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Chemotherapy-Induced Oral Mucositis

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Updated: Oct 31, 2008

Introduction

Background

Most patients receive chemotherapy on an outpatient basis and are admitted to the hospital if they develop fever and neutropenia, obvious infection, or some other complication. Most of the data cited here are from studies performed on patients in an inpatient setting. Nevertheless, oral complications, when they arise in either the inpatient setting or the outpatient setting, are similar.

Chemotherapy, either at conventional levels or at the higher-dosed regimens used in conditioning regimens (with or without total body radiation in preparation for hematopoietic cell transplantation [HCT]), often results in erythema, edema, atrophy, and ulceration of the oral mucosa, a condition generally referred to as oral mucositis (OM). Oral mucositis leads to pain and restriction of oral intake, and, in severe cases (eg, patients undergoing myeloablative therapy prior to HCT), necessitates total parenteral nutrition (TPN) and increased use of narcotic analgesics.

In patients undergoing HCT, oral mucositis is reported as the most debilitating aspect of their treatment. Ulcers may act as a site for local infection and a portal of entry for oral flora that, in some instances, may cause septicemia. Approximately half of all patients who receive chemotherapy develop severe oral mucositis that is dose-limiting such that the patient's cancer treatment must be modified, compromising the prognosis. Durable disease remission and cure rates may be enhanced if more intensive therapies could be used without the untoward consequences of dose-limiting oral mucositis. In addition to direct morbidity, oral mucositis contributes indirectly to increased length of hospitalization and increased cost of treatment.

A related Medscape CME course is NCCN Task Force Report: Prevention and Management of Mucositis in Cancer Care (Slides With Transcript).

Pathophysiology

Oral mucositis results from a complex interaction of local tissue damage, the local oral environment, the patient's level of myelosuppression, and the patient's intrinsic predisposition to develop this condition.

The current working biological model for oral mucositis is based on 5 interrelated phases, including an initiation phase, a message generation phase, a signaling and amplification phase, an ulceration phase, and a healing phase. In the initiation phase, the chemotherapeutic agents lead to the generation of free radicals and DNA damage. In the message generation phase, transcription factors such as NFkB are activated, which then up-regulate a number of proinflammatory cytokines such as interleukin (IL)–1 beta and tumor necrosis factor-alpha (TNF-alpha). IL-1 beta mediates inflammation and dilates vessels, potentially increasing the concentration of chemotherapeutic agents at the site. TNF-alpha causes tissue damage, perhaps in an escalating fashion.

During the signaling and amplification phase, positive feedback loops are activated. For example, TNF-alpha activates NFkB, mitogen-activated protein kinase (MAPK), and sphingomyelinase pathways while also contributing directly to cellular and tissue injury. The result is erythema from increased vascularity and epithelial atrophy 4-5 days after the initiation of chemotherapy. Microtrauma from day-to-day activities, such as speech, swallowing, and mastication, leads to ulceration.

During the ensuing ulcerative/bacteriologic phase (during which time neutropenia has developed), putative bacterial colonization of ulcerations occurs, resulting in the flow of endotoxins into mucosal tissues and the subsequent release of more IL-1 and TNF-alpha. This ialvato da Windows Internet Explorer 8> Subject: Chemotherapy-Induced Oral Mucositis: [Print] - eMedicine Dermatology Date: Fri, 4 Sep 2009 01:01:48 +0200 MIME-Version: 1.0 Content-Type: multipart/related; type="text/html"; boundary="----=_NextPart_000_0347_01CA2CFB.479BB280" X-MimeOLE: Produced By Microsoft MimeOLE V6.00.2900.5579 This is a multi-part message in MIME format. ------=_NextPart_000_0347_01CA2CFB.479BB280 Content-Type: text/html; charset="Windows-1252" Content-Transfer-Encoding: quoted-printable Content-Location: http://emedicine.medscape.com/article/1079570-print

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During the signaling and amplification phase, positive feedback loops are activated. For example, TNF-alpha activates NFkB, mitogen-activated protein kinase (MAPK), and sphingomyelinase pathways while also contributing directly to cellular and tissue injury. The result is erythema from increased vascularity and epithelial atrophy 4-5 days after the initiation of chemotherapy. Microtrauma from day-to-day activities, such as speech, swallowing, and mastication, leads to ulceration.

During the ensuing ulcerative/bacteriologic phase (during which time neutropenia has developed), putative bacterial colonization of ulcerations occurs, resulting in the flow of endotoxins into mucosal tissues and the subsequent release of more IL-1 and TNF-alpha. This is likely the phase most responsible for the clinical pain and morbidity associated with oral mucositis.

During the fifth and final healing phase, cell proliferation occurs with reepithelialization of ulcers. Signals from the extracellular matrix induce epithelial cells to migrate underneath the pseudomembrane (fibrin clot) of the ulcer. The epithelium then proliferates so that the thickness of the mucosa returns to normal. Reconstitution of the WBCs in neutropenic patients effects local control of bacteria, which also contributes to resolution of the ulcers.

Frequency

United States

Approximately 400,000 patients per year may develop acute or chronic oral complications during chemotherapy. Some degree of oral mucositis occurs in approximately 40% of patients who receive cancer chemotherapy. At least 75% of patients who receive conditioning regimens (chemotherapy with or without total body irradiation) in preparation for HCT develop oral mucositis. The incidence is also higher in patients who receive continuous infusion therapy for breast and colon cancer and in those who receive adjuvant therapy for head and neck tumors. However, in patients of the same age with similar diagnoses and treatment regimens and equivalent oral health status, the incidence of oral mucositis may vary considerably. This is most likely because of genetic differences and other factors that are not yet fully characterized or understood.

International

Figures are similar to those in the United States.

Mortality/Morbidity

Oral mucositis causes pain, restricts oral intake, may act as a portal of entry for organisms, frequently contributes to interruption of therapy, may increase the use of antibiotics and narcotics, may increase the length of hospitalization, and may increase the overall cost of treatment. Patients with oral mucositis and neutropenia have a relative risk of septicemia more than 4 times that of patients with neutropenia without oral mucositis.

- Patients with pulpal disease from dental caries or trauma, advanced periodontal disease, and low-grade soft tissue infections (especially those associated with partially erupted third molars) are at increased risk for developing septicemia of odontogenic origin when they are myelosuppressed (eg, in preparation for HCT). The incidence of alpha-hemolytic streptococcal infection increases in patients who undergo conditioning regimens in preparation for HCT.[1] Risk factors include prophylactic antibiotic therapy with quinolones, severe neutropenia, high-dose chemotherapy regimens, oral mucositis, strong colonization with viridans streptococci, and the use of Hickman and other long-term intravascular catheters. Viridans streptococci now account for more than 65% of bacteremic episodes in these patients and are associated with fever, hypotension, toxic shock–like syndrome, pneumonia, and adult respiratory distress syndrome (ARDS).[2]
- Mortality rates range from 6-30%. Oral mucositis lesions have been implicated as an important portal of entry for these organisms into the systemic circulation because many of these organisms are native to the oropharyngeal region. Combination prophylaxis, including the use of penicillin and other antibiotics effective against gram-positive streptococci, has been effective in reducing the incidence of septicemia.

Race

No racial predilection is apparent.

Sex

No sexual predilection is reported.

Age

Younger patients tend to develop oral mucositis more often than older patients being treated for the same malignancy with the same regimen. This is apparently because of the more rapid rate of basal cell turnover noted in children. However, the healing of oral mucositis is also more rapid in the younger age group.

Clinical

History

- Oral pain contributes to patient morbidity. Difficulty with eating, drinking, speaking, and maintenance of oral hygiene regimens typifies morbidity.
- A dry mouth from decreased salivary flow (hyposalivation) secondary to chemotherapy reduces natural lubrication and contributes to the accumulation of debris in the mouth, to the ease of trauma-induced ulceration, and to difficulty in eating and swallowing (dysphagia). A hairy tongue and superficial mucoceles may develop as a result (see Media Files 1-2).
- Dysgeusia, or altered taste sensation, may further reduce the patient's appetite contributing to poor oral intake, requiring parenteral nutrition.

Physical

The earliest changes are those of leukoedema, although these changes cannot always be appreciated. These changes present as diffuse, poorly defined areas of pallor or milky-white opalescence most noticeable on the buccal mucosa. These areas disappear if the mucosa is stretched.

Oral mucositis begins 5-10 days following the initiation of chemotherapy and lasts 7-14 days. Therefore, the whole process lasts 2-3 weeks in more than 90% of patients. Resolution (in the case of HCT) coincides with recovery of the WBC count, specifically when the absolute neutrophil count becomes greater than 500 cells/µL. In patients being treated for solid tumors, the duration of oral mucositis depends on the type, dose, and course of treatment.

Oral mucositis begins as areas of erythema (see Media File 3) and atrophy on the mucosa that may then break down to form ulcers that are covered by a yellowish white fibrin clot (the pseudomembrane). Peripheral erythema is usually present. Ulcers may range from 0.5 cm to greater than 4 cm in maximum dimension. At the height of oral mucositis, patients experience marked pain, difficulty opening the mouth, difficulty with any form of oral intake, and difficulty with mouth care regimens.

