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PRIKAZ SLUČAJA
*CASE REPORT*

Bianca Piscinato Piedade Rosa[1], Fábio Augusto Ito[1] Fausto Celso Trigo[2], Lauro Toyoshi Mizuno[1], Ademar Takahama Junior[1]

# Oralne manifestacije kao glavni znak uznapredovale akutne promijelocitne leukemije

# *Oral Manifestation as the Main Sign of an Advanced Stage Acute Promyelocytic Leukemia*

[1] Katedra za oralnu medicinu i dječju odontologiju Sveučilišta Estadual u Londrini, Rua Pernambuco 540, Londrina-PR. Brasil
*Department of Oral Medicine University Estadual de Londrina. Rua Pernambuco 540, Londrina-PR. Brasil*
[2] Katedra za kliničku medicinu Sveučilišta u Londrini, Av. Robert Koch 60, Londrina PR. Brasil
*Departamento de Clínica Médica – Universidade Estadual de Londrina. Av. Robert Koch 60, Londrian-PR. Brasil*

**Sažetak**
Akutna mijeloična leukemija agresivna je maligna neoplazma koja se uglavnom pojavljuje kod starijih osoba u dobi od 65 godina. Oralne manifestacije i najčešće spontano krvarenje uobičajeni su nalazi u slučaju te bolest i mogu upućivati na početnu fazu. U ovom izvještaju opisan je slučaj 47-godišnjeg muškarca s jednomjesečnim spontanim oralnim krvarenjem. Pacijent je već prije zatražio mišljenje dvaju profesionalaca, ali bez ikakva rezultata. Fizikalni pregled pokazao je bljedoću, vrućicu, krvarenje iz nosa (*epistaxis*) i ekhimoze u oralnoj sluznici. Kompletna krvna slika upućivala je na anemiju, tešku trombocitopeniju i leukocitozu sa skretanjem KS-a ulijevo, pojačavajući tako dijagnozu hipoteze akutne leukemije. Pacijent je odmah prevezen u bolnicu i unatoč tomu što mu je pružena hitna pomoć, umro je tri dana poslije zbog difuznoga plućnog alveolarnog krvarenja. Na uzorku periferne krvi bila je obavljena imunofenotipizacija i dobivena je dijagnoza hipogranularne inačice akutne promijeloične leukemije. Kašnjenje u postavljanju dijagnoze moglo je utjecati na nepovoljan ishod. Rana dijagnoza i liječenje prijeko su potrebni za preživljavanje pacijenata s leukemijom pa su i doktori dentalne medicine odgovorni za rano otkrivanje oralnih manifestacija leukemije i za brzo upućivanje pacijenta odgovarajućem stručnjaku.

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**Adresa za dopisivanje**
Ademar Takahama Junior
University Estadual de Londrina
Department of Oral Medicine
Rua Pernambuco 540, Londrina-PR.
Brasil

**Ključne riječi**
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## Uvod

Leukemije su skupina neoplastičnih bolesti koje obilježava proliferacija nezrelih bijelih stanica u koštanoj srži i/ili krvi, što često rezultira impresivnom leukocitozom (1 – 3). Klasificirane su ovisno o progenitorskoj stanici (limfoidna ili mijeloična loza ) i slijedi li bolest akutni ili kronični tijek (4). To je najčešća neoplastična bolest bijelih krvnih stanica s incidencijom od 9 slučajeva na 100.000 ljudi (5). Točna etiologija leukemije je nepoznata, no njezin razvoj povezan je s nekoliko rizičnih čimbenika kao što su genski poremećaji, izloženost zračenju, kemoterapija te fizička i kemijska izloženost (6).

Kliničke manifestacije leukemije mogu biti posljedica supresije hematopoetskih staničnih linija, izravne infiltracije leukemijskih stanica u tkiva ili gubitka normalne funkcije leukocita (4). Zato su glavni znakovi i simptomi najčešće krvarenje, purpura, umor, anemija, limfadenopatija i infekcije (2, 4). Oralne manifestacije često se pojavljuju i mogu upozoravati na početak bolesti (5). To su petehijalna krvarenja jezika, usnica, stražnjeg tvrdog i mekog nepca, gingivne hiperplazije, spontana krvarenja gingive, oralne ulceracije i bljedoća sluznica (1, 5).

