 individuals (18.18%);^{15,17,23,38} and loss of appetite in 5 individuals (18.18%).^{9,16,23,26,32} Adjacent areas, such as the head and neck regions, presented submandibular lymphadenopathy,^{9,10,15,26,34} cervical lymphadenopathy,^{17,27,34} dysphagia,^{9,16,17} facial asymmetry^{10,26,31,37} and trismus.^{10,14}

Other clinical signs and symptoms that were present, but were less frequent, included genital ulcers,¹³ vomiting,¹¹ nausea,^{11,17} diarrhea,¹¹ dizziness,¹⁷ abdominal swelling,¹² petechiae in the leg and forearm,^{12,21} musculoskeletal pain,²⁶ increased volume in the pre-sternal region²⁶ and chills and joint pain.²¹

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%);^{9,10,24,25,31–38,12,39,40,14,15,17,18,21–23} anemia was present in 23 cases (63.63%);^{9,10,25,26,31–38,12,39,40,14,15,17,20,22–24} leukocytosis was present in 19 cases (45.45%);^{9,11,31–40,13,15,17,18,22–25} and leukopenia was present in 5 cases (22.72%).^{10,12,14,19,26}

Table 1 – Principal characteristics of individuals with oral manifestations as first 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)
Madhu Singh Ratre, 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 2.68 M (Low), leukocyte count 198,800 (High), neutrophils 0.3%, platelets 30 (Low), blast cells 95%.	Erythrocyte count 3.50 - 5.50 M/ μ L, leukocyte count 4,000 - 11,000/ μ L, neutrophils 40 - 75%, platelets 150 - 450 $\times$ 10 ³ / μ L, 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 ($\times$ 10 ³ / μ L) 16.24, ($\times$ 10 ⁶ red blood cells/ μ L) 3.88, hemoglobin (g/dL) 11.2, hematocrit (%) 31.0, platelets ($\times$ 10 ³ / μ L) 16	White blood cells ($\times$ 10 ³ / μ L) 4.8 - 10.8, red blood cells (μ L) 4.6 - 6.2, hemoglobin (g/dL) 13.0 - 18.0, hematocrit (%) 40.0 - 50.0, platelets ($\times$ 10 ³ / μ L) 130 - 400	Acute sialadenitis	Acute leukemia	Acute lymphoblastic leukemia (B-lymphoid lineage)
Dalirsani 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. Occlusal radiograph: the resorption of the cortical border of the anterior mandible. Periapical radiograph: lamina dura was unclear and indistinct.	White blood cells 53,900/ μ L, red blood cell 5.3 M/ μ L, platelet count 319,000/ μ L; 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 (0.19), platelet count (23*109/L) and leukocytes (0.5*109/L)	Hemoglobin 130 – 175 g/L, hematocrit 0.4 – 0.52, platelets 150 – 400 *109/L, leukocytes 4 – 11 *109/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	Leukemia	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 $\times$ 10 ⁶ , 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	Inflammatory enlargement, conditioned enlargement, systemic enlargement and neoplastic enlargement	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) 2.8*106, 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 - 6.2*106, 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	Occlusal radiograph with no signs of abnormality.	Anemia, leukopenia and thrombocytopenia (there were not reference values),	Not mentioned	Hematopoietic malignancy	None	Chronic lymphocytic leukemia
Suárez-Cuenca JA, et al., 2009	M/24	Right lower third molar region	2 days	None	white blood cells 1.5 $\times$ 109/L, red blood cells 3.6 $\times$ 10 ¹² /L, platelets 6.3 $\times$ 10 ⁹ /L, hemoglobin 107.0 g/L, hematocrit 0.30,	Not mentioned	Coagulation disorder	Postoperative complication of tooth extraction	Acute myeloid leukemia (sub-type M3)

Table 1 (continued)