- Location
    - The mouth is a trauma-intense environment. When the oral mucosa becomes atrophic from chemotherapy and renewal of oral epithelium has been slowed by chemotherapy, local trauma leads to ulceration with nonkeratinized sites being the most vulnerable. Therefore, lesions occur bilaterally, mainly on the nonkeratinized sites in the mouth, namely the buccal mucosa, the ventral and lateral parts of the tongue, the labial mucosa, the floor of the mouth, the soft palate, and the oropharyngeal fauces (see Media Files 4-6).
    - Spontaneous healing (from the occurrence of erythema to resolution) without scar formation occurs within 2-3 weeks. Healing of ulcers usually takes 7-10 days.
    - Because many patients (especially those undergoing HCT) are profoundly thrombocytopenic, bleeding may occur from sites of ulcerative oral mucositis.
- In patients undergoing HCT, those who are conditioned with total body irradiation in preparation for allogenic transplantation are at a somewhat higher risk of experiencing more severe and prolonged oral mucositis. Patients treated with methotrexate as part of their graft versus host disease (GVHD) prophylaxis are also at increased risk.
- With decreased salivary flow, debris that is normally washed away by saliva builds up in the oral cavity. One major manifestation of this is hairy tongue (see Media File 1). Hairy tongue is not a candidal infection; retention of keratin on the filiform papillae of the tongue from hyposalivation, alteration of constituents of the saliva, and eating a soft diet or not eating at all causes hairy tongue. The retention of keratin on other sites, such as the gingiva, may also be mistaken for oral candidiasis; however, hyposalivation changes the intraoral milieu and predisposes to candidiasis so that the conditions may coexist. Candidiasis is less likely when patients are on antifungal prophylaxis.

Causes

The underlying malignancy and chemotherapy regimens (that, in turn, determines the degree of neutropenia) are the 2 most important factors in determining the occurrence and the severity of oral mucositis. Hematologic malignancies and stomatotoxic regimens lead to more severe oral mucositis, but many factors can modify the occurrence and the degree of oral mucositis.

Other factors that modify the occurrence and the severity of oral mucositis include age, level of pretreatment oral health, oral care during treatment, and salivary flow. Young age, poor oral health before and during treatment, and hyposalivation all contribute to an increased risk and increased severity of mucositis. The use of methotrexate for chronic GVHD prophylaxis may exacerbate lesions of oral mucositis, although this is less of a concern with newer prophylaxis regimens. Nevertheless, as mentioned earlier, other factors that as yet are poorly understood can affect oral mucositis so that patients who are controlled for these above factors may still experience different severities of oral mucositis.

- Generally, patients with hematologic malignancies have an increased rate of oral mucositis compared with those with solid tumors. This is to some extent related to the treatment regimens.
- Great variability exists in the stomatotoxicity of different treatment regimens. Some of the most stomatotoxic agents include the antimetabolites 5-fluorouracil, methotrexate, and cytarabine.
- Concomitant radiation therapy (especially to the head and neck region) increases the risk of oral mucositis because of synergistic effects with the chemotherapeutic agents.
- Younger age is associated with more severe oral mucositis.
- Chronic irritation from ill-fitting prostheses or faulty restorations predisposes patients to the development of oral mucositis due to local irritation and trauma.
- Hyposalivation prior to and during treatment is associated with an increased risk of oral mucositis.
- Oral mucositis occurs independently of oral mucosal infections of viral and fungal etiology, but it may be exacerbated by such concomitant infections.
- Better pretreatment oral health is probably associated with a reduced incidence of and less severe oral mucositis.

Differential Diagnoses

Candidiasis, Cutaneous
Graft Versus Host Disease
Herpes Simplex
Herpes Zoster

Other Problems to Be Considered

Chemotherapy and bone marrow transplantation–induced mucositis

Overall, candidiasis is the most frequent oral infection in patients who are myelosuppressed (see Media File 7), whereas recurrent herpes simplex virus 1 (HSV-1) is the most frequent oral viral infection in these patients (see Media Files 8-9). Consider other viral infections, including human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7), and cytomegalovirus (CMV).

Acute GVHD occurs within the first 100 days after transplantation and involves the skin; the liver; and the mucosa of the eye, the mouth, and the GI tract. Acute GVHD lesions in the oral cavity occur 3-4 weeks after HCT, following engraftment and restoration of the white cell count. Acute GVHD typically presents well after the resolution of oral mucositis (OM) lesions, although in some cases, they may manifest as a continuation or exacerbation of oral mucositis. An important difference is that lesions of acute GVHD may affect the keratinized mucosa, which is not a feature of oral mucositis (see Media File 10). Risk factors include HLA disparity, sex mismatching, multiple donor pregnancies, and advanced age. Management includes controlling systemic acute GVHD with systemic immunosuppressive therapy, controlling pain, and providing local palliative measures.

Workup

Laboratory Studies

- Diagnosis is primarily based on the clinical findings and the chronology of the development of lesions.

- WBC count with differential (absolute neutrophil count in particular) is a helpful test. Oral mucositis usually occurs when the absolute neutrophil count is less than 500 cells/µL.
- Cultures (particularly for herpetic infection) should be performed if erythema and ulcers (or vesicles) are located on the keratinized tissues of the hard palate, the attached gingiva, or the dorsum of the tongue or if lesions persist after the period of profound neutropenia has passed. If the patient is on prophylactic antiviral agents, the possibility of breakthrough infection or the development of resistant strains must be considered.
- Biopsy is indicated, especially if a deep fungal infection is suspected. Infection may present as a rapidly growing discrete ulcer on either the keratinized mucosa or the nonkeratinized mucosa (see Procedures). Biopsy should be considered when oral ulcerations are exacerbated with engraftment and restoration of the white cell count, especially when skin changes are absent, as this is suggestive of emerging acute GVHD. However, biopsy is not routinely necessary for oral mucositis.

Other Tests

- The severity of oral mucositis can be evaluated using several different instruments. The 2 most commonly used are the World Health Organization (WHO) Oral Toxicity score and the National Cancer Institute (NCI) Common Toxicity Criteria for oral mucositis. While the NCI system has separate scores for objective (erythema and ulceration) and functional (pain and ability to eat solids, liquids, or nothing by mouth) components, the WHO score combines both elements into a single score that is useful for measuring severity over time. The Oral Mucositis Daily Questionnaire (OMDQ), which evaluates mouth and throat soreness and its impact on daily activities, has been recently validated and shown to correlate with oral mucositis severity based on the WHO score.[3] Of note, symptoms have been found to precede objective findings by 1-3 days.

Procedures

- A biopsy may be necessary, particularly to rule out a deep fungal infection or CMV infection (although CMV infection usually occurs as a later event).
    - The patient should have a minimum of 50,000-80,000 platelets/µL. Antibiotic coverage may be necessary if the patient has less than 1000 neutrophils/µL. The antibiotics should be administered 30 minutes to 1 hour prior to the biopsy to reduce bacteremia and the possibility of a central venous line infection, if such a line is present, and should continue for 5-7 days after the biopsy. Infectious disease physicians should be consulted for their recommendation for the most appropriate antibiotic if the patient is already on a variety of antimicrobial agents.
    - The biopsy is performed under local anesthesia. If indicated, a portion of the tissue should be submitted fresh for fungal culture (for speciation) and viral culture. The wound should be primarily closed with sutures.

Histologic Findings

Routine biopsies are not performed on oral mucositis lesions unless other pathology is suspected, such as a deep fungal infection. In banal oral mucositis, the oral mucosa exhibits ulceration that unlike other ulcerative conditions shows a paucity of neutrophils in the fibrin clot. Granulation tissue is present at the base of the ulcer with chronic inflammatory cells. Stains for fungi and viruses may be necessary to identify organisms.

Treatment

Medical Care

Because oral mucositis (OM) is self-limited, management of lesions is divided into 5 main approaches, including the following:

- Oral debridement: Because patients with oral mucositis lesions are neutropenic and thrombocytopenic, perform oral debridement with caution because toothbrushing can cause gingival bleeding and, more importantly, result in transient bacteremia. In some centers, sponge-tipped applicators and gauze soaked in sodium chloride solution are used for oral debridement because of these concerns. Dried secretions may become caked on the mucosal surfaces, particularly the palate. Mucolytic agents, such as Alkalol, help to soften and dislodge them.