## Introduction

Leukemias represent a group of neoplastic diseases characterized by proliferation of immature white cells in the bone marrow and/or blood, often resulting in an impressive leukocytosis (1-3). The leukemias are classified according to the progenitor cell involved (lymphoid or myeloid lineage) and whether the disease follows an acute or chronic course (4). It is the most common neoplastic disease of the white blood cells with an incidence of 9 cases per 100,000 people (5). The exact etiology of leukemia is unknown and your development has been associated with several risk factors, such as genetic disorders, radiation exposure, chemotherapy, and physical and chemical exposures (6).

Clinical manifestations of leukemia may result from suppression of hematopoietic cell lines, direct infiltration of leukemic cells into tissues or loss of normal leukocyte function (4). Therefore, the main signs and symptoms may include bleeding, purpura, fatigue, anemia, lymphadenopathy and infection (2,4). Oral manifestations occur frequently in leukemic patients and may present as initial evidence of the disease (5). They include petechial hemorrhages of the tongue, lips, posterior hard and soft palate, gingival hyperplasia, spontaneous gingival bleeding, oral ulcerations and mucosal pallor (1,5).

S obzirom na važnu zadaću koju doktori dentalne medicine imaju u ranom otkrivanju oralnih manifestacija složenih sustavnih bolesti, ističemo da to izvješće opisuje slučaj napredne akutne mijeloične leukemije koja je dijagnosticirana na temelju oralnih manifestacija.

## Prikaz slučaja

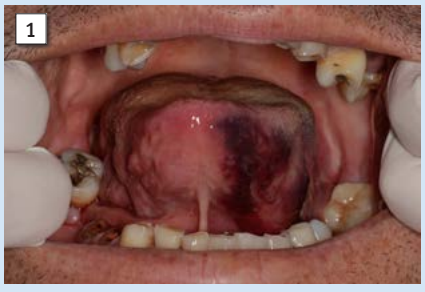
Muškarac od 47-godina došao je u našu kliniku žaleći se na tegobe u ustima, a prema njegovim riječima, uzrokovala ih je mandibularna djelomična proteza. Također je istaknuo jednomjesečno spontano oralno krvarenje i umor. Zbog tih znakova i simptoma otišao je liječniku koji ga je pregledao i uputio doktoru dentalne medicine koji ga je pregledao i odmah uputio k nama. Između prvoga medicinskog pregleda i naše procjene prošlo je oko 30 dana, što znači da se kasnilo u postavljanju dijagnoze. Fizikalni pregled pokazao je da je pacijent slab, blijed, febrilan, s ekhimozama na lijevoj ventralnoj površini jezika (slika 1.) te s hematomom u gingivi oko mandibularnog lijevog očnjaka i prvog pretkutnjaka (slika 2.).

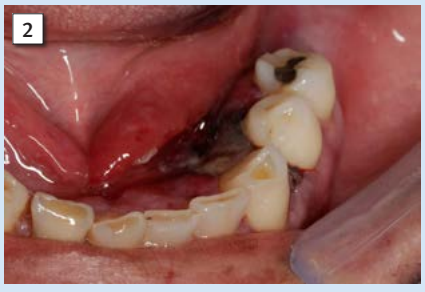
Uz to, tijekom pregleda pacijent je počeo spontano krvariti i iz gingive i pojavila se epistaksija (slike 3. i 4.) koja su zaustavljena lokalnim kompresijom s pomoću gaze. Prema tim nalazima postavljena je radna dijagnoza akutne leukemije i hitno je zatražena kompletna krvna slika. Nalaz je pokazao anemiju, tešku trombocitopeniju i leukocitozu s dominantnim nezrelim oblicima (75 %), potvrđujući hipotezu da je riječ o leukemiji (tablica 1.). Pacijent je istog dana prevezen na Odjel za hematologiju Sveučilišne bolnice Državnoga sveučilišta u Londrinu, gdje mu se pojavilo frontalno subarahnoidno krvarenje. Premda je intervencija bila brza, umro je tri dana poslije hospitalizacije zbog difuznoga plućnog alveolarnog krvarenja. Istaknimo da je aspirat koštane srži iz prsne kosti otkrio hipercelularnu mijeloblastnu infiltraciju koštane srži, a imunofenotipizacija periferne krvi potvrdila je dijagnozu hipogranularne inačice akutne promijelocitne leukemije.

