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Gingival Tumescence and a Palatal Ulcer-a case of AML with an Adverse Drug Reaction to Chemotherapy

Bowers LM[1*], **Brennan MT**[2]

[1]*Assistant Clinical Professor, University of California, San Francisco, San Francisco, California; former resident in Oral Medicine at the Carolinas Medical Center*

[2]*Chairman, Department of Oral Medicine, Carolinas Medical Center, Charlotte, North Carolina*

[*]**Corresponding author:** Bowers LM, Department of Oral and Maxillofacial Surgery, University of California, San Francisco, California- 94143, Tel: 1-415-476-3584; E-mail: leah.bowers@ucsf.edu

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Abstract

Acute and chronic forms of leukemia may initially present with oral manifestations. These manifestations may include gingival swelling, petechiae, ecchymosis, gingival hemorrhage, mucosal pallor and oral infections (e.g. herpes simplex, Candidiasis). Treatment for leukemia may involve the use of chemotherapeutics, some of which are associated with adverse drug reactions which may also present with oral signs and symptoms. It is paramount for all health care providers to consider both local and systemic causes of oral manifestations in their differential diagnoses and to be cognizant of oral manifestations of adverse drug reactions.

Keywords: Leukemia; Adverse drug reactions; Oral ulcers

Clinical Presentation

A 72-year-old gentleman presented to the Carolinas Center for Oral Health, Charlotte, NC, upon referral from a Health Care provider for a chief complaint of gingival enlargement of 3 weeks' duration which had a sudden onset. The patient complained of "discomfort" and "sensitivity" of the affected areas particularly upon contact with coarse, acidic and spicy foods.

Previous treatment for his complaint was comprised of a course of oral Penicillin and a 0.12% chlorhexidine rinse, which had no discernable effect on the presentation. Clinical examination revealed diffuse bogginess of the maxillary and mandibular facial gingivae, with extension toward the mucogingival junction, and involvement of isolated lingual papillae (Figures 1 and 2). The tumescent gingivae were tender to palpation and hemorrhaged easily. The remainder of the head and neck and intraoral examinations revealed no other abnormalities.

The patient's medical history was significant for hypothyroidism, hypercholesterolemia, hypertension, gout, environmental allergies and erectile dysfunction. He underwent a total thyroidectomy for goiter in 2008. His medications included levothyroxine, lovastatin, metoprolol, losartan, allopurinol, loratadine, sildenafil citrate and ibuprofen. He denied any drug allergies. He was a former cigarette smoker who quit in 1975 and admitted to occasional use of alcohol but denied illicit drug use. His Mother died of a lymphoma and his brother died of lung cancer. His vital signs were within normal limits, but he complained of shortness of breath.

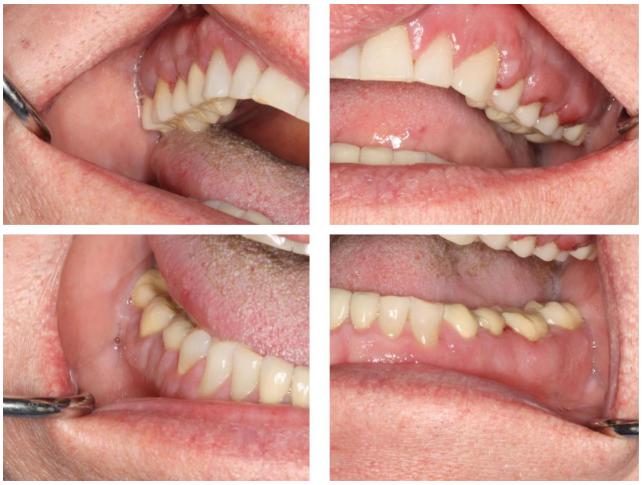

Figure1: Clinical appearance of mandibular and maxillary facial gingivae at initial presentation.

