History and Physical Examination, Screening and Diagnostic Testing

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KEYWORDS
- Oral mucosal disorders • Oral examination
- Oral cancer screening • Optical detection techniques
- Oral cancer biomarkers

INTRODUCTION

Oral diseases often reflect systemic health as well as local reactions to irritation. It is the role of the oral health professional to understand these disease processes for a timely diagnosis and treatment of potentially life threatening conditions. A precise history and physical examination and appropriate screening and diagnostic testing are at the center this process. This paper reviews this process and discusses the accuracy of screening and diagnostic testing for the patient with oral pathology. Newer oral cancer screening technology like salivary biomarkers and optical detection techniques are exciting developments in oral cancer detection and are discussed here. A more complete review should include the many excellent resources in oral medicine and oral pathology including Burket's *Oral Medicine* 11th edition, 2008,[1] and *Oral & Maxillofacial Pathology* by Brad Neville DDS, 3rd edition, 2008.[2]

HISTORY

A detailed patient history is the foundation for an accurate diagnosis. An incomplete history leads to a flawed diagnosis, unnecessary testing, a delay in disease management, and possibly a misdiagnosis. The surgeon has the responsibility to minimize patient risk by defining the patient's comorbidities and instituting appropriate measures and treatments. Previous medical records, including operative reports, radiographic and laboratory information pertaining to the patient's problem are important sources of information and should be used whenever possible to supplement an accurate history.

The chief complaint should be evaluated by determining onset, location, duration, intensity, frequency, progression, character, severity, triggers, factors that improve or worsen the condition, effect on function, and results of previous treatments. The symptoms of pain, burning, dry mouth, paresthesia, hypesthesia, swelling, texture, and visual abnormality evaluated with the patient's pertinent medical history gives the surgeon an initial level of concern regarding the urgency of the complaint.

The past medical and surgical history can often reveal pertinent information from childhood and adult illnesses, previous surgery, and anesthetic complications that can be critical in the patient's care. More often than not oral soft tissue disease represents infectious, traumatic, or a reactive systemic process rather than a neoplastic process. Therefore, additional comprehensive histories of autoimmune disease, allergic disease, cardiovascular disease, hypertension, diabetes, hyperthyroidism, infectious disease, as well as cancer are important considerations in developing an accurate diagnosis.

A drug allergy history should differentiate true allergies from side effects of medications. Latex protein allergens can rapidly incite anaphylactic shock in sensitive individuals; children with spina bifida are a high-risk group for latex allergy. Patients with soy or egg allergies may react to propofol, and patients allergic to shellfish may have contrast allergies. Patients with ester type local anesthesia allergies should avoid cocaine, procaine hydrochloride (Novocain), and tetracaine (Pontocaine). Ester class anesthetics have 1 letter i in the name; the amide class has 2 (lidocaine, mepivacaine). The medication history of current prescription and nonprescription medications, their dosages, schedules, and patient compliance should be reviewed and recorded.

The social and family history can indicate social, environmental, and genetic risk factors associated with certain diseases that can affect the diagnosis. Tobacco exposure, specifically cigarette, cigar, pipe and chewing tobacco history should be recorded. If possible, alcohol consumption should be quantified as type, frequency, and duration of use. Recreational drug use and lifestyle risk factors for communicable diseases like human immunodeficiency virus (HIV), hepatitis, and tuberculosis should be addressed. Exposures to hazardous materials, environmental toxins, and accidental radiation exposure may be important to discuss and document. Family history for genetic disorders, diabetes, heart disease, allergic and autoimmune diseases, and cancer can be important questions when looking for diseases that can have a genetic basis and have not been considered before.

Table 1 lists a recent history of the pertinent system disorders that may contribute to the chief oral complaint. It should include recent constitutional changes such as weight loss, fatigue, night sweats, rashes, heat and cold intolerance, and others that might give insight into the patient's problem.