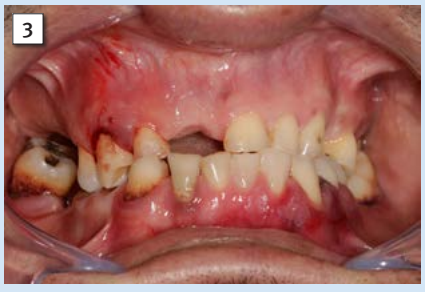
In view of the important role that dentists play in the early detection of oral manifestations of complex systemic diseases, this report describes a case of an advanced acute myeloid leukemia that was diagnosed through oral manifestations.

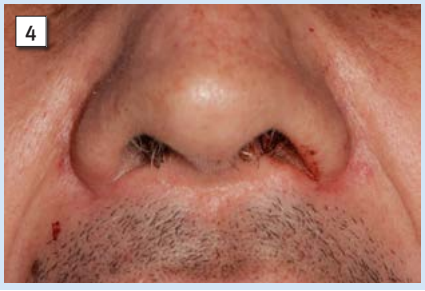
## Case report

A 47-year-old man was referred to our clinic complaining of pain in the mouth. According to the patient, it was caused by the mandibular removable partial denture. He also reported a one-month history of spontaneous oral bleeding and fatigue. According to these signs and symptoms, the patient looked for a physician, who examined and referred him to a dentist. The dentist examined the patient and promptly referred him to our service. The time between the first medical appointment and our evaluation was about 30 days, leading to a delay in the diagnosis. Physical examination revealed that the patient was weak, pale, febrile and presenting ecchymoses in the left ventral surface of his tongue (Figure 1) and a hematoma in the gingiva around the mandibular left canine and first premolar (Figure 2). Besides, during the examination, the patient developed a spontaneous gingival bleeding and epistaxis (Figures 3 and 4), that were controlled by local pressure using a gauze. According to these findings, morphologic features were inconclusive and diagnosis of an acute leukemia was established and an urgent complete blood count was indicated. The result revealed anemia, severe thrombocytopenia and leukocytosis with blasts predominance (75%), reinforcing the diagnosis hypothesis of an acute leukemia (Table 1). On the same day, the patient was referred to the Hematology Department of the University Hospital of the State University of Londrina where he developed a frontal subarachnoid hemorrhage. Despite having received a quick intervention, the patient died 3 days after his admission to the Hospital due to a diffuse pulmonary alveolar hemorrhage. A bone marrow aspirate from the sternum revealed a hypercellular bone marrow infiltration of myeloblasts, and the peripheral blood immunophenotyping confirmed the diagnosis of hypogranular variant of acute promyelocytic leukemia.




**Slika 1.** Difuzna ekhimoza na lijevoj ventralnoj površini jezika
**Figure 1** Diffuse ecchymoses in the left ventral surface of the tongue.
**Slika 2.** Hematom unutar gingive oko mandibularnpg lijevog očnjaka i prvog pretkutnjaka
**Figure 2** The presence of a hematoma in the gingiva around the mandibular left canine and first premolar.
**Slika 3.** Spontano krvarenje iz gingive iznad gornjeg desnog očnjaka
**Figure 3** Spontaneous gingival bleeding in the right superior canine.
**Slika 4.** Epistaksija koja se pojavila tijekom fizikalnog pregleda
**Figure 4** Epistaxis developed during the physical examination.

**Tablica 1.** Kompletna krvna slika – nalaz je otkrio anemiju, leukocitozu i tešku trombocitopeniju; otkriveno je i previše nezrelih oblika (75 %) te anizocitoza
**Table 1** A complete blood count. The result revealed anemia, leukocytosis and severe thrombocytopenia. The exam also revealed blasts predominance (75%) and anisocytosis.