- Oral decontamination (mouth care): This regimen consists of antifungal and antibacterial rinses. The fluoride rinses and gels used in some oral care regimens are used primarily for antibacterial activity against gingival plaque; they are not used expressly for the prevention of dental caries. Candidal prophylaxis usually includes nystatin rinses and clotrimazole troches. If patients have a very dry mouth, troches are not as effective because they do not dissolve well in a dry environment. Amphotericin rinses also are occasionally used in place of nystatin. Fluconazole may be used for candidal prophylaxis or for treatment of suspected candidiasis.
- Topical and systemic pain management: Pain in patients with oral mucositis may be severe and not just limited to the oral mucosa. Local rinses (eg, 2% viscous lidocaine) and systemic analgesics are used together to control pain. Frequent rinsing with sodium chloride solution helps to keep the mucosa moist, reduces caking of secretions, and soothes inflamed/ulcerated mucosa.
- Prophylaxis: Systemic prophylaxis for oral mucositis is generally limited to antivirals; however, some centers use fluconazole as prophylaxis against candidiasis.
- Control of bleeding: Maintaining platelets at 20,000 cells/µL and using topical thrombin packs and topical antifibrinolytic agents, such as tranexamic acid, may control bleeding from ulcers.
- Comprehensive, evidence-based guidelines for the prevention and treatment of oral mucositis was published in 2007.[4]

Consultations

Involving dentists and oral medicine specialists in the care of a patient with oral mucositis is important because oral hygiene modifies the occurrence and the severity of oral mucositis and alpha-hemolytic streptococcal sepsis has become increasingly prevalent (in patients undergoing HCT).

- In the outpatient setting, a dentist or an oral medicine specialist should see patients several weeks or months prior to the initiation of chemotherapy, especially in the case of HCT. If this is not possible, the patient should be seen for an evaluation during his or her hospitalization for a baseline dental evaluation, even if intervention may not be possible at that visit.
    - The role of the dentist/oral medicine specialist is to identify and remove dental/oral sources of infection prior to myelosuppression and HCT.
    - Procedures may include but are not limited to comprehensive oral and head and neck examination, full mouth series of dental radiographs, and pulp-vitality testing.
    - Appropriate therapy includes identification and management of soft tissue lesions, restoration of carious teeth, extraction of nonsalvageable teeth, extraction of third molars as necessary (particularly those that are not full bony impacted and not fully erupted), and scaling and root planing. Treatment should be completed at least 1 week before initiation of conditioning therapy for HCT.
- After the patient has been admitted to the hospital, the dentist/oral medicine specialist should follow up with these patients to monitor oral mucositis, identify signs and symptoms of secondary infection, evaluate slow healing of oral mucositis, identify non-oral mucositis oral mucosal pathology, and adjust the oral care regimen as needed.

Diet

A bland, soft diet is recommended. Patients should keep the mouth moist with frequent sips of water, ice chips, or popsicles. Patients with severe oral mucositis may require total parenteral nutrition. Patients should avoid acidic, spicy, salty, coarse, and dry foods.

Activity

Patients with chemotherapy-induced oral mucositis are generally seen in the hospital. Activities are prescribed for them as part of the daily physical therapy regimen.

Medication

Oral mucositis (OM) is a self-limited condition. Currently, no approved preventive or therapeutic agent consistently prevents oral mucositis in all clinical settings. Human recombinant keratinocyte growth factor (KGF) given intravenously was recently demonstrated to significantly reduce the incidence, duration, and severity of oral mucositis in patients undergoing autologous HCT and has been approved for use in patients with

hematologic malignancies undergoing high-dose chemotherapy with or without concomitant total body irradiation. More studies of KGF in other patient populations are ongoing to evaluate safety and efficacy, especially in patients with solid cancers that are known to express growth factor receptors because tumor growth promotion is a concern. Other biological-based treatments are currently in clinical trials, and it is not unreasonable to expect a number of these agents to be approved for treatment of oral mucositis in the future.

Medications are used for prophylaxis against viral and fungal infections, decontamination of the oral cavity, and palliation for pain. This section discusses common medications used for prophylaxis, decontamination, and topical palliation only. Topical palliation for pain may be as simple as frequent sodium chloride solution or salt/bicarbonate of soda rinses and ice chips. Often, 2% viscous lidocaine is mixed in equal volumes with diphenhydramine hydrochloride and bismuth subsalicylate (Kaopectate) or even aluminum hydroxide/magnesium hydroxide (Maalox) as a soothing mouth rinse. In general, most patients require systemic pain control using centrally acting narcotic agents.

Experimental therapies that have been reported include the use of topically applied agents, such as misoprostol (a cytoprotectant), cytokines, and other modifiers of inflammation (eg, IL-1, IL-11, TGF-beta3), amino acid supplementation (eg, glutamine), vitamins, topical morphine, colony-stimulating factors, cryotherapy, and laser therapy.

Antifungals

These agents are used prophylactically against candidal infections in all patients.

Nystatin (Nystex, Mycostatin, Nilstat)

Fungicidal and fungistatic antibiotic obtained from *Streptomyces noursei*. Effective against various yeasts and yeastlike fungi. Changes permeability of fungal cell membrane after binding to cell membrane sterols, causing cellular contents to leak. Continue treatment until 48 h after disappearance of symptoms. Not absorbed significantly from GI tract.

Dosing

Adult

500,000 U swish and swallow 4-5 times/d

Pediatric

Administer as in adults

Interactions

None reported

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Do not use to treat systemic mycoses; Stevens-Johnson syndrome has rarely been reported; more common but less severe associated adverse effects include nausea, vomiting, diarrhea, and local irritation

Clotrimazole (Lotrimin, Mycelex, Femazole)

Broad-spectrum antifungal agent that inhibits yeast growth by altering cell membrane permeability, causing death of fungal cells. Reevaluate diagnosis if no clinical improvement after 4 wk.

Dosing

Adult

10 mg troche may be dissolved 3 times/d for 7-10 d or for duration of chemotherapy

Pediatric

Children: Not established
Adolescents: Administer as in adults

Interactions

None reported

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Not for treatment of systemic fungal infections; avoid contact with the eyes; if irritation or sensitivity develops, discontinue use and institute appropriate therapy

Fluconazole (Diflucan)

Fungistatic activity. Synthetic oral antifungal (broad-spectrum bistriazole) that selectively inhibits fungal cytochrome P-450 and sterol C-14 alpha-demethylation, which prevents conversion of lanosterol to ergosterol, thereby disrupting cellular membranes.

Dosing

Adult

100-200 mg for 3-10 d depending on severity of infection

Pediatric

3-6 mg/kg PO qd for 14-28 d or 6-12 mg/kg PO qd depending on severity of infection

Interactions

Levels may increase with hydrochlorothiazides; levels may decrease with long-term coadministration of rifampin; coadministration may decrease phenytoin clearance; may increase concentrations of theophylline, tolbutamide, glyburide, and glipizide; effects of anticoagulants may increase with coadministration; cyclosporine concentrations may increase when administered concurrently

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Adjust dose for renal insufficiency; monitor closely if rash develops, and discontinue drug if lesions progress; may cause clinical hepatitis, cholestasis, and fulminant hepatic failure (including death), with underlying medical conditions (eg, AIDS, malignancy) and while taking multiple concomitant medications; not recommended in breastfeeding

Antibacterials

Rinses are the basis of the oral decontamination regimen.

Chlorhexidine gluconate (Peridex, PerioGard)

Effective, safe, and reliable antiseptic mouthwash. A polybiguanide with bactericidal activity; usually supplied as gluconate salt. At physiologic pH, salt dissociates to a cation that binds to bacterial cell walls. Active against gram-positive and gram-negative organisms, facultative anaerobes, aerobes, and yeast. Precede use of solution by flossing and brushing teeth, if possible. Completely rinse toothpaste from mouth.

Dosing

Adult

Swish 15 mL undiluted oral rinse around mouth for 30 seconds, then expectorate; caution patient not to swallow medication; do not ingest food for 2-3 h following treatment

Pediatric

Not established; suggested as in adults

Interactions

None reported

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Staining of oral surfaces, tooth restorations, and dorsum of tongue may occur; keep out of eyes and ears; for topical use only; case reports of anaphylaxis exist following chlorhexidine disinfection; because of drug interactions, do not use within 30 min of nystatin rinse

Anesthetics

Oral rinses are used to reduce pain and discomfort.

Viscous lidocaine 2% (Xylocaine, Dilocaine, Anestacon)

Decreases permeability to sodium ions in neuronal membranes. Results in inhibition of depolarization, blocking transmission of nerve impulses.

Dosing

Adult

5 mL swish and expectorate

Pediatric

Apply to affected area prn

Interactions

None reported

Contraindications

Documented hypersensitivity; avoid use in Adams-Stokes syndrome and Wolf-Parkinson-White syndrome

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

For external or mucous membrane use only; do not use in eyes

Antivirals

Nucleoside analogs are initially phosphorylated by viral thymidine kinase to eventually form a nucleoside triphosphate. These molecules inhibit HSV polymerase with 30-50 times the potency of human alpha-DNA polymerase.

Acyclovir (Zovirax)

For patients who have been exposed to HSV or VZV infection. Reactivation of such infections occurs in 70-90% of patients who have antibodies to these agents and can aggravate preexisting OM and result in systemic infection. Inhibits activity of HSV-1 and HSV-2. Has affinity for viral thymidine kinase, and, once phosphorylated, it causes DNA chain termination when acted on by DNA polymerase. Patients experience less pain and faster resolution of cutaneous lesions when used within 48 h from rash onset. May prevent recurrent outbreaks. Early initiation of therapy is imperative.