PHYSICAL EXAMINATION

This physical examination section is limited to a comprehensive head and neck examination. References for examination of systems other than the head and neck can be found in *Bates' Guide to Physical Examination and History Taking*[3] or other guides to the physical examination. During the comprehensive head and neck examination it is important to look, listen, and feel the site being examined. Manual and bimanual palpation of high-risk areas, especially the tongue base, tonsils and floor of mouth (FOM), salivary glands, and thyroid may detect primary cancers early before they become metastatic. Listening to the patient's voice and speech are important in consideration of tumor location. A hot potato voice may represent an oropharyngeal tumor and a raspy hoarse voice might suggest a laryngeal neoplasm. The examination

proceeds in 3 phases: (1) obtaining vital signs; (2) examination of the head, neck, and the oral cavity; (3) obtaining radiographic and laboratory studies. Additional special examinations of other organ systems may be necessary for patients whose signs and symptoms are suggestive of a systemic cause. A detailed physical examination of a patient of the opposite sex should be done in the presence of a medical assistant of the same gender as the patient. History taking helps the clinician to develop a rapport with the patient to allow the patient to feel comfortable and confident during the examination. Explaining what you are about to do helps put the patient at ease; it is also a time to educate the patient about the early signs and symptoms of head and neck cancer. The examination must be done using universal precautions, protective gloves, eyewear, and a mask if indicated. The clinician should have adequate equipment and supplies on hand for an efficient and professional examination, such as a good light source, mirrors, tongue blades, 2×2 gauze pads, topical decongestants, anesthesia, suction, flexible nasopharyngoscope, pneumatic otoscope, and a nasal speculum.

HEAD AND NECK EXAMINATION
General Appearance

Changes in appearance such as weight loss, anorexia, and fatigue could indicate malignancy.

Head and Neck

Inspect the head and neck for facial tone or palsy, skin changes, discoloration, pigmentation, ulceration, asymmetry, neck range of motion in flexion, extension, and lateral bending. Palpate the facial bones for asymmetry, masses, scalp abnormalities, swelling, and temporal wasting. Palpate the cervical chain lymph nodes. These are divided into large and smaller anatomic triangles or into lymph node regions (levels). The latter are endorsed by the American Head and Neck Society and the American Academy of Otolaryngology - Head and Neck Surgery. Level IA are the submental nodes, level IB are the submandibular nodes. Level II is part of the upper jugulodigastric chain above the hyoid bone (**Fig. 1**A). Level II is divided into IIB above and IIA below the spinal accessory nerve. Level III extends from the hyoid to the cricoid and level IV from the cricoid to the clavicle (see **Fig. 1**B). Level V is the posterior triangle and is separated into VA (spinal accessory nodes) above and VB (transverse cervical and supraclavicular nodes) below (see **Fig. 1**C). The parotid (or preauricular), retroauricular, and suboccipital node regions are denoted P, R, and S but are not part of this classification system. Infection produces mobile and tender nodes, whereas malignancy produces asymptomatic and fixed nodes. Auscultation of the neck with the bell of the stethoscope of a thyroid goiter can indicate Graves disease, carotid bruits, or the sounds of airway obstruction over the larynx and trachea.

Thyroid

Inspect the thyroid gland first then proceed to palpation. The normal thyroid gland is often difficult to feel. Palpation can be from the front or for the heavy neck by standing behind the patient. Palpate the entire gland. Have the patient turn toward the examining side to relax the sternocleidomastoid muscle. During palpation of the lobe ask the patient to swallow, this elevates the gland upward and may help identify a nodule. Note the characteristics of any nodules or abnormality as cystic or hard and record tender areas. If the inferior pole of the gland is difficult to palpate it may suggest substernal extension of the thyroid gland.