| Parametri • Parameter | Vrijednosti pacijenta • Patient value | Raspon normalnih vrijednosti • Normal value range |
|---|---|---|
| Eritrociti • Erythrocytes | 3.35 Million/mm³ | 4.3 A 6,1 million/mm³ |
| Hemoglobin • Hemoglobin | 10.40 G/dl | 12.8 A 17,8 g/dl |
| Hematokrit • Hematocrit | 30.10% | 38.8 A 54,0% |
| M.C.V | 89.9 Fl | 77.0 A 100,0 fl |
| M.C.H. | 31.0 Pg | 26.0 A 34,0 pg |
| M.C.H.C. | 34.6 G/dl | 29.0 A 36,0 g/dl |
| Rdw | 18.5 % | 9.0 A 15,0% |
| Leukociti • Leukocytes | 67.200/Mm³ | 3.500 A 11.000/Mm³ |
| Neutrofili • Neutrophils | 4.032/Mm³ | 1.500 A 8.500/Mm³ |
| Limfociti • Lymphocytes | 9.408/Mm³ | 900 A 3.900/Mm³ |
| Monociti • Monocytes | 3.360/Mm³ | 100 A 1.100/Mm³ |
| Eozinofili • Eosinophils | 0/Mm³ | 100 A 700/mm³ |
| Bazofili • Basophils | 0/Mm³ | 0 A 200/mm³ |
| Trombociti • Platelets | 22.000/Mm³ | 150.000 A 450.000/Mm³ |
| M.P.V. | 9.70 Fl | 8.3 A 11.3 Fl |

## Rasprava

Oralne manifestacije često su povezane s teškom sustavnom bolešću, tako da je njihovo prepoznavanje ključno za brzu dijagnozu i liječenje (1, 2). Te manifestacije mogu se pojaviti u bilo kojoj vrsti leukemije, ali su češće u akutnoj (prema kroničnoj) i mijeloidnoj (prema limfoidnoj) leukemiji (4). Akutna mijeloična leukemija (AML) agresivna je bolest uglavnom starijih osoba – prosječno u dobi iznad 65 godina – i nešto češća kod muškaraca (1, 7). Akutna promijeloična leukemija poseban je podtip akutne mijeloične leukemije s karakterističnim kliničkim i molekularnim obilježjima, a čini od 5 do 8 % svih slučajeva AML-a (8). Hipogranularna varijanta obuhvaća od 10 do 25 % odraslih s APL-om i ima jedinstvena biološka svojstva kao što su veći broj bijelih krvnih stanica na početku bolesti (9).

Opće manifestacije leukemije mogu uključivati groznicu, umor, anemiju, limfadenopatiju, rekurentnu infekciju, bolove u kostima i abdomenu, krvarenje i purpuru (10). Glavne oralne manifestacije pacijenata s leukemijom opisane u literaturi su spontano krvarenje i petehijalna krvarenja gingive, nepca, jezika ili usana kao rezultat trombocitopenije. Tu se još bljedoća sluznica zbog anemije i gingivalna hiperplazija uzrokovana leukemijskim infiltriratom, a oralne ulceracije mogu biti rezultat neutropenije ili neposredne infiltracije malignih stanica (1, 4, 5).

Najčešće oralne manifestacije kod bolesnika s AML-om povezane su s krvarenjem i pojavljuju se kao gingivalna krvarenja, petehije, hematomi ili ekhimoze (10, 11). Krvarenje gingive najčešći je početni oralni znak u slučaju akutne i kronične leukemije (12). Niska razina trombocita – općenito od 25 000 mm-3 do 60 000 mm-3 – dovoljna je da rezultira spontanim krvarenjem. Uz to, prevalencija trombocitopenije bila je viša kod bolesnika s akutnom leukemijom od onih s kroničnom (10). Oralne manifestacije pri prvom pojavljivanju leukemije češće su u slučaju AML-a negoli u ostalim

## Discussion

Oral manifestations are often associated with a variety of serious systemic diseases, hence recognizing them is crucial for a prompt diagnosis and management (1, 2). These manifestations may occur in any type of leukemia, but they are more prevalent in acute (vs chronic) and myeloid (vs lymphoid) leukemias (4). Acute myeloid leukemia (AML) is an aggressive disease that mainly occurs in elderly people, with a median age of over 65 years at diagnosis and with a slight male predominance (1, 7). Acute promyelocytic leukemia is a distinct subtype of acute myeloid leukemia with characteristic clinical and molecular features, and accounts for 5-8% of all cases of AML (8). The hypogranular variant accounts for approximately 10-25% of adult APL cases and has unique biological characteristics such as a higher white blood cell count at presentation (9).