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/mm ³ , platelet 30,000/mm ³ and red blood cells 2.7 million/mm ³ .	Not mentioned	Acute leukemia	Human immunodeficiency virus (HIV)	Acute myeloid leukemia (sub-type 4)
Zacharias Vourexakis, 2015	M/30	Hard palate and the floor of the mouth	3 days	None	5 platelets/nL, 1.1 leukocytes/nL and 22% hematocrit	Not mentioned	Leukemia	None	Acute myeloid leukemia
(promyelocytic) 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: 4.4×10^6 , platelets: 274×10^3 , leukocytic: 8.3×10^3	Red blood cells: $3.8 - 4.9 \times 10^6$, platelets: $158 - 348 \times 10^3$, leukocytes: $3.3 - 8.6 \times 10^3$ (40% were abnormal)	Candidiasis	Malignant lesion	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 ($\times 10^3/\mu\text{L}$) 44.78, red blood cells ($\times 10^3/\mu\text{L}$) 1.47 4.00 - 6.00, hemoglobin (g/dL) 4.9 13.5 - 17.5, hematocrit (%) 14.5, platelet ($\times 10^3/\mu\text{L}$) 65	White blood cell ($\times 10^3/\mu\text{L}$) 4.00 - 11.00, red blood cells ($\times 10^3/\mu\text{L}$) 4.00 - 6.00, hemoglobin (g/dL) 5 - 17.5, hematocrit (%) 42 - 52, platelet ($\times 10^3/\mu\text{L}$) 150 - 450	Acute leukemia	Acute manifestaion of systemic disease	Acute monocytic leukemia (sub-type M5b)
M.Alessandrinaet,et al., 2012	F/74	The upper left vestibule next to the left upper central incisor and upper left secondary premolar	Not mentioned	Computed tomography confirmed a tissue-like mass, $3.2 \times 0.7 \times 0.3$ cm located in the left vestibule of the maxillary bone.	17,300 platelets/mL, 12,300, white blood cells/mL with 51% of lymphocytes and 4.1 million, red blood cells/mL.	Not mentioned	Squamous cell carcinoma, deep fungal infections	Leukemia	Chronic lymphocytic leukemia
A. Chatzipantelis, P. 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 21, red blood cell count 3.31, hematocrit 0.3, neutrophil count 0.1	White blood cell count 74.4 1.3 0.5 4 - 11 $\times 10(9)/\text{L}$, hemoglobin 130 - 180 g/L, platelet count 150 - 400 $\times 10(9)/\text{L}$, red blood cell count 4.50 - 6.00 $\times 10(12)/\text{L}$, 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 panorama: diffuse opacification in the right maxillary sinus cavity, non-contrast computed tomography showing osteoblastic 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	Acute myeloid leukemia (sub-type M5a)
Zhang Y, et.al., 2010	F/9	Right facial asymmetry, the maxillofacial 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 $31.6 \times 10^9/\text{L}$, 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 (biopsia)	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 $3.93 \times 10^6/\text{ml}$, but normal white blood cell count ($10.39 \times 10^3/\text{ml}$), platelet count ($261 \times 10^3/\text{ml}$)	Not mentioned	Hematologic malignancy	Acute osteomyelitis of the mandible, osteosarcoma	Acute lymphoid leukemia (Burkitt type)

Table 1 (continued)