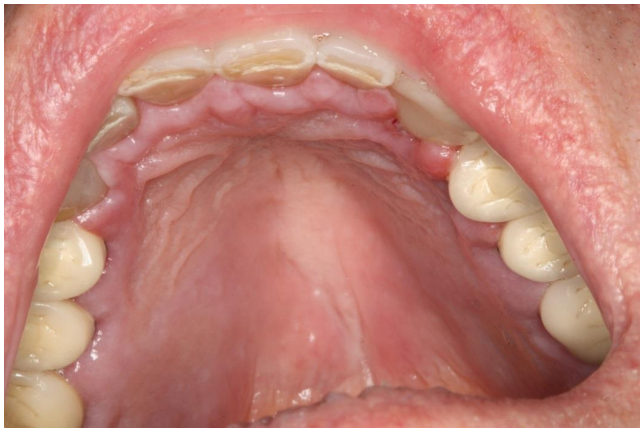

Figure 2: Clinical appearance of the palate at initial presentation.

Differential Diagnosis

Based upon the clinical presentation and symptomatology, we suspected that the gingival tumescence represented leukemic infiltrate. Both acute and chronic forms of leukemia were considered, namely acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML). While CLL is the most common form of leukemia in this patient's age group, AML has a greater predilection for extramedullary site presentation than the types of leukemia [1].

Drug-induced gingival hyperplasia was also considered. Although, there was no history of the use of medications associated with this phenomenon such as anticonvulsants, calcium channel blockers and immunosuppressants, a thorough review of the patient's medications was made.

Consideration was also made for plaque- and calculus-associated periodontal disease due to its near ubiquity in the general population. It was established through interview and clinical examination however, that it was unlikely that a chronic or acute periodontal process could adequately account for the patient's clinical appearance.

We also considered conditions falling under the rubric of orofacial granulomatosis (OFG) including sarcoidosis, tuberculosis, fungal infections and Crohn's disease. While OFG classically presents as labial swelling, gingival enlargement has been described. The patient's additional complaint of dyspnea, which can be a presenting symptom of sarcoidosis, provided additional credence to this differential diagnosis.

A gingival manifestation of amyloidosis was also vetted in our differential diagnoses. Reports of localized amyloidosis, confined to the gingiva, while rare, describe dusky red-blue, persistent, nodular, tender masses which bleed with little provocation. A systemic amyloidosis presenting with gingival manifestations, secondary to multiple myeloma or a Non-Hodgkin lymphoma for example, was also considered.

A gingival manifestation of ascorbic acid (vitamin C) deficiency (hypovitaminosis C or scurvy) was also considered. Scorbutic gingivae are described as intensely erythematous, swollen and painful and bleed with little instigation [2]. Progression to scorbutic periodontitis results in an ulcerative gingivitis, rapid periodontal pocket development and tooth exfoliation [2,3]. No other clinical stigmata supporting this differential diagnosis, however, were observed.

A plasma cell gingivitis (PCG) was also elected for consideration. In PCG, a hypersensitivity reaction to an agent (often flavoring agents found in toothpastes and chewing gums or spices such as cinnamon), results in a localized area of swollen but friable, erythematous and painful gingiva

The key histopathologic finding in PCG is the presence of a dense, plasma cell-rich infiltrate within the connective tissue [4].

A foreign body gingivitis (FBG) arising from impregnation of components of dental restorative or prophylaxis agents into the gingival connective tissue, was also contemplated, as this can affect the marginal and attached gingivae as well as the interdental papillae. However, as the common presentation of FBG is that of a lichenoid desquamation and mottling of the gingivae or gingival recession and the remote history of the patient having undergone any such dental procedure, this possibility was excluded.

Diagnosis

Further immediate evaluation including possible biopsy for definitive diagnosis with our Oral and Maxillofacial Surgeon was advised at the initial visit. The patient asked to defer this, and an additional appointment was established. Three days following his visit, however, he presented to the Emergency Department of the Carolinas Medical Center complaining of a one-week history of progressive dyspnea on exertion. A complete blood count with differential showed an elevated white blood cell (WBC) count of 86.8 K/µl (reference range 3.6-10.4 K/µl) and a platelet count of 29 K/µl (reference range 142-328 K/µl). Lateral and PA chest radiographs showed no gross abnormalities. Computed tomography with and without contrast of the chest demonstrated some ground-glass opacities in the right upper lobe, thought to possibly represent edema, and mediastinal lymphadenopathy. Based upon the clinical and radiographic findings, CLL was suspected and a consultation with the Oncology department was initiated.