General manifestation of leukemia may include fever, fatigue, anemia, lymphadenopathy, recurrent infection, bone and abdominal pain, bleeding and purpura (10). Oral manifestations of patients with leukemia reported in the literature are spontaneous bleeding and petechial hemorrhages of gingivae, palate, tongue or lip as a result of thrombocytopenia; mucosal pallor due to anemia; gingival hyperplasia caused by leukemic infiltration. Oral ulcerations may result from either neutropenia or direct infiltration by malignant cells (1, 4, 5). The most common oral manifestations reported in patients with AML were associated with bleeding and were manifested as gingival oozing, petechiae, hematomas, or ecchymoses (10, 11). Gingival bleeding is reported to be the most common initial oral sign in both acute and chronic leukemia (12). Low-levels of platelet counts, generally from 25 000 $mm^{-3}$ to 60 000 $mm^{-3}$ are sufficient to result in spontaneous bleeding. Besides, the prevalence of thrombocytopenia was higher in patients with acute leukemia than those with chronic leukemia (10). The presence of oral manifestation at

podtipovima (10).

Pacijenti s leukemijom mogu patiti i od rekurentne virusne, bakterijske i gljivične infekcije, poput herpesa ili kandidijaze, što je posljedica imunosupresije (4, 5). Zato oboljeli od AML-a često imaju simptome i znakove pancitopenije kao što su povišena temperatura, umor, bljedoća, krvarenje i purpura te bolovi u trbuhu i kostima (1). Oralne manifestacije pancitopenije ne mogu se zbog leukemije razlikovati od ostalih njezinih uzroka, poput nuspojava lijekova, imunosnih stanja i virusnih infekcija (13). Nedavno je također opisana neobična miješana maksilarna osteoblastna i osteolitička lezija kao početna manifestacija AML-a (12). U svakodnevnoj stomatološkoj praksi rijetki su pacijenti s leukemijom kojima su oralni simptomi rani pokazatelji leukemije. Zato katkad doktori dentalne medicine mogu propustiti dragocjeno vrijeme za odgovarajuće liječenje i upućivanje hematologu, što može biti kobno (14). Naš pacijent imao je gotovo sve klasične znakove i simptome maligne akutne hematološke bolesti kao što su vrućica, umor, bljedilo, krvarenje u usnoj šupljini i epistaksija. Unatoč tomu, kašnjenje u postavljanju dijagnoze moglo je utjecati na nepovoljan ishod.

Prognoza bolesnika s AML-om je varijabilna, no starija dob, slab citogenetski rizik i status uspješnosti najčešće se koriste za predviđanje kliničkih ishoda (15). Mlađi bolesnici imaju bolju prognozu, a neki izvještaji sugeriraju da se čak oko 50 % mlađih od 40 godina izliječi, a kod osoba starijih od 60 godina samo njih 10 do 15 % živjet će još godinu dana (16). Velik broj leukocita u perifernoj krvi povezan je s lošijom prognozom bolesnika mlađih od 60 godina (15). Rano postavljanje dijagnoze prijeko je potrebno za preživljavanje. Na taj način su i doktori dentalne medicine odgovorni za rano otkrivanje oralnih manifestacija leukemije i brzo upućivanje hematologu (17). Kompletna krvna slika (KKS) može im pomoći u slučajevima koji upućuju na leukemiju, ali je za konačnu dijagnozu potrebna biopsija koštane srži i imunofenotipizacija periferne krvi.

Za postavljanje dijagnoze zloćudnih bolesti u zemljama u razvoju treba dosta vremena. Zato se dijagnoza raka može obično postavljati u kasnijim stadijima bolesti (18). Glavni uzroci za to kašnjenje mogu biti kliničke značajke bolesti, dob pacijenata, lokacija tumora, razina sumnje kod liječnika primarne zdravstvene zaštite te sustav zdravstvene zaštite dostupan lokalnom stanovništvu (19). Glavni uzroci rane smrti bolesnika s akutnom leukemijom uključuju infekciju, sindrom lize tumora, leukostasis i diseminiranu intravaskularnu koagulaciju (20). Rana dijagnoza i učinkovita terapija vrlo su važni u izbjegavanju tih komplikacija (21).

Akutna promijelocitna leukemija agresivna je maligna neoplazma koja zahtijeva ranu dijagnozu i liječenje. Oralne manifestacije, uglavnom spontano krvarenje, vrlo su česte kod bolesnika s akutnom leukemijom i mogu biti početni znak bolesti, pojačavajući tako važnost doktora dentalne medicine u ranoj dijagnozi te bolesti.

initial presentation of leukemia is more common in AML than in other subtypes (10).