Table 1
Review of systems

System	Review
General	General health, blood pressure, weight change, appetite, weakness, fatigue, fever, night sweats, sleeping pattern, unexplained falls
HEENT	Head: headache or facial pain, head injury; change in vision, pain, inflammation, infections Eyes: double vision, scotomata, blurring, tearing, glaucoma Ears: hearing loss, tinnitus, deafness, ear pain, or discharge; light-headedness, dizziness *Nose:* nasal obstruction, bleeding, discharge, sinusitis, allergies Throat: dental problems, ulcers or sores in the mouth, bleeding, dryness, tumors; saliva gland diseases, bad breath or taste in mouth, denture fit, hoarseness, dysphagia, sore throat, swollen glands in the neck, neck masses, thyroid disease, neck pain, or decreased motion
Breasts	Masses, change in contour or skin color, nipple discharge, pain
Respiratory	Cough, sputum color, hemoptysis, dyspnea, wheezing, pleurisy, asthma, bronchitis, emphysema, pneumonia, tuberculosis, chronic obstructive pulmonary disease, night sweats, nocturnal dyspnea
Cardiovascular	Cardiac: heart disease, arrhythmias, hypertension, angina, rheumatic fever, murmur, palpitations, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, myocardial infarction, congestive heart failure, swelling feet or ankles, bacterial endocarditis, electrocardiogram or other test results. Heart surgery and prosthetic heart valve patient is at risk for sub-acute bacterial endocarditis (SBE) Vascular: claudication, varicosities, blood clots, extremity swelling or color change in cold weather, redness, or tenderness. Vascular diseases common to head and neck include hemangioma, arterial/venous/lymphatic malformations, Kaposi sarcoma, Sturge-Weber syndrome, hereditary hemorrhagic telangiectasia or Osler-Weber-Rendu (see **Fig. 3**A)
Gastrointestinal and hepatic diseases	Dysphagia, globus, heartburn, appetite, nausea, bowel habits, stool size and color, pain on defecation, bleeding, hemorrhoids, constipation, diarrhea, food intolerance, jaundice, liver or gall bladder problems, hepatitis, cirrhosis, peptic ulcer disease. Inflammatory bowel disease (IBD)/ulcerative colitis and Crohn disease are associated with increased risk of aphthous stomatitis in both, cobblestone mucosa, lymphadenopathy, and periodontitis in active Crohn disease. Immunosuppressants used to treat IBD including steroids, azathioprine (Imuran), cyclosporine (Neoral), and methotrexate can aggravate infection and may cause gingival hyperplasia
Urogenital	Urinary frequency, retention, polyuria, dysuria, nocturia, urgency, pain/burning, bleeding, infections, flank pain, stones colic, suprapubic pain, incontinence, chronic renal failure, dialysis

Endocrine	Thyroid disease, goiter, exophthalmus, heat or cold intolerance, excessive sweating, thrust or hunger, tremor, palpitations, polyuria, polydipsia, mood swings, depression, visual changes, thin hair, constipation, dry skin, change in hat, glove or shoe size, diabetes mellitus, adrenal disorders, steroid therapy, lactation, pregnancy. intravenous bisphosphonates (Aredia, Bonefos, Didronel, or Zometa) for hypercalcemia and bone pain associated with metastatic breast cancer, prostate cancer, and multiple myeloma are at high risk for bisphosphonate-associated osteonecrosis of the jaw especially after dental extraction (see **Fig. 14**A)
Neurologic	Headaches, strokes, seizures, attention, speech, memory, judgment, dizziness, weakness, imbalance, blackouts, paralysis, numbness, tingling, tremors, incontinence, seizure disorders, cerebrovascular disease, orofacial neurologic disorders (glossodynia, trigeminal neuralgia, Costen syndrome, burning mouth syndrome, and others)
Hematologic	Anemia, purpura, bruising or bleeding, anticoagulant therapy, past transfusions and reactions, hematologic malignancies, leukemia (see **Fig. 14**B and C), lymphoma (Hodgkin and non-Hodgkin lymphoma), transplantation, hemostasis during surgery, infection risk (HIV, hepatitis), hematologic disease may cause oral lesions (see article on this topic in this issue)
Infectious	Viral infections: HSV-1 and HSV-2, chicken pox, varicella zoster, herpangina, coxsackievirus (hand foot and mouth disease), Epstein-Barr (NPC), hepatitis (A,B,C), HIV, human papilloma virus Fungal infections: *Candida albicans*, histoplasmosis, mucormycosis, aspergillosis, blastomycosis, coccidiomycosis Bacterial infections: previous systemic infection, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Staphylococcus aureus*, tuberculosis, previous odontogenic infection, pseudomembranous colitis, oral infections by sexually transmitted disease
Cutaneous	Rashes, lumps, sores, ulcers, decubitus, pruritus, dryness, color change, hair/nails change, change in size/color of moles. Sun exposure history. May have oral manifestations of systemic disease. Oral mucosa pigmented lesions are: endogenous, bilirubin from cirrhosis, iron in hemochromatosis or melanin deposition in Addison disease, Peutz-Jeghers syndrome, McCune-Albright syndrome, Von Recklinghausen disease; exogenous, heavy metal in lead and bismuth toxicity, chromophilic bacteria or fungi in black hairy tongue, foreign material deposits in amalgam tattoo. Mucosal melanoma are dark brown to bluish black and must be differentiated from other oral pigmentation
Musculoskeletal	History and location of muscle or joint pain, redness, weakness, decreased motion, trauma, stiffness, arthritis, gout, backache, or prosthetic joint. High-risk infection in prosthetic joints occurs in new joints (<2 years), prior joint infection, hemophilia, diabetes mellitus, rheumatoid arthritis, and patients on immunosuppressive therapy. Temporomandibular joint is affected by arthritis and is a common source of ear pain. Bone diseases such as osteoporosis can cause thinning of the cortical plate, loss of trabeculation, loss of edentulous ridge, delayed healing of extraction sites, and thinning of maxillary sinuses that may refer pain to the teeth. Other systemic resorptive bone diseases that affect the oral cavity include vitamin D deficiency, osteomalacia (malabsorption syndromes, chronic renal failure), hyperparathyroidism, fibrous dysplasia, McCune-Albright syndrome, Paget disease, histiocytosis, multiple myeloma
Psychiatric	Nervousness, instability, tension, insomnia, mania, memory loss, mood swings, disorientation, depression, suicide ideation. Psychiatric disease and psychotropic medications can cause xerostomia

