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Oral Manifestations of Acute Lymphocytic Leukemia

By Angela M. Yepes DDS, MS, MBA, Juan F. Yepes DDS, MD, MPH, MS, DrPH, and James E. Jones, DMD, MSD, EdD, PhD

Abstract

Leukemia is the most prevalent malignancy of leukocytes and can occur in children and adults. Oral manifestations are part of the complexity of signs and symptoms in patients with leukemia, and in some patients, oral manifestations precede systemic manifestations. Oral signs of leukemia include spontaneous bleeding, gingival enlargement, and paleness of the oral mucosa. Head and neck lymphadenopathy is common in patients with leukemia. Oral manifestations result from the direct invasion of immature cells in oral tissues or are indirectly caused by the replacement of the normal blood cells for immature cells, causing anemia, leukopenia, and thrombocytopenia. The dentist and allied oral health care providers must be aware of the oral signs and symptoms that may suggest leukemia, facilitating early diagnosis and indicating the patient's medical treatment.

This case report presents a 10-year-old female with acute lymphocytic leukemia (ALL), with oral lesions appearing in the maxillary gingiva. This presentation emphasizes the importance of the intra- and extra-oral exam and the assessment of the etiology for manifestations present in the head and neck regions.

Keywords: Leukemia, oral manifestations, acute lymphocytic leukemia.

Leukemia is the most prevalent cancer in children and can also occur in adults.¹ Leukemia is a malignancy that disseminates a proliferation of immature cells of the bone marrow. These cells replace the normal bone marrow cells and accumulate in different sites of the body.² Although there are several different classifications of leukemia, typically it is classified according to the presentation into acute or chronic, and the type of blood cell affected (lymphoid, myeloid).³ The National Cancer Institute estimates new cases of leukemia in the United States in 2022 at 60,650, representing 3.2% of all new cancer cases diagnosed in the same year in the United States. The rate of new cases per 100,000 people has remained constant between 12% to 14% since 1975, except for a mild increase between 2010 to 2015 at 15%. The five-year survival percentage has been increasing from 1975 (around 30%) to 2016 (approximately 70%). The significant improvement in the survival is the consequence of early diagnosis and improvements in supportive care.⁴

The etiology of leukemia is not well understood. However, genetic susceptibility, together with environmental factors (exposure to ionizing radiation, smoking, pesticides, and alcohol consumption), may lead to the development of leukemia.⁵ The four subtypes of leukemia that primary care providers, including the dentist, will see in practice are acute myelogenous (AML), acute lymphocytic (ALL), chronic myelogenous (CML), and chronic lymphocytic leukemia (CLL).

The clinical presentation of leukemia is not always the same and is related to the subtype. The most common subtype in children is acute lymphocytic leukemia (ALL), which accounts for 3 out of 4 leukemias among children. The most common leukemia in adults is CLL, while AML is the most common acute adult leukemia. Clinical signs associated with ALL presentation include fever, lethargy, and spontaneous bleeding (often from the gingiva).⁶ About 33% of the children affected by ALL have musculo-

skeletal symptoms, and close to 65% present with lymphadenopathy.⁷

In adults, the majority (close to 80%) of patients are diagnosed with the subtype acute myelogenous leukemia (AML). Fever, weight loss, and fatigue are common symptoms reported by patients with AML. Adults are less likely to present with musculoskeletal symptoms as well as lymphadenopathy. Painful and persistent mouth ulcers and unexplained weight loss have been reported as initial signs/symptoms of chronic subtypes of leukemia.⁸ The chronic forms of leukemia occur almost exclusively in adults.

Sixty percent of patients diagnosed with leukemia have oral manifestations that are the initial reason for consulting a primary health care provider.⁹ The oral signs of leukemia have been classified into primary, secondary, and tertiary lesions.¹⁰ The term “primary” manifestation — for example, gingival enlargement — is associated with the infiltration of the leukemic cells into the gingiva.¹¹ The term “secondary” manifestation is used when the oral manifestation relates to anemia or leukopenia, for example, candidiasis. Finally, “tertiary” manifestations are associated with the immunosuppression associated with the treatment.¹

Case report

A 10-year-old female was referred to the Riley Hospital for Children emergency department (ED) in Indianapolis, Indiana. The mother told the ED physician that her daughter had not been feeling well for about one week and thought she had a “viral” infection. The patient had a mild fever and was not eating or sleeping well. Approxi-

mately three days before arriving at the hospital, her mother noted several lesions on her gums and took her to their family dentist for evaluation. The dentist sent her to the hospital for immediate assessment. The past medical history was unremarkable. No history of trauma was reported, and the child was not taking any medication.