A bone marrow biopsy showed an abnormal immature cellular infiltrate with predominantly monocytic morphology (Figure 3) and a diagnosis of AML was assigned. Flow cytometric analysis was performed using 29 antibodies (CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11c, CD13, CD14, CD15, CD16, CD19, CD20, CD22, CD24, CD33, CD34, CD36, CD38, CD45, CD56, CD64, CD81, CD117, CD123, HLA-DR, and kappa and lambda light chains) which confirmed AML with monocytic differentiation. Cytogenetic analysis revealed an abnormal karyotype of 46, XY, t (11;19) (q23;p13.1) (Figure 4). Fluorescent in situ hybridization was performed on interphase nuclei using 8 different probes (5q, 7q, cep8, 20q12, t (8;21), KMT2A, t (15;17) and CBFß) (Figure 5) and a rearrangement at region 11q23 (KMT2A) was detected in 93% of the cells.

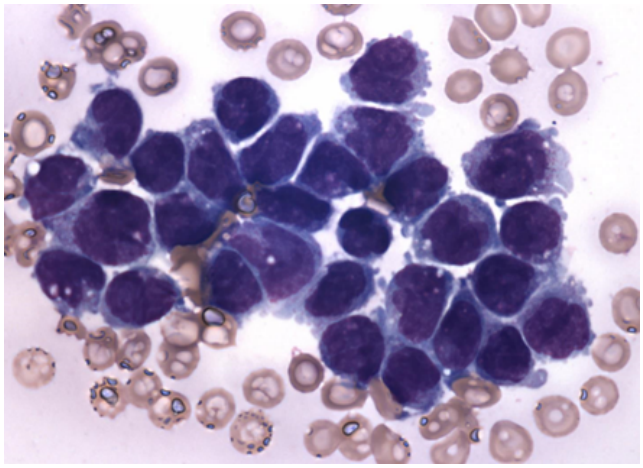

Figure 3: Bone marrow aspirate showing an atypical immature cellular infiltrate with monocytic morphology and lobulated nuclei consistent with AML with monocytic differentiation (Wright-Giemsa stain, original magnification 1000x).

Figure 4: Patient's karyogram indicating abnormal karyotype 46, XY, t (11;19) (q23; p13.1). Arrows indicate abnormal chromosomes 11 and 19 resulting from translocation.

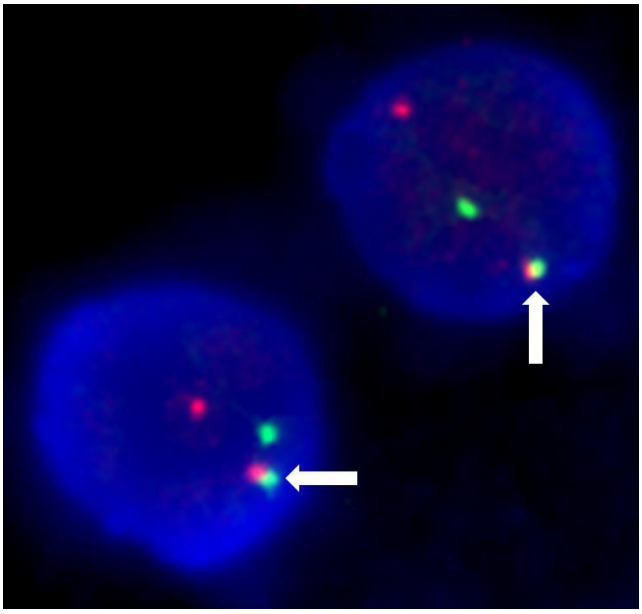

Figure 5: FISH using a KMT2A break-apart probe. Fusion signal (arrows) indicates normal KMT2A gene; single red and green signals indicate KMT2A gene rearrangement.

Management

Following the diagnosis of AML, to lower the WBC count, cytoreduction with hydroxyurea was initiated. Induction chemotherapy with azacitidine was then started, but due to a continued elevation in WBC level, cyclophosphamide was added to enhance cytoreduction. Subsequently, the patient developed several painful, non-healing coalescing ulcers of the central hard palate (Figure 6) for which he was given viscous lidocaine and a palliative mouth rinse composed of aluminum hydroxide with magnesium hydroxide (Maalox™), diphenhydramine and viscous lidocaine.