Fig. 1. (*A*) 38-year-old man with level II lymphadenopathy with histology consistent with Castleman disease. (*B*) 29-year-old woman with isolated level III adenopathy consistent with *Mycobacterium tuberculosis*. (*C*) 34-year-old man with HIV infection and a level V adenopathy from recurrent histoplasmosis abscess.

Salivary Glands

The second most common extra oral mass after lymphadenopathy is a salivary gland neoplasm. Parotid neoplasms are palpated in the preauricular and infra-auricular regions. Sublingual and submandibular gland masses are often tender and are more effectively evaluated by bimanual palpation.

Eyes

The cranial nerves II, III, IV, and VI can be tested here by examining extraocular movements and visual acuity by using a Snelen chart. Eye swelling, epiphora, or neural deficits could represent invasive cancer arising from the nose, sinuses or facial skin.

Ears

The external ears should be closely inspected noting color changes, ulcers, or deformities especially in the sun-exposed areas. Evaluate the external auditory canal for masses, drainage, or obstructing cerumen that may need to be removed to be able to see the tympanic membrane. Assess the integrity of the tympanic membranes by pneumatic otoscopy and hearing acuity with a finger rub or using tuning forks. Exclude ear pathology in the differential diagnosis for referred otalgia.

Nose

The nasal septum and anterior turbinates can be evaluated by anterior rhinoscopy using a headlight and nasal speculum. Nasal endoscopy allows examination of the posterior portions of the nasal cavity and the nasal pharynx. The scope is passed after

applying local anesthetic spray to the nose. It is helpful to view the nose in its native state before and after decongestant use to determine soft tissue obstruction.

Throat

Note the position of the trachea in the anterior neck; deviation may suggest a neck mass or lung abnormality. The oral and pharyngeal examinations are discussed less later.

Temporomandibular Joint

Temporomandibular joint (TMJ) disease can be best identified by TMJ palpation during opening and closing. Examine both joints simultaneously by gently placing the middle finger anterior to the tragus. Tenderness on opening and closing can localize the problem to the TMJ. Maximum opening distance, opening symmetry, popping, clicking, or grinding should be noted. Ear pain after normal ear and TMJ examinations may be referred from cranial nerves IX and X and represent an upper airway carcinoma. Patients at risk for throat cancer should undergo nasopharyngoscopy before treatment of a suspected temporal mandibular disorder.

Cranial Nerves

The cranial nerve (CN) examination (**Table 2**) begins when the patient walks in the room. Eye movement and vision assessment clears CN II–VI and VI. Olfactory nerves can be checked by a simple alcohol sniff test[4] using a 70% isopropyl alcohol disposable pad. Motor assessment of CN V, VII, XI, and XII is by simple jaw, face, shoulder, and tongue movement. Afferent and efferent gag reflex tests CN IX and X. CN VIII can be tested by finger rub or more sophisticated tuning fork testing.