Dosing

Adult

400 mg PO tid

Pediatric

5 mg/kg/dose IV q8h or 750 mg/m^2/d divided q8h

Interactions

Concomitant use of probenecid or zidovudine prolongs half-life and increases CNS toxicity

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Caution in renal failure or when using nephrotoxic drugs

Valacyclovir (Valtrex)

Prodrug and is rapidly converted to the active drug acyclovir. More expensive but has better bioavailability and a more convenient dosing regimen than acyclovir.

Dosing

Adult

First episode herpes simplex: 1 g bid for 10 d, preferably beginning within 48 h of onset
Recurrent episode herpes simplex: 500 mg bid for 5 d beginning within 24 h of onset
Suppressive dosing for HSV: 500 mg to 1 g/d

Pediatric

Not established

Interactions

Probenecid, zidovudine, or cimetidine coadministration prolongs half-life and increases CNS toxicity of valacyclovir

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Caution in renal failure (decrease dose) and coadministration of nephrotoxic drugs; associated with onset of hemolytic uremic syndrome

Famciclovir (Famvir)

For prophylactic use to prevent recurrent HSV infections. Prodrug that, when biotransformed into active metabolite, penciclovir, may inhibit viral DNA synthesis/replication. Inhibits viral DNA polymerase.

Dosing

Adult

Prophylaxis: 500-1000 mg PO bid for up to 1 y

Pediatric

Not established

Interactions

Coadministration of probenecid or cimetidine may increase toxicity; coadministration increases bioavailability of digoxin

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Caution in renal failure or coadministration of nephrotoxic drugs

Gastrointestinal agents

These agents are used to protect the GI tract from irritants.

Sucralfate (Carafate)

Forms viscous adhesive substance that protects oral and GI lining against pepsin, peptic acid, bile salts, and other irritants. Use susp.

Dosing

Adult

1 g PO qid

Pediatric

Not established

Interactions

When swallowed (if used for duodenal ulcers), may decrease effects of ketoconazole, ciprofloxacin, tetracycline, phenytoin, warfarin, quinidine, theophylline, and norfloxacin

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Caution in renal failure and conditions that impair excretion of absorbed aluminum (when swallowed)

Gelclair Bioadherent Oral Gel

Adheres to mucosal surface of mouth and forms protective coating that shields exposed and overstimulated nerve endings. Ingredients include polyvinylpyrrolidone, hyaluronic acid, glycyrrhetinic acid, and water.

Dosing

Adult

Prepare single-dose packet; rinse and gargle for 1 min then spit out

Pediatric

Administer as in adults

Interactions

None

Contraindications

None

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

None

Growth factors

Human KGF may be considered for hematologic malignancies.[5]

Palifermin (Kepivance)

Human KGF that enhances epithelial cell proliferation, differentiation, and migration. KGF receptor not present on hematopoietic cells, but has enhanced growth of human epithelial tumor cell lines in vitro. Indicated to decrease severe OM incidence and duration in patients with hematologic malignancies.

Dosing

Adult

60 mcg/kg/d IV for 3 consecutive days before and 3 consecutive days after myelotoxic therapy for a total of 6 doses

Pediatric

Not established

Interactions

Data limited; binds to heparin in vitro (if heparin used to maintain an IV line, rinse line with 0.9% NaCl before and after administration)

Contraindications

Documented hypersensitivity to *Escherichia coli* –derived proteins, palifermin, or other product components

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Safety has not been established with nonhematologic malignancies; common adverse effects include skin toxicities (eg, rash, erythema, edema, pruritus), oral toxicities (eg, tongue discoloration, tongue thickening, dysgeusia), pain arthralgias, and dysesthesia; potential for immunogenicity (antibodies to palifermin), as with other proteins; do not filter; protect from light

Follow-up

Further Inpatient Care

- Oral mucositis (OM) is self-limiting in most patients. If lesions persist or secondary complications occur, consider other etiologies and treatments as discussed above.

Deterrence/Prevention

- Although oral mucositis cannot be effectively prevented, measures discussed in Treatment may help to reduce the severity of lesions and the risk of developing septicemia.

Complications

- A wide range of complications are associated with oral mucositis, including, but not limited to, the following:
    - Increased risk of local and systemic infection
    - Poor nutrition
    - Dehydration
    - Interruption of cytoreductive therapy
    - Increased length of hospitalization
    - Increased cost of treatment

Prognosis

- Oral mucositis is self-limiting.

Patient Education

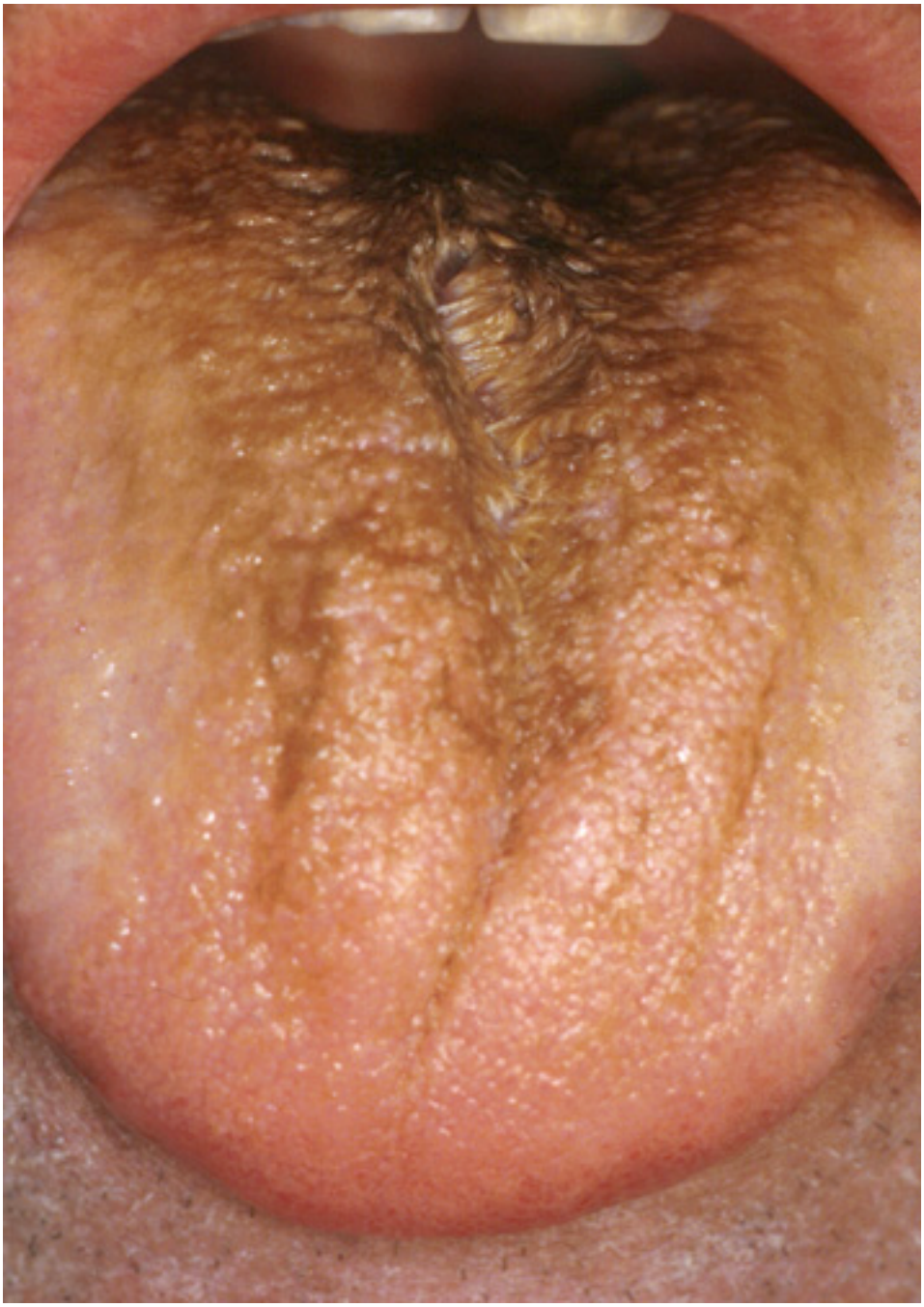
- The patient should understand the predisposing factors and the natural course of oral mucositis. Adherence to an oral hygiene regimen during hospitalization helps to minimize the risk of infection or the exacerbation of lesions.
- For excellent patient education resources, visit eMedicine's Cancer and Tumors Center. Also, see eMedicine's patient education article Cancer of the Mouth and Throat.