Patients with leukemia may also develop recurrent viral, bacterial and fungal infections, like herpes or candidiasis, as a consequence of immunosuppression (4, 5). Therefore, AML patients frequently present with symptoms and signs of pancytopenia, such as fever, fatigue, pallor, bleeding and purpura, bone and abdominal pain (1). Oral manifestations of pancytopenia due to leukemia are indistinguishable from other causes of pancytopenia, such as adverse drug reactions, immune conditions, and viral infections (13). Recently, a rare case of unusual maxillary mixed, osteoblastic and osteolytic, lesions as an initial manifestation of AML has also been presented (12). In routine dental practice, it may be rare to find leukemic patients who have oral symptoms as an early indicator of leukemia. Therefore, dentists may miss the correct timing for referral to a hematologist, which can be fatal (14). Our patient developed almost all classical signs and symptoms of a malignant acute hematological disease, such as fever, fatigue, pallor, oral bleeding and epistaxis. Nevertheless, the delay in the diagnosis may have influenced the unfavorable outcome.

The prognosis of patients with AML is variable, and older age, poor risk cytogenetics, and performance status are most commonly used to predict clinical outcomes (15). Younger patients tend to cope with it in a better way, and some series would suggest that about 50% of patients less than 40 years of age are cured, whereas in those who are over 60 years old, only 10–15% of patients will survive 1 year after the diagnosis (16). A high peripheral blood leucocyte count at diagnosis is associated with worse prognosis in patients younger than 60 years (15). Effective early diagnosis is indispensable for survival. Therefore, dentists are responsible for early detection of oral manifestations of leukemia and for a fast referral to a hematologist (17). A complete blood count (CBC) can be helpful for dentists in cases suggestive of leukemia, but a bone marrow biopsy and immunophenotyping of peripheral blood are necessary for a final diagnosis.

The time for diagnosis of malignancies has been historically long in developing countries. Therefore, the diagnosis of cancer may occur in advanced stages of the disease (18). Main causes for delays in diagnosis may include clinical features of the disease, patient age, tumor site, level of suspicion by a primary care physician and health care system available to the local population (19). The main causes of early death in patients with acute leukemia include infection, tumor lysis syndrome, leukostasis, and disseminated intravascular coagulation (20). Early diagnosis and effective management are very important to minimize these complications (21).

The acute promyelocytic leukemia is an aggressive malignant neoplasm that requires an early diagnosis and management. Oral manifestations, mainly the spontaneous bleeding, are very common in patients with acute leukemia and may present as the initial evidence of the disease, reinforcing the importance of dentists in the early diagnosis of this disease.

**Abstract**
Acute myeloid leukemia is an aggressive malignant neoplasm occurring mainly in elderly, with the median age of 65 years. Oral manifestations, mainly spontaneous bleeding, are a common finding in acute myelocytic leukemia and may represent the initial evidence of the disease. This report describes a case of a 47-year-old man with a one-month history of spontaneous oral bleeding. The patient had already been consulted by two professionals but he remained undiagnosed. The physical examination revealed paleness, fever, epistaxis and ecchymoses in the oral mucosa. The complete blood count revealed anemia, severe thrombocytopenia and leukocytosis with blasts predominance, reinforcing the diagnosis hypothesis of an acute leukemia. The patient was immediately referred to the Hospital and despite having received a quick intervention, he died 3 days after the admission due to diffuse pulmonary alveolar hemorrhage. According to the peripheral blood immunophenotyping the diagnosis of hypogranular variant of acute promyelocytic leukemia was established. The delay in the diagnosis may have influenced the unfavorable outcome. Early diagnosis and management are indispensable for survival of leukemia patients. In this way, dentists may be responsible for an early detection of oral manifestations of leukemia and for a fast referral to an adequate professional.

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**Address for correspondence**
Ademar Takahama Junior
Universidade Estadual de Londrina
Departamento de Medicina Oral e Odontologia Infantil
Rua Pernambuco 540, Londrina-PR. Brasil

**Key words**
Leukemia, Promyelocytic, Acute; Oral Manifestations; Oral Hemorrhage; Delayed Diagnosis

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