Table 2
Cranial nerve examination

Cranial Nerve	Examination
Olfactory (I)	Test with coffee, vanilla, peppermint, alcohol sniff test, or University of Pennsylvania Smell Identification Test
Optic (II)	Visual fields (Snelen chart), pupillary light reflex, swinging flashlight
Oculomotor (III)	Ptosis, nystagmus, pupillary size (PERRLA), eye movement, accommodation reflex
Trochlear (IV)	Eye movement, superior oblique
Trigeminal (V)	Light touch, pain, temperature, corneal reflex, jaw movement toward side of lesion
Abducens (VI)	Eye movement, lateral rectus
Facial (VII)	Motor: facial muscles, close eyes, wrinkle forehead, smile and show teeth Sensory: taste testing
Auditory (VIII)	Hearing acuity, Rinne test, Weber test, balance function testing
Glossopharyngeal (IX)	Mostly sensory to tonsils, pharynx, posterior tongue, loss of gag reflex (afferent limb)
Vagus (X)	Uvula away from side of lesion, hoarseness, dysphagia, loss of gag reflex (efferent limb)
Spinal accessory (XI)	Shrug shoulders, turn head right and left
Hypoglossal (XII)	Movement deviates toward side of lesion, tongue atrophy or fasciculations

ORAL SOFT TISSUE ANATOMY

The oral examination evaluates the lips, oral cavity, and oropharynx. The oral cavity is the anterior two-thirds of the tongue, the gingiva, buccal mucosa, FOM, hard palate, and retromolar trigone. The oropharynx is the posterior one-third of the tongue, soft palate, tonsils, and the lateral and posterior walls of the visible pharynx.

The oral soft tissues are covered by 3 types of mucosa: nonkeratinized, keratinized, and specialized. Nonkeratinized mucosa is nonmasticatory mucosa, the unattached lining mucosa on lips, cheeks, FOM, ventral tongue, soft palate, and the alveolar mucosa that is not firmly attached to underlying bone. This mucosa can be stretched or compressed and has a basal layer, an intermediate layer, and a superficial layer that does not produce keratin. This is the common site of the aphthous ulcer formation (**Fig. 2**A).

Keratinizing mucosa is masticatory mucosa that is the attached to gingiva around the teeth and hard palate, and is the common site for herpetic ulcer formation. It occurs in parakeratin and orthokeratin forms. Both forms of keratinized epithelium have basal layers, a prickle cell layer (bulk of the epithelium), a granular layer (keratohyaline granules), and a superficial keratin of varying thickness. Parakeratin contains nucleated keratinocytes, whereas the less common orthokeratin contains none. Hyperkeratosis is a microscopic diagnosis of the thickening of the stratum corneum, often associated with a qualitative abnormality of the keratin[5] and can be the result of an irritant or vitamin A deficiency.

Specialized mucosa is papillae on the dorsum and lateral tongue. The filiform papillae are most numerous and guide food in swallowing, and contain no taste buds. In addition to normal filiform papillae in **Fig. 3**A, the patient has small angiomas consistent with her diagnosis of Osler-Weber-Randu. The child in **Fig. 3**B exhibits