Miscellaneous

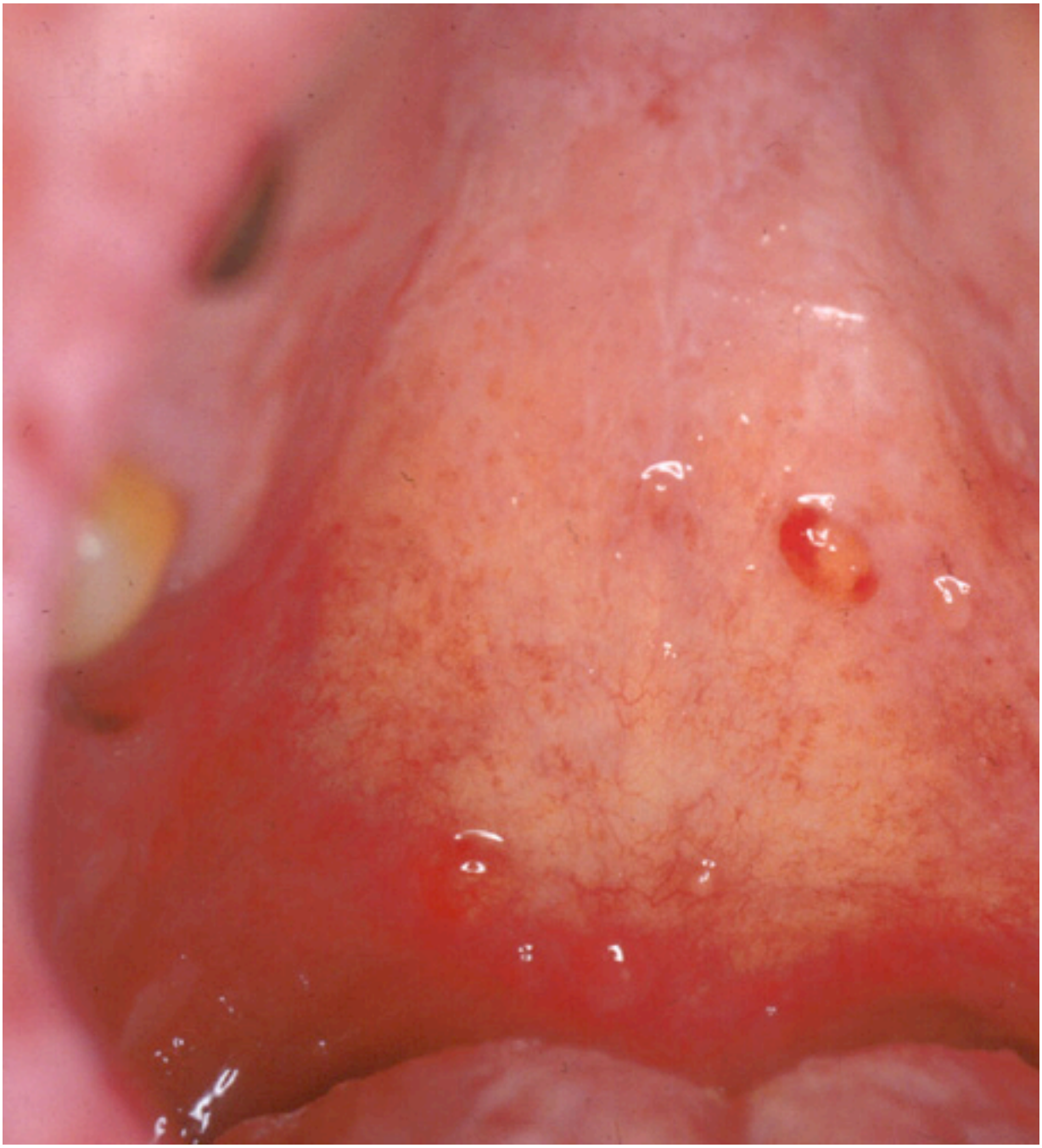
Medicolegal Pitfalls

- A high index of suspicion of secondary or concomitant infection in lesions of oral mucositis is imperative. Cultures should be obtained to rule out such infections. Effective antimicrobial treatments are available for herpetic infections or secondary bacterial infections. The failure to make the diagnosis and, therefore, to treat such conditions may lead to dissemination of infection or unnecessary and prolonged pain and suffering.