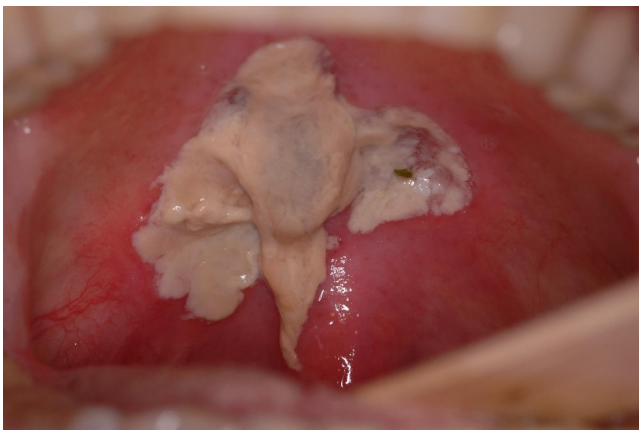

Figure 6: Non-healing ulcer of hard and soft palate.

The patient's Oncologist suspected that the oral ulcers were related to the use of hydroxyurea and discontinued the drug. When the lesions

did not resolve accordingly, a biopsy was advised. The differential diagnoses considered included a neutropenic stomatitis, necrotizing sialometaplasia, deep fungal infection and traumatic ulceration. After establishing that there were no contraindications for the procedure and following the receipt of platelets, a biopsy specimen of the lesion with a rim of perilesional tissue was collected which was signed out as "benign squamous mucosa; PAS (fungus) negative". At a follow-up visit in our out-patient clinic two weeks later, we noted that the ulcer had diminished significantly in size, despite a persistent neutropenia. We also noted that the previously observed gingival swelling had resolved. The oral ulcers were therefore attributed to the use of the hydroxyurea.

The patient continued treatment with azacitidine. His treatment was complicated by neutropenic fever, pneumonia, new-onset atrial fibrillation and later, a spike in his WBC and blast count occurred. Hydroxyurea, at a reduced dose, was started but this did not achieve the desired cytoreduction necessitating the addition of cyclophosphamide. The patient developed no additional oral lesions. Unfortunately, after several cycles of chemotherapy, the patient succumbed to disease.

Discussion

AML arises from an accumulation of recurrent genetic alterations in hematopoietic stem cells [5]. These progenitor cells undergo abnormal proliferation and differentiation resulting in an accumulation of immature myeloid cells which crowd and replace bone marrow resulting in a decreased production of erythrocytes, leukocytes and platelets. Consequently, patients with AML may develop anemia, and are at increased risk of infection and bleeding.

The annual incidence of AML in the United States is approximately 4.1 cases per 100,000 and appears to be increasing concomitant with the rising median age. In 2016, 19,950 new cases and 10,430 deaths due to AML are expected to occur in the U.S. The median age at diagnosis is 67 years and there is a male predilection for the disease [6]. Risk factors for AML include exposure to ionizing radiation, chemicals (e.g. benzene), previous exposure to cytotoxic drugs, genetic disorders (e.g. Down syndrome), chronic myeloproliferative disorders (e.g. myelodysplastic syndrome) and cigarette smoking [7-10].

The two most recognized staging systems for leukemia are the French-America-British (FAB) system, which classifies entities based upon the status of the predominant leukemic cell, and that of the World Health Organization (WHO), which distinguishes disease based upon specific cytogenetic or molecular genetic abnormalities [7]. According to the FAB system, AML may be divided into eight subtypes, M0 to M7. Mucosal surface lesions, gingival infiltration, and other manifestations of extramedullary disease, occur most commonly among the myelomonocytic and monocytic lineages; subtypes M4 and M5, respectively [9,11,12]. Our patient, having a primarily monocytic morphology, would be classified as having subtype M5 (Figure 3).

The WHO classification underwent a significant update in April of 2016 to reflect advances in the understanding of the pathogenesis of AML attributed to the application of genomic techniques. Unique biomarkers identified by gene expression analysis and next-generation sequencing have allowed for improved diagnostic criteria and prognostication [13].