Fig. 2. (*A*) Aphthous ulcer formation (*arrow*) on nonkeratinized (unattached) mucosa. (*B*) Pyogenic granuloma (lobular capillary hemangioma) on keratinized (attached) mucosa. (*C*) Similar in appearance to (*B*), this lesion is a peripheral giant cell reparative granuloma, which occurred bilaterally in this patient.
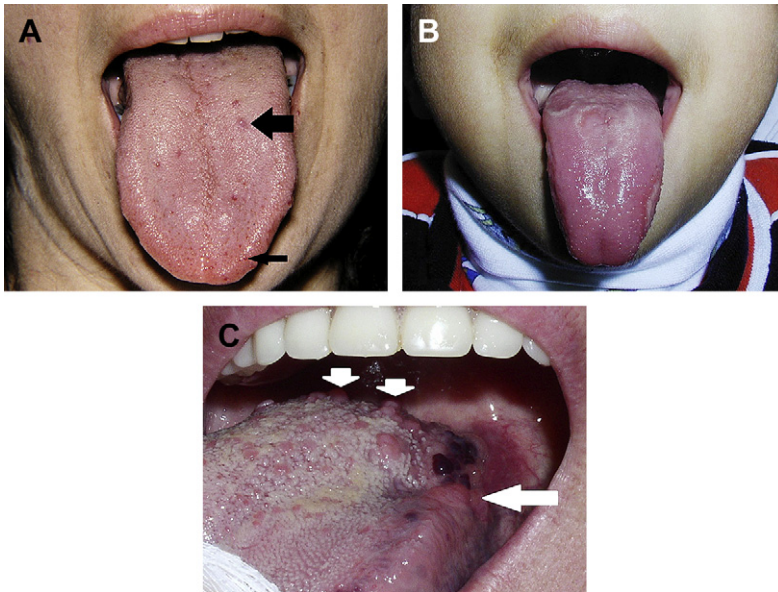
Fig. 3. (*A*) Normal-appearing tongue, small arrow identifies fungiform papillae, and large arrow points to angiomas associated with Osler-Weber-Randu disease. (*B*) Geographic tongue (benign migratory glossitis) and anterior glossitis with prominent fungiform papillae gives a strawberry tongue appearance. (*C*) Posterior tongue with large arrow on folate papillae, small arrows on circumvallate papillae, and a lingual varicosity between the two.

filiform papillae atrophy from benign migratory glossitis. Note the anterior tongue appears similar to strawberry tongue, with fungiform hypertrophy and filiform atrophy giving the tongue an enanthema or bright red background. Strawberry tongue is seen in scarlet fever and can occur in Kawasaki disease. The fungiform papillae (see **Fig. 3**A and B) are red mushroom like structures over the dorsum of the tongue and contain taste buds. The folate papillae (see **Fig. 3**C) appear on the lateral boarders of the tongue and have taste buds. The large circumvale papillae (see **Fig. 3**C) also have taste buds and are 10 to 14 large, raised, round papillae in a V-shaped pattern at the boarder of the anterior two-thirds and posterior one-third of the tongue. In addition, lingual varices can be seen in this region and on occasion the surgeon may be asked to take a biopsy from one of these normal posterior tongue structures because of abnormal presentation.

ORAL EXAMINATION

The areas of greatest risk for oral cancer occur in a U-shaped zone from the tonsillar pillars and oropharynx to the anterior FOM. The relative incidence rates of oral squamous cell carcinoma (SCC) are: tongue (25%), lower lip (30%–40%), FOM (20%), and oropharynx/soft palate (15%).[6] The patient should first remove lipstick and dental appliances so that all oral surfaces can be evaluated. An external light source will allows hands-free examination for bimanual palpation, retraction, and visualization of the posterior tongue and FOM. Mucosal surfaces and salivary duct openings are dried with an air syringe or gauze to allow visualization of color, texture changes, and salivary flow. Early oral cancers present as persistent erythroplastic lesions.[7]

Clinicians should be on the lookout for red lesions as well as white (leukoplakia) lesions, ulcers, bleeding, and indurations.

The oral cavity and adenexa should be examined in a sequential and consistent manner to minimize the possibility of overlooking disease. Start with the upper and lower lip, proceeding to the buccal mucosa and gingiva. Evaluate the oral tongue, FOM, and hard palate. Examine the oral pharynx, tonsils, soft palate, posterior pharynx, and tongue base. Then evaluate the hypopharynx and nasopharynx with the aid of a mirror or nasopharyngoscope.

Lip

Lip cancer can originate primarily from the lip (**Fig. 4**A) or as SCC from the oral cavity or as basal cell carcinoma from the facial skin. Examine the lips visually for intraoral and extraoral lip color, consistency, and shape. The vermilion boarder should be sharp and smooth. Palpate the lip for masses, the gingivolabial sulci, then the gingival mucosa, and teeth. The lower lip may have thickening or leukoplakia from sun damage and can show loss of the vermilion boarder. Edentulous patients who lose vertical dimension (lower facial height) have over closure of the oral commissure and can develop angular cheilitis caused by *Candida albicans.* Recurrent herpes labialis (see **Fig 4**B) can produce target lesions or erythema multiforme of the extremities (see **Fig. 4**C).