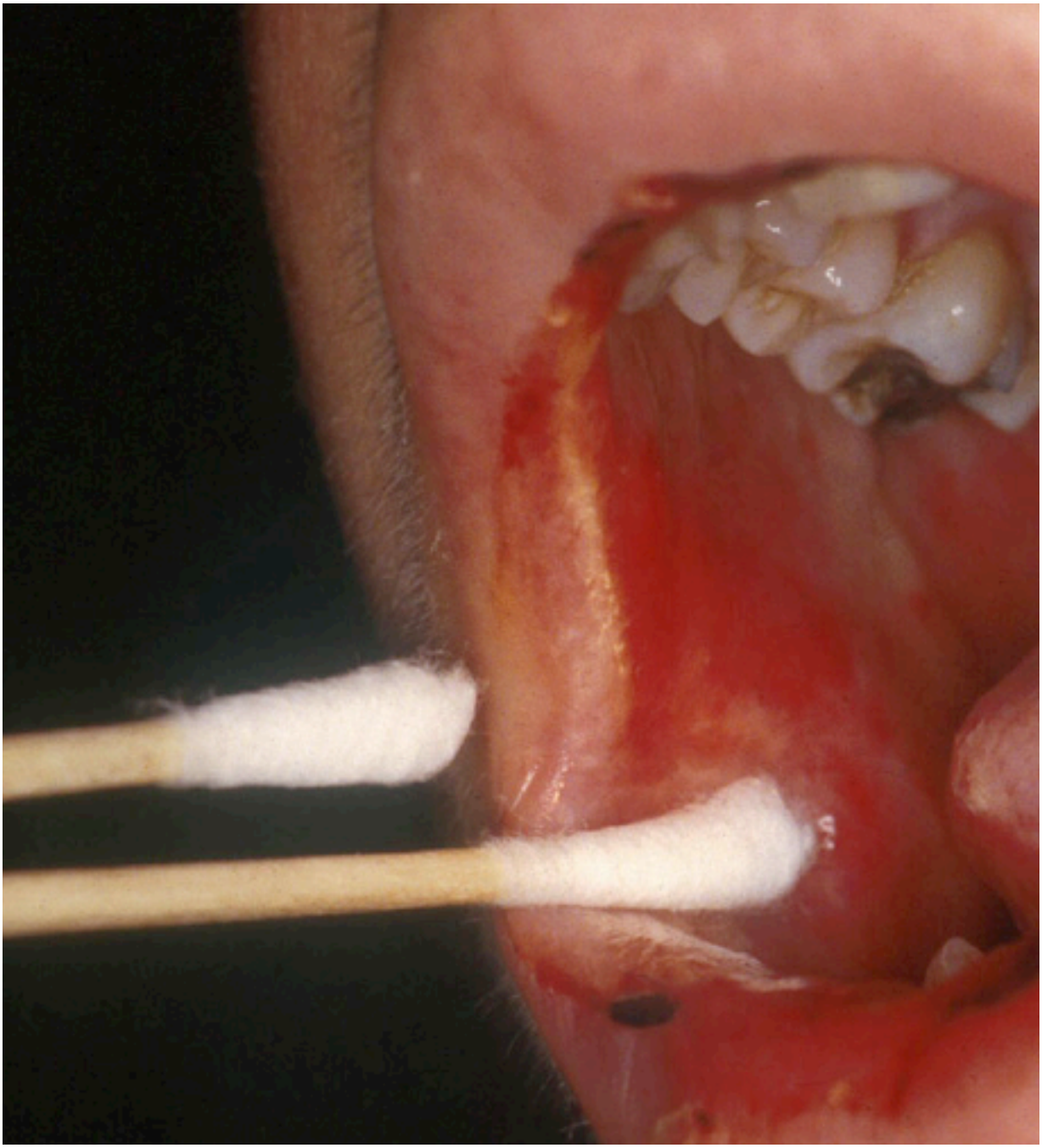
Multimedia



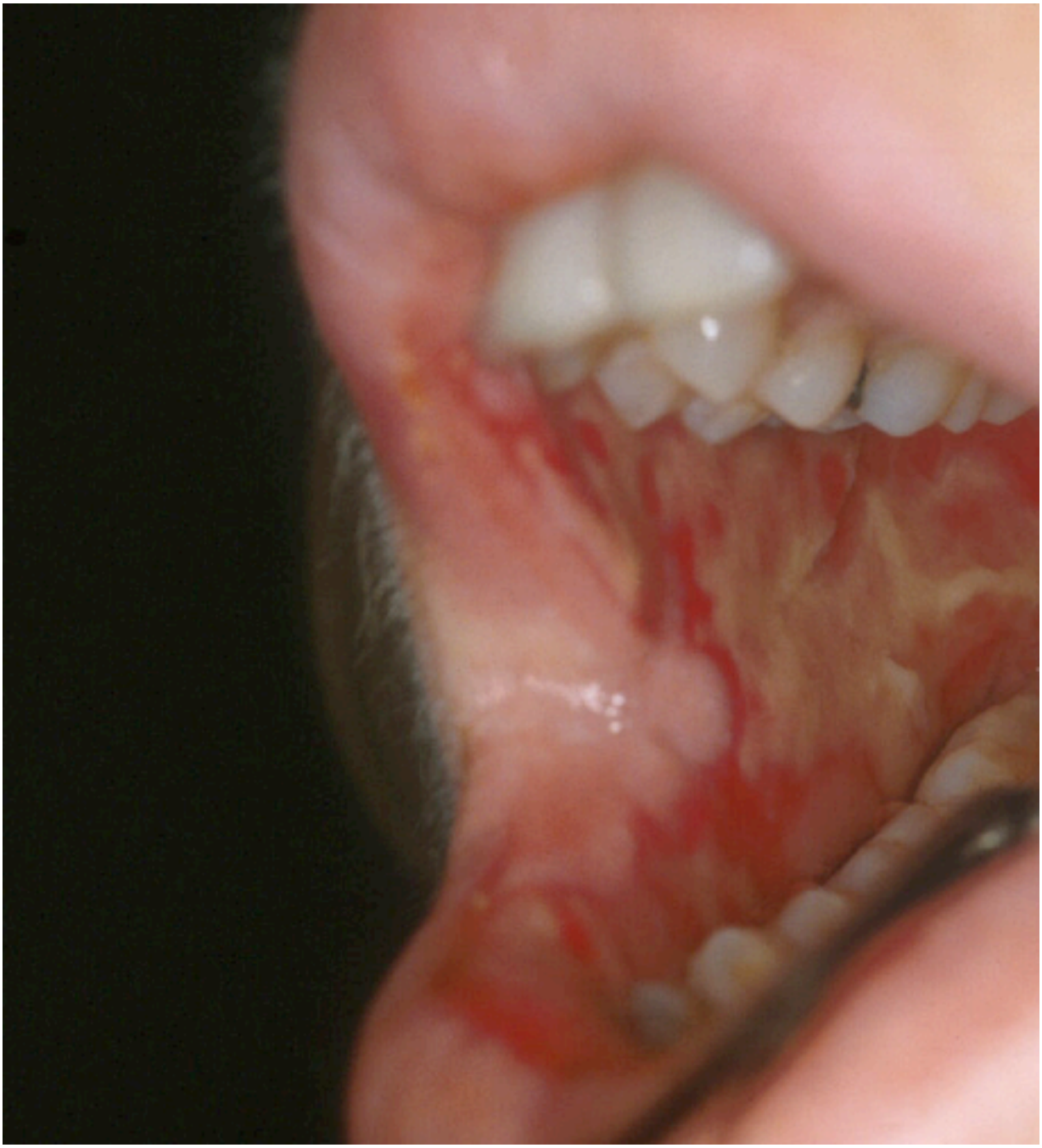
Media file 1: Hairy tongue.



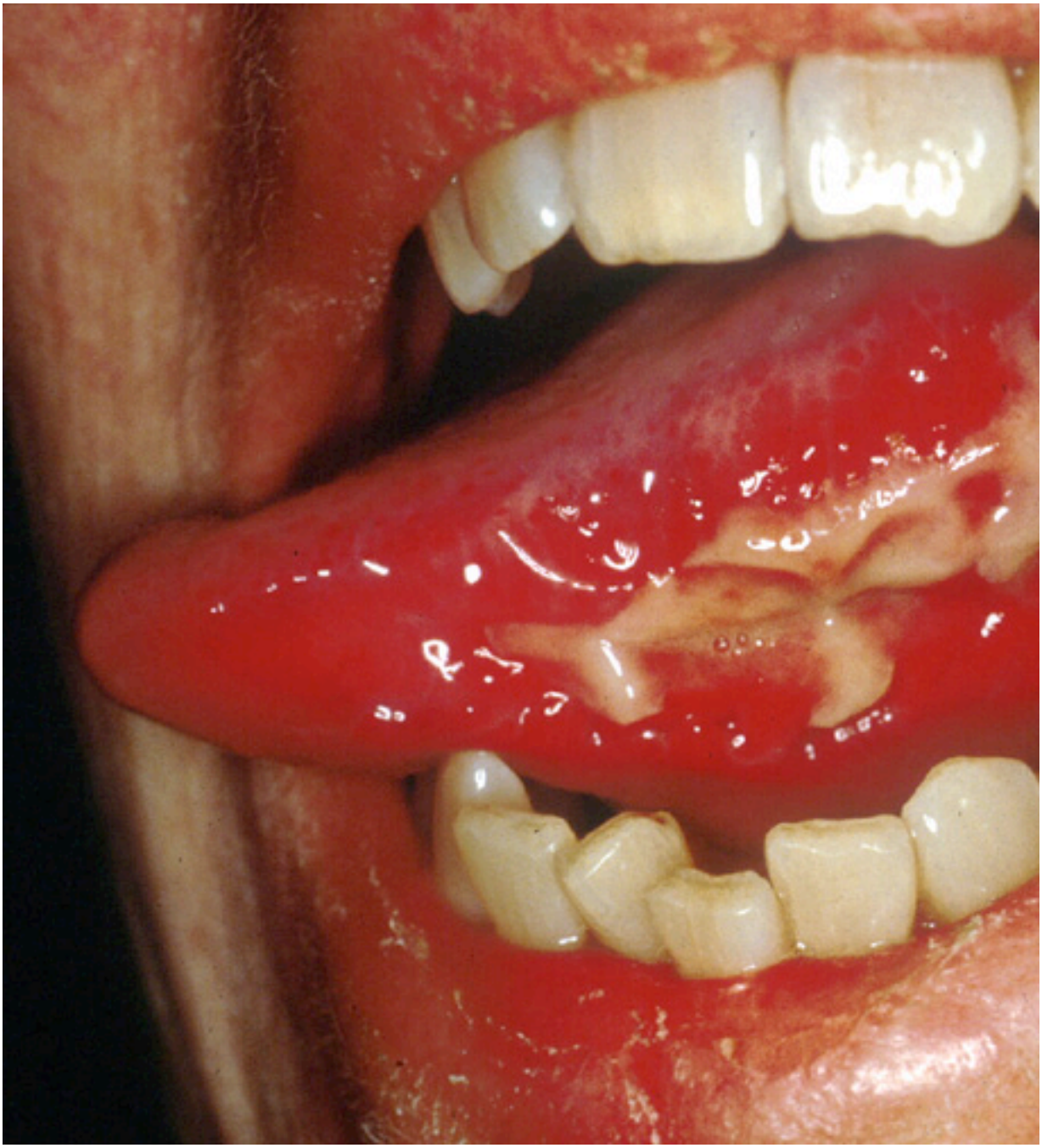
Media file 2: Multiple mucoceles on the hard palate.



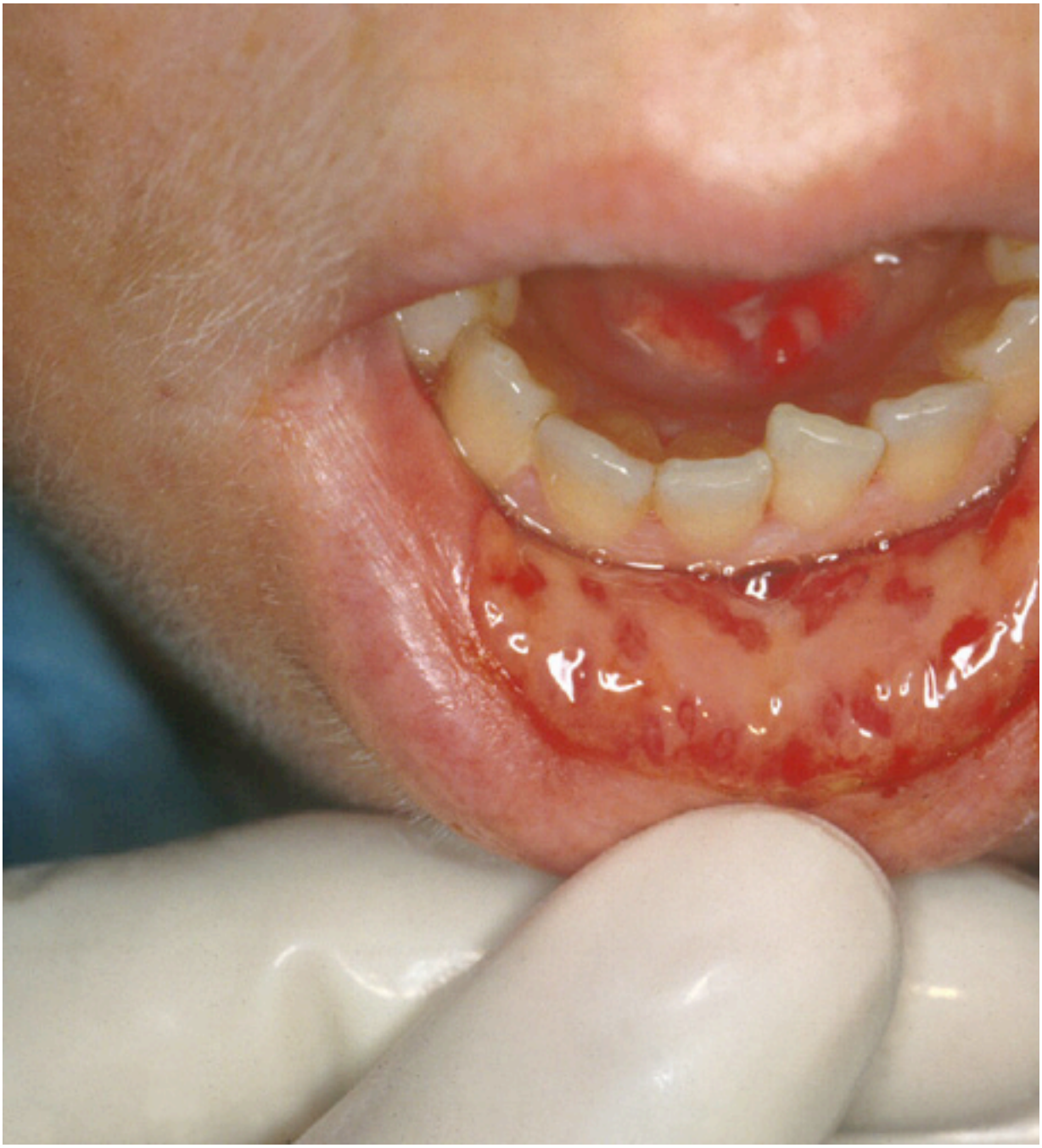
Media file 3: Erythematous oral mucositis lesion on the buccal mucosa.