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	M/18	Mandibular left third molar	1 week	A panoramic radiograph showed a 30° mesial tilt of the mandibular left third molar with minor ovate 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/mm ³),	Not mentioned	Pericoronitis with occlusal trauma	None	Acute lymphoblastic leukemia
Sepúlveda 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/tl [^] , neutrophil absolute count 530 (cells/ml [^]), lymphocyte absolute count 14,900 (cells/ml [^] , platelets 20,000 (cells/mP)	Hemoglobin (g/dl) hematocrit (%) white blood cells (cells/tl [^] neutrophil absolute count (cells/ml [^]) Lymphocyte absolute count (cells/ml [^] platelets (cells/mP) 0 CONFIRM DIAGNOSIS	Leukemia	Complication of hemorrhage after tooth extraction	Acute myeloid leukemia (sub-type M3)
Preeti 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 mm ³ and low platelet count 25,000 mm ³	Not mentioned	Aphthous stomatitis and HIV-associated oral ulcers	None	Acute myeloid leukemia
	M/25	Generalized gingival enlargement	One month	None	hemoglobin level (5 g %), leukocyte count 65,000 mm ³ , platelet count 25,000 mm ³ and red blood count 1.69 million mm ³	Not mentioned	Gingival enlargement induced by drugs	Gingival enlargement due to leukemia	Acute myeloid leukemia
Mahnaz Fatahzadeh and A. Michael Krakow, 2008	M/26	Anterior gingival enlargement	3 days	It was not mentioned what kind of radiograph was made. It revealed no significant changes.	White blood count: 112,000 cells/mL ³ ; platelets 15,000 cells/mL ³ ; hemoglobin: 6.6 g/dL	White blood count: normal/nl 5,000 – 10,000; platelets: 150,000 – 400,000; hemoglobin: 13.8 – 17.2 g/dl	Generalized gingivitis, acute herpetic	gingivostomatitis	Systemic disorders of hematological, immunosuppressive and infectious etiology
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 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 (71.52 × 10 ³ /μL), decreased red blood cell (2.14 × 10 ⁶ /μL) and platelet (83 × 10 ³ /μL) counts,	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 of 38.01 × 10 ³ /μL and decreased red blood cell (1.46 × 10 ⁶ /μL) and platelet (20 × 10 ³ /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 21 st , 22 nd and 25 th teeth	Not mentioned	Not mentioned	Metastatic tumor of unknown origin	Small round cell tumor (after biopsy)	Acute myeloid leukemia

Table 1 (continued)

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)
Mechery Reenesh, Singh Munishwar, Saroj Kumar Rath, 2012	M/32	generalized gingival enlargement. Echinosis in the floor of the mouth	5 months	None	Hemoglobin 5.6 gm%; red blood count 1.41 million/cu mm; platelets 25,000/cu mm; white blood cell count 112,000/cu mm	Hemoglobin 11.5 - 16.5 gm%; 3.5 - 6.0 million/cu mm; 1,50,000 - 4,50,000/cu mm; 4,000 - 11,000/cu mm	Oral manifestation of systemic disease	None	Acute myeloid leukemia (sub-type M4)
Bianca Piscinato Piedade Rosa, et al., 2018	M/47	Echinosis in the left ventral surface of the tongue and a hematoma in the gingiva around the mandibular left canine and first premolar	1 month	None	Red blood count 3.35 million/mm ³ ; platelets 22,000/mm ³ ; leukocytes 67,200/mm ³	Red blood count 4.3 to 6.1 million/mm ³ ; 150,000 to 450,000/Mm ³ ; leukocytes 3,500 to 11,000/Mm ³	Acute leukemia	None	Acute myeloid leukemia (hypogranular variant)
Paulo Sérgio da Silva Santos, et al., 2010	M/43	Generalized gingival enlargement	15 days	Panoramic radiograph had no significant findings	Hemoglobin, 10.5 g/dL; hematocrit, 30.3 percent; leukocytes, 153,000/L with 13 percent of blasts; platelets, 73,000/L; white blood cell count 165,000/mm ³ ; platelets 95,000/mm ³ ; hemoglobin 11.7 g/dl	Not mentioned	Necrotizing acute gingivitis	Opportunistic infection caused by AIDS; extramedullary leukemic infiltrate	Acute myeloid leukemia (sub-type M5)
Cristina Vázquez-Martínez, et al., 2018	F/16	Inflammatory lesion in the right mandibular body	4 days	Ultrasound of soft tissue revealed hypoechogenic mass of 13 mm in the right mandibular body, probably related to a dental germ		Not mentioned	Cyst of dental eruption	Myeloid sarcoma (biopsy)	Acute myeloid leukemia (sub-type Mab)