Oral manifestations have been described in both acute and chronic forms of leukemia, but are more common in the acute forms of the disease. These manifestations may be due to direct leukemic infiltration or because of immunodeficiency, anemia or thrombocytopenia [9,14,15]. Gingival swelling, petechiae, ecchymosis, gingival hemorrhage, mucosal pallor and oral infections (e.g. herpes simplex, Candidiasis) are reported findings associated with AML. Oral infections in those with immunosuppression can be atypical in appearance and severity and be refractory to treatment.

In our patient, once the diagnosis of AML was established, flow cytometry, fluorescent in situ hybridization (FISH) and karyotyping were employed to detect significant genetic abnormalities. Our patient was found to have an abnormal karyotype of 46, XY, t(11;19)(q23;p13.1) indicating a translocation (t) between the long arm (q) of chromosome 11 and the short arm (p) of chromosome 19 at regions 23 and 13.1 respectively (Figure 4). The gene KMT2A (also known as the mixed lineage leukemia [MLL] gene) is located at 11q23 and encodes for a protein involved in coordination of chromatin modification. Applying a series of genetic probes using FISH indicated the patient had a rearrangement of KMT2A (Figure 5). Mixed lineage leukemia occurs predominantly in pediatric patients but shows a second peak incidence in adults [16]. Recurrent cytogenetic abnormalities in chromosome 11q23 involving the KMT2A gene have been observed in 3%–4% of adult patients with AML [17] and are associated with a very aggressive disease and dismal prognosis.

Despite a greater understanding of the pathogenesis of AML and identification of new drug targets, treatment has remained largely unchanged in the past 3 decades; most patients eventually relapse and succumb to disease. Rapid remission, the goal of intensive induction chemotherapy, reduces number of leukemic cells below levels of clinical detection allowing restoration of normal hematopoiesis [11]. Morphologic complete remission (CR) is evaluated by bone marrow biopsy and is defined based upon the quantity of morphologically distinct cells (e.g. blasts), absence of extramedullary disease, absolute neutrophil count (ANC) and platelet levels [5]. Once remission has been achieved, consolidation therapy, in the form of chemotherapy and stem cell transplant, often in combination, aims to eliminate all remaining leukemic cells in the bone marrow to prevent relapse, achieve cure or as a bridge to transplant [5]. Relapse can occur due to proliferation of residual leukemic cells or through accumulation of newly acquired mutations. Patients who relapse may undergo "salvage chemotherapy" followed by allogeneic stem cell transplant.

Treatment planning takes into consideration multiple factors, especially a patient's age; treatments differ for patients above or below the age of 60 years. As reflected in the recently updated WHO classification scheme, chromosomal and molecular aberrations, in addition to age, performance status and comorbidities, are now the most important factors for outcome prediction in AML [5]. For adults younger than 60 years and selected more senior patients, an intensive regimen of anthracyclines (idarubicin or daunorubicin) and cytarabine is the standard of care for AML [5]. Older patients are generally treated with lower intensity therapies such as decitabine, azacitidine, or hydroxyurea to minimize treatment-related mortality [5,7].

Hydroxyurea (HU) is an antimetabolite most commonly used for myeloproliferative disorders, sickle cell anemia and psoriasis. While it is generally well tolerated, it is associated with mucocutaneous side effects including a painful ulcerative stomatitis and glossitis with depapillation, dermal and mucosal atrophy and hyperpigmentation [18]. High doses of HU may prompt a rapid development of oral lesions. Long-term use of HU is associated with development of oral and dermal squamous cell carcinomas and keratoacanthomas [19]. HU-associated lesions and changes can occur at any time during

therapy, independent of neutrophil count or status of the primary disease. Remission of these side effects may be seen upon withdrawal of the medication [18].

Our patient received cycles of azacitidine with hydroxyurea and developed a large painful palatal ulcer suspected to represent an adverse reaction to hydroxyurea. The lesion, however, did not resolve as quickly as expected upon discontinuation of the drug thereby warranting biopsy. The biopsy results ruled out some additional possible causes of the ulcer such as a necrotizing sialometaplasia and a deep fungal infection. The ulcer ultimately resolved, and no new lesions developed upon re-introduction of the drug, albeit at a lower dose.

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