The patient’s temperature was 39.5°C, with a heart rate of 134 beats per minute. Extraoral examination revealed painless bilateral lymphadenopathy below the mandibular angle. Intraoral examination observed no salivary gland swelling and revealed buccal mucosa pallor with well-demarcated, painless, soft, bilateral maxillary gingival overgrowth. Significant bleeding of the gingival tissues was observed upon palpation. The exam noted mobility of the mandibular primary molars (Figures 1 and 2).

The Pediatric Dentistry Service evaluated the patient and requested a panoramic film and bitewings (Figures 3 and 4, see Page XX). Both radiographic exams showed no specific signs of dental infection or decay contributing to the patient’s condition, and although the mandibular primary molars had minimal mobility, radiographic evaluation of the periodontal ligament space did not show enlargement for these or other teeth.

A differential diagnosis included leukemia, aplastic anemia, acute anemia, or autoimmune thrombocytopenic purpura. The emergency department physician ordered a complete blood count (CBC) with differential, blood chemistry and coagulation tests, and c-reactive protein. Following consultation with pediatric hematology-oncology, the patient was admitted to the Riley Hos-

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Figure 1 — Localized gingival hyperplasia with ecchymoses and active bleeding (upper right quadrant).



Figure 2 — Localized gingival hyperplasia with ecchymoses and active bleeding (upper left quadrant).



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pital for Children Department of Pediatric Hematology. The patient's CBC revealed severe anemia (low hemoglobin, 11.2 grams/dl; normal values 13.2 to 16.6 grams/dl), thrombocytopenia (low platelet count, 45,000 platelets/mcL; normal values 150,000-300,000 mcL), and leukopenia (low white blood

cell count, 600 per microliter; normal value 5,000 to 10,000 per microliter). The peripheral-blood smear demonstrated the presence of lymphoblasts, and a subsequent bone marrow biopsy confirmed the diagnosis of ALL.

The pediatric hemato-oncologists immediately initiated treatment, divided into three main phases: induction, consolidation, and maintenance. Initially, the patient went into a rapid phase of induction chemotherapy to achieve remission. The patient re-

ceived three medications: L-asparaginase, vincristine, and dexamethasone, each given during the first month. It is highly recommended that patients receive a comprehensive oral exam before starting chemotherapy. The dental team's involvement in patient management should include prophylaxis against oral infections and early treatment of potential oral sources in these neutropenic patients to avoid sepsis.

The patient developed mild mucositis during the induction phase. The multidisciplinary oncology team, which included dentists, addressed the mucositis with a compound mix of nystatin, hydrocortisone, and diphenhydramine (30 ml every 4-6 hours; see Table 1).

The patient then went into the consolidation phase for five months (with methotrexate and vincristine) and maintenance (with daily 6-mercaptopurine) sessions. During this phase, the patient is immune-suppressed. To avoid sepsis, dental members of the patient's care team must provide prophylaxis against oral infections. Early treatment of potential oral sources in these neutropenic patients is essential.

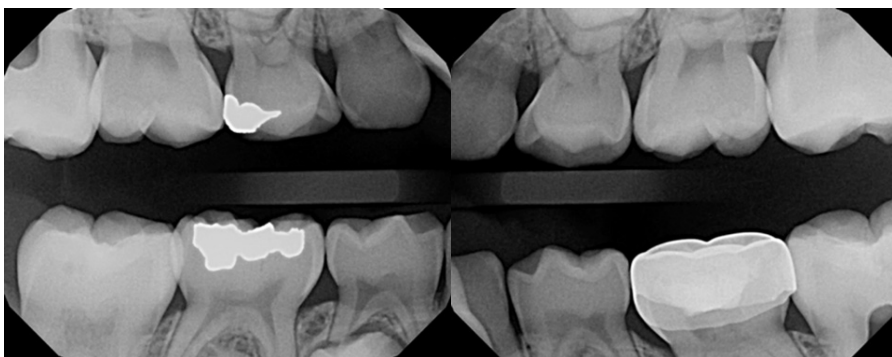
Discussion

The extra-oral and intra-oral examinations are part of the routine dental exam, where dentists must be alert to the early signs of leukemia. Head and neck signs and symptoms are present in approximately two-thirds of patients with leukemia.¹² Lymphadenopathy (enlargement of lymph nodes) is a frequent single finding suggestive of leukemia.¹² Lymphadenopathy of the cervical and submandibular regions is the most common finding in all types of leukemia.² The value of including lymph node examination cannot be overstated. In some patients, the oral signs and symptoms precede the systemic conditions. Mouth ulcers, gingival abnormalities, petechiae, and spontaneous bleeding are also initial oral signs of leukemia observed upon

Figure 3 — Panoramic and bitewing radiographs reveal no indications of dental infection or decay contributing to the patient's condition. These images are a useful baseline for assessing oral conditions during cancer therapy.