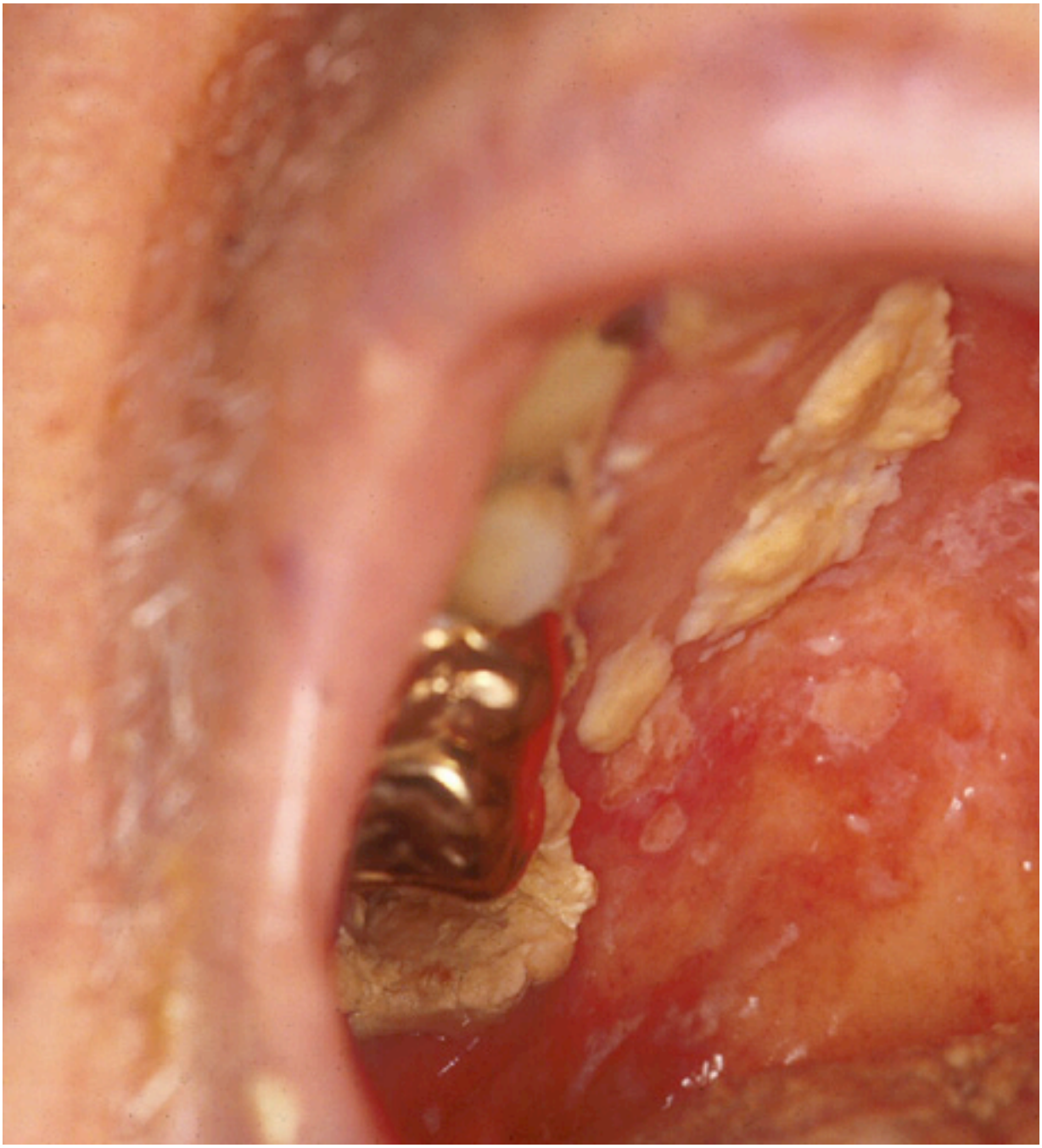
Media file 4: Ulcerative oral mucositis lesion on the buccal mucosa.



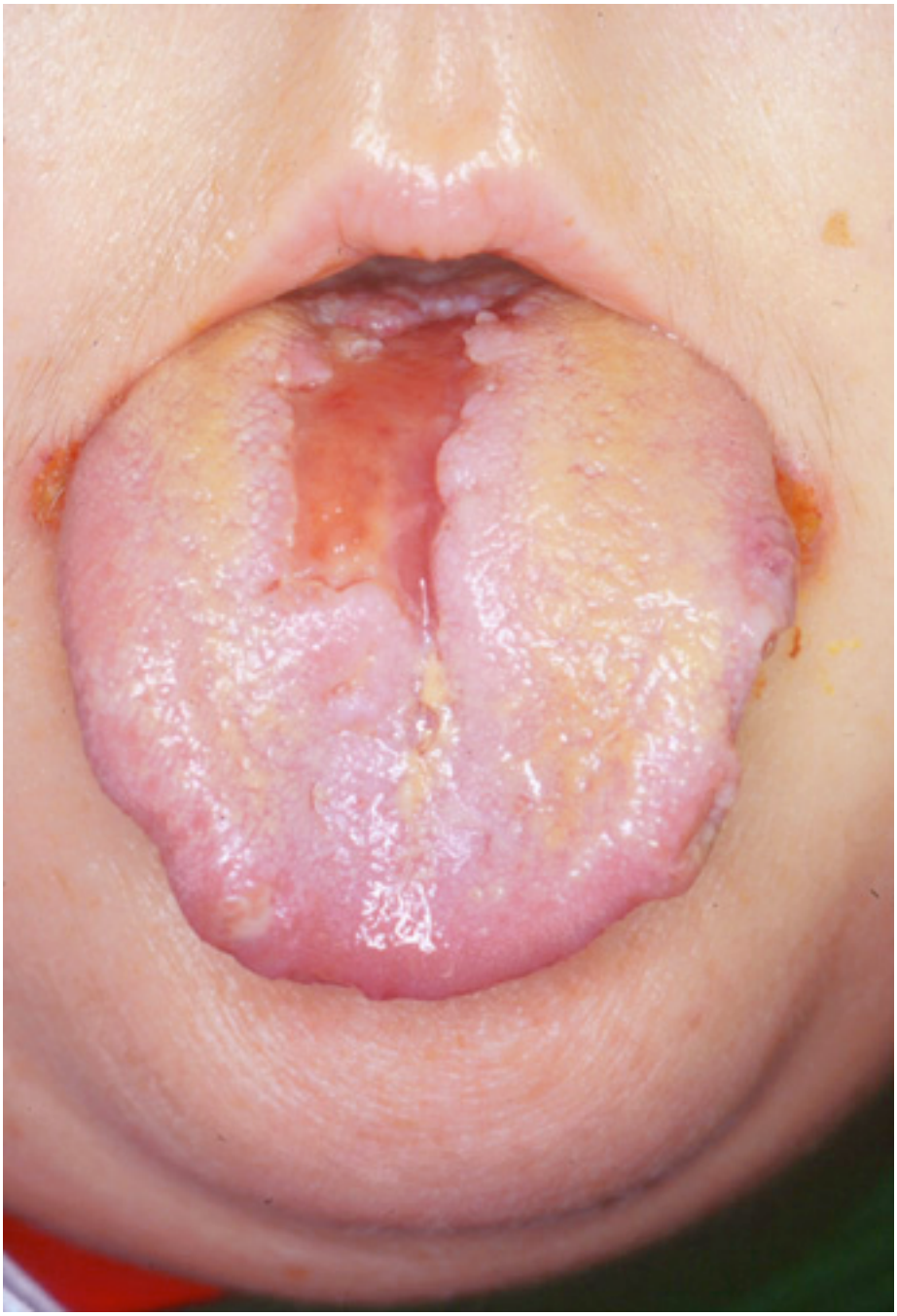
Media file 5: Ulcerative oral mucositis lesion on the lateral and ventral surfaces of the tongue.