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.^{6,42} Early diagnosis allows the individual to start antineoplastic treatment as soon as possible, thus increasing the chance of survival and improving the prognosis.⁴³

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.^{6,43} These symptoms and clinical signs may be similar and appear in other systemic diseases, thus hindering an early diagnosis.² 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.^{5,44,45} The first oral MOLs include gingival bleeding, gingival hyperplasia, ulcers and petechiae.^{4,5,44–46} 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.⁵ 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^{9,12,26,27,30,15,17–19,21,23–25} among the types of leukemia and the mouth floor, parotid, tongue and nasolabial region^{10,13,16,23,26} 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.^{11,19,20,28,31}

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.^{19,20}

Other dentists used the radiographs to guide the incisional biopsy, which was also useful for early referral to a

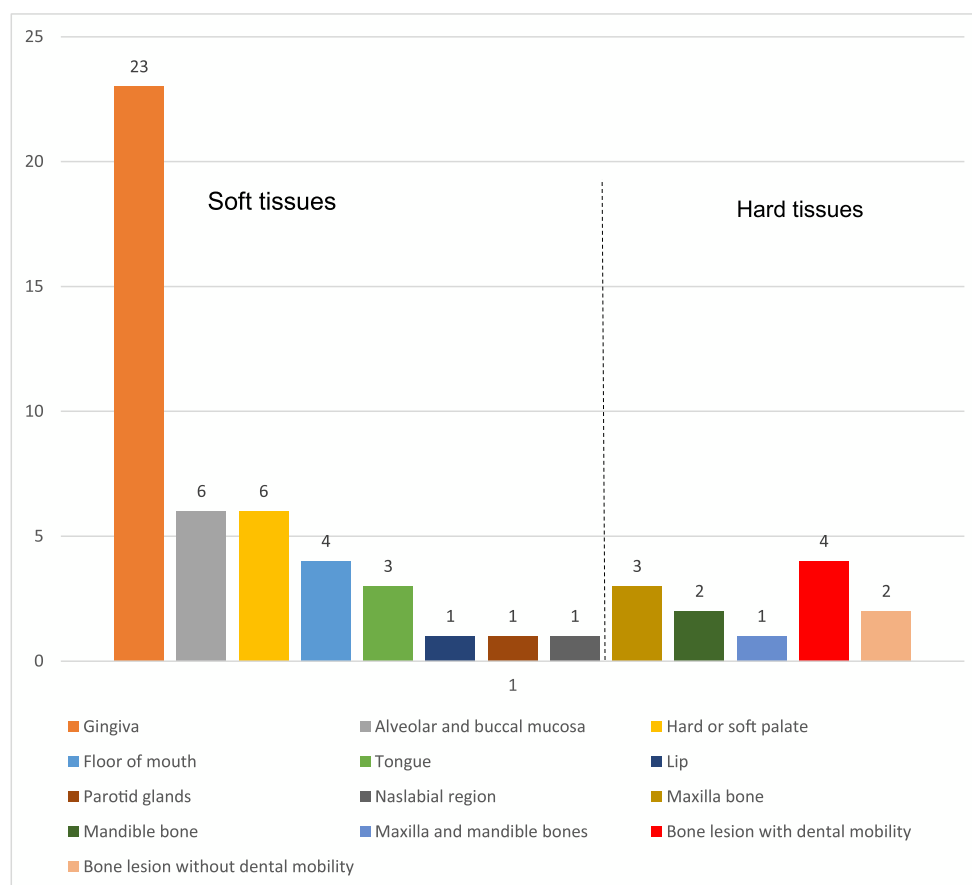


Figure 2 – Site of first clinical signs of leukemia in oral cavity.

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.¹¹ 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

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.

Funding

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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