Figure 4 — Bitewing radiographs.



exam. Tooth mobility and dental radiographs showing enlargement of the periodontal ligament space may suggest an infiltration of leukemic cells.

Some initial symptoms are not specific, and include malaise, fever, pallor, or weight loss. A frequent oral sign is gingival bleeding and gingival hyperplasia. Early symptoms of leukemia are usually associated with anemia (low red blood cell count), neutropenia (low white blood cell count), or thrombocytopenia (low platelet count). While the absolute white blood cell count may be high in leukemia, the effective infection-fighting cells (normal neutrophils and even normal lymphocytes) are often low, leaving patients at risk for infection, particularly from oral bacteria, due to neutropenia. This is further complicated by chemotherapy. Dental professionals should not assume that a normal or high white blood cell count is “safe.” The cells may be blasts, leaving the normal differential strikingly abnormal.

Immature cells may also infiltrate anatomical sites, including the lymph nodes, bones, and gingiva.¹³ Gingival infiltration by leukemic cells may be a sign of ALL and other subtypes of leukemias.¹¹ Oral ulcerations are frequently related to direct infiltration by blast cells or neutropenia (low neutrophil count).¹⁴ Opportunistic infections can also be the first sign that may indicate a disturbance in the immune system. Oral candidiasis in a patient without a past medical history of immunodeficiency warrants deeper investigation. Gingival hyperplasia or enlargement is a common sign associated with leukemia.¹⁵ Rapid onset of gingival hyperplasia is more often associated with leukemia than with other etiologies of gingival hyperplasia, which include medications (nifedipine, phenytoin, cyclosporine, etc.), poor oral hygiene, idiopathic gingival fibromatosis, and associations with syndromes (Zimmermann-Laband) or malignancy (leukemia).¹⁶ Tooth mo-

Table 1 — Oral Rinse to Manage Mucositis

Diphenhydramine 0.075%
Hydrocortisone 0.125%
Nystatin 100,000 U/ml (units/milliliter)
Mix and dispense:
30 milliliters (ml) of nystatin suspension at 100,000 U/ml, or 3 million units of nystatin powder with 60 milligrams hydrocortisone and diphenhydramine HCL syrup to bring the total volume up to 240 ml.

bility in the primary or permanent dentition, without an apparent origin, can also be correlated with leukemia. An increase in the periodontal ligament space (PDL) is likely the etiology of tooth mobility observed with leukemic patients, where infiltration of the PDL by blast cells is a confirmed cause of this enlargement.¹⁷

Lymph node enlargement, ulcerations, spontaneous bleeding, and gingival hyperplasia are common in all four leukemia subtypes. Signs and symptoms may differ according to the leukemia subtype. In chronic lymphocytic leukemia (CLL) (about 25% to 35% of all types of leukemia), the oral manifestations are centered in the lymphoid tissues (tonsils).¹⁸ Intraoral swelling without any reason has also been reported in patients with CLL. In chronic myelocytic leukemia (CML) (about 20% of all cases of leukemia), oral manifestations infrequently occur and are mainly related to the invasion of the bone marrow by the blast cells if the disease progresses to a more acute phase.¹⁴

Conclusion

Oral health care providers must know the signs and symptoms that may suggest leukemia. The initial signs of leukemia are often present in the mouth, and patients will visit the dentist, thinking they are experiencing a gum or tooth problem. In close to one-third of patients, the initial primary signs for leukemia diagnosis are

discoverable by the dentist.⁹ Therefore, dentists need to keep current in providing thorough exams and differential diagnoses by regularly attending continuing education courses that improve their knowledge about oral manifestations of systemic diseases, including leukemia. An extra-oral examination is a critical component of every dental examination. The dental team’s role in the early diagnosis includes proper referral of patients with signs and symptoms that suggest leukemia.

Prophylaxis against oral infections and early treatment of potential oral sources in these neutropenic patients can avoid sepsis. Furthermore, the management of complications associated with cancer therapy (such as mucositis, burning mouth syndrome, opportunistic infections, and oral sores) should include a multidisciplinary approach (hemato-oncologist, nursing, and dental teams), and stakeholders must advocate for benefit coverage to ensure access to these essential services for leukemic patients. ●

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