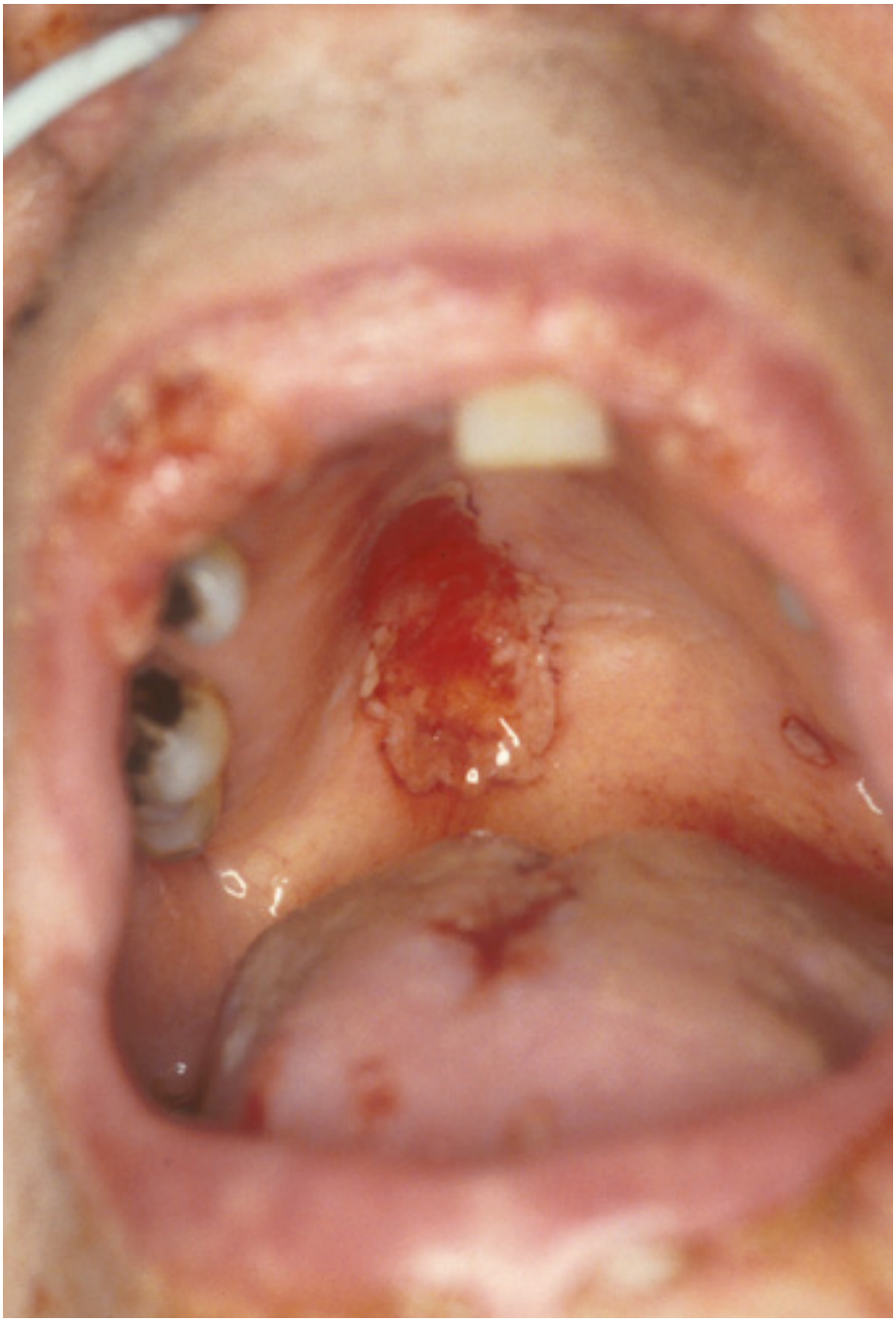
Media file 6: Ulcerative oral mucositis lesions on the labial mucosa and the floor of the mouth.



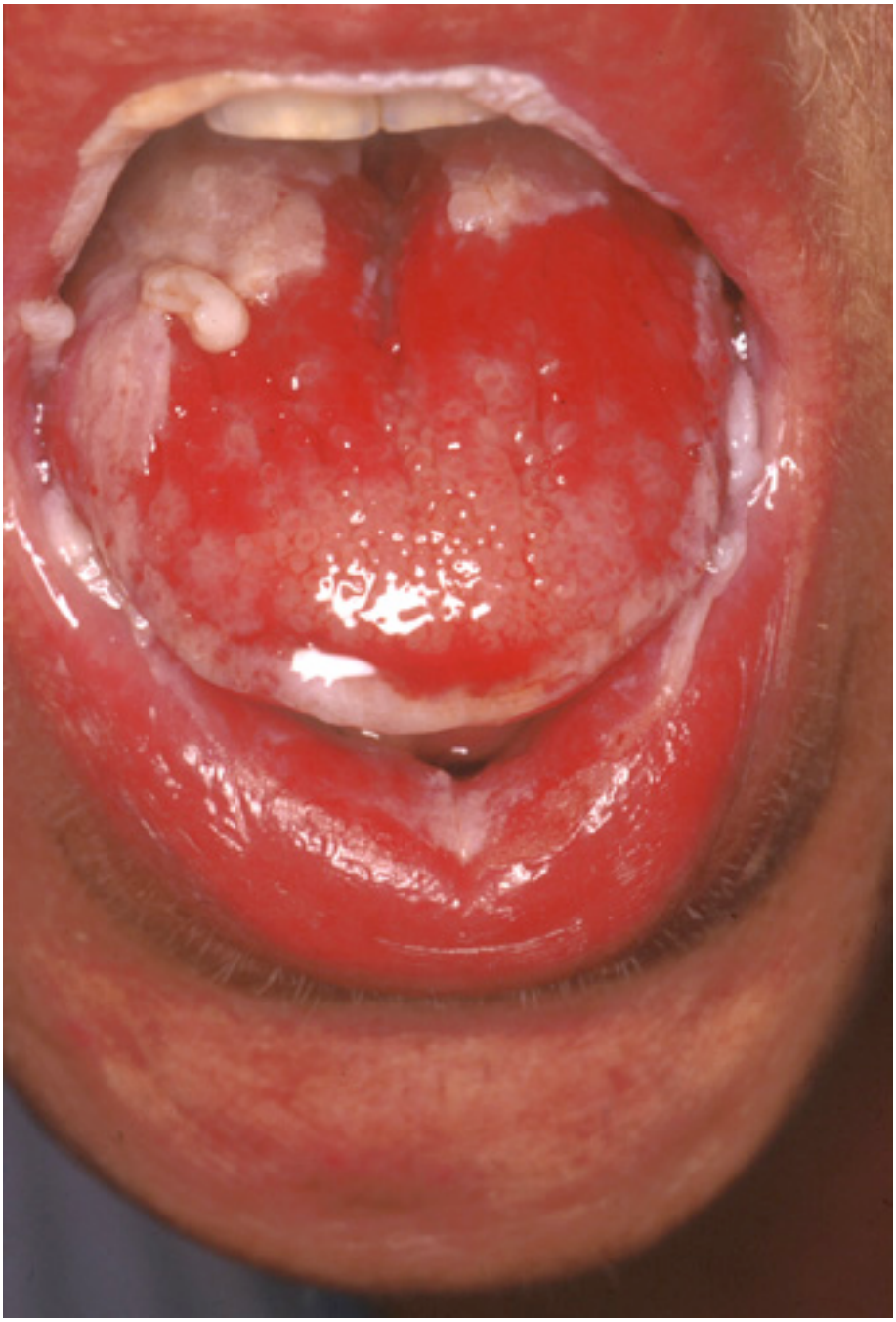
Media file 7: Oral pseudomembranous candidiasis on the hard palate.



Media file 8: Herpes simplex virus ulceration on the dorsal surface of the tongue.



Media file 9: Herpes simplex virus ulceration on the hard and soft palate. Note lesions on the right upper lip and the dorsum of the tongue.



Media file 10: Acute graft versus host disease involving the dorsal surface of the tongue. This is a keratinized site that is usually not involved by oral mucositis.

References

1. Ruescher TJ, Sodeifi A, Scrivani SJ, Kaban LB, Sonis ST. The impact of mucositis on alpha-hemolytic streptococcal infection in patients undergoing autologous bone marrow transplantation for hematologic malignancies. *Cancer*. Jun 1 1998;82(11):2275-81. [Medline].
2. Bochud PY, Calandra T, Francioli P. Bacteremia due to viridans streptococci in neutropenic patients: a review. *Am J Med*. Sep 1994;97(3):256-64. [Medline].

3. Stiff PJ, Erder H, Bensinger WI, Emmanouilides C, Gentile T, Isitt J, et al. Reliability and validity of a patient self-administered daily questionnaire to assess impact of oral mucositis (OM) on pain and daily functioning in patients undergoing autologous hematopoietic stem cell transplantation (HSCT). *Bone Marrow Transplant*. Feb 2006;37(4):393-401. [Medline].
4. Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer*. Mar 1 2007;109(5):820-31. [Medline].
5. Spielberger R, Stiff