Buccal Mucosa and Gingiva

Stretch the buccal mucosa with a mirror or tongue blade and visualize the gingiva, gingivobuccal sulcus, and buccal mucosa. Racial differences are often apparent; dark-skinned patients often have gingival mucosal pigmentation and buccal leukoedema (**Fig. 5**A), which is a benign hydration of the buccal mucosa that may appear as leukoplakia in the posterior regions. Linea alba (white line) is a horizontal line of raised
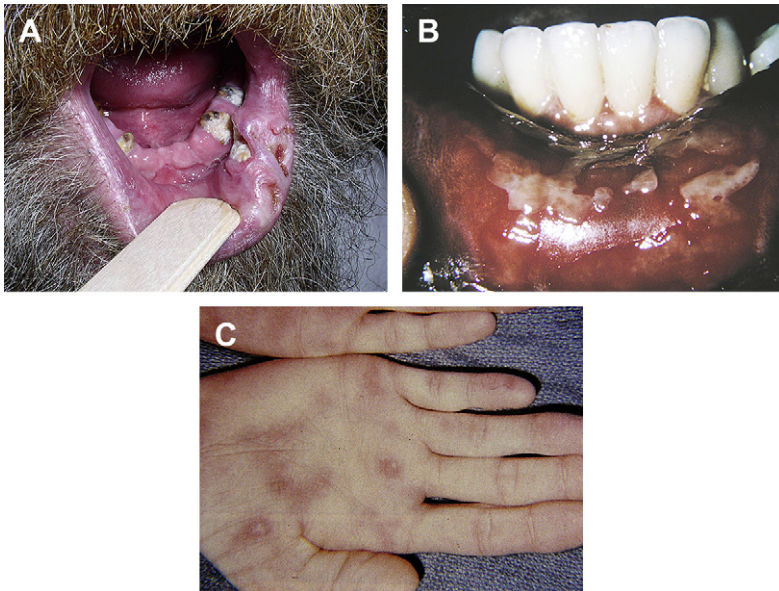

Fig. 4. (*A*) Left lip SCC arising from a previous small lip ulcer left untreated. (*B*) Lower lip herpetic lesion and erythemia multiforme (*C*) hand lesions as a result of the herpetic lip infection.
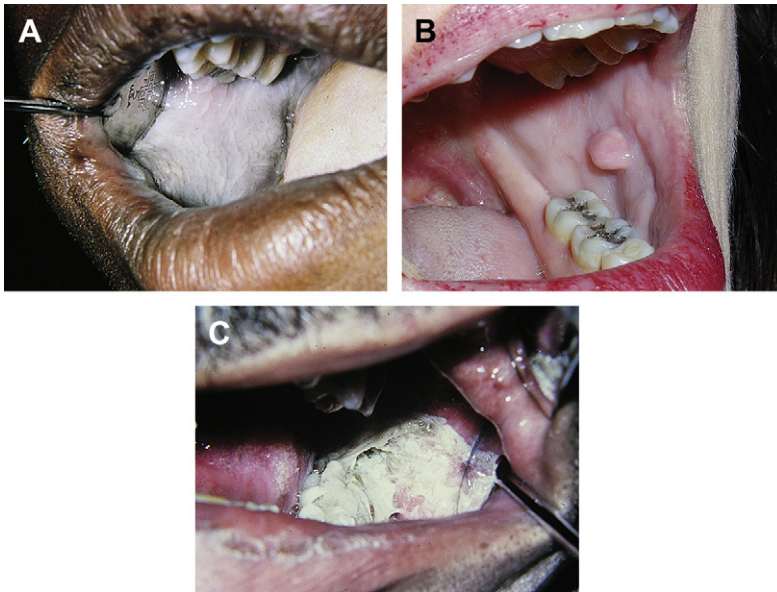
Fig. 5. (*A*) 38-year-old black man with right buccal mucosa leukoedema. (*B*) 31-year-old woman with chronic cheek bit trauma resulting in an irritation fibroma. (*C*) Oral mucosal aspirin burn injury from topical aspirin tablet use for adjacent tooth pain.

buccal mucosa adjacent to the occusal plane. This again is a benign hyperkeratosis from chronic dental irritation in the occusal plane and can also be seen in patients who are nervous cheek biters.[2] Irritation fibroma (see **Fig. 5**B) can occur from cheek bite trauma. Aspirin burn (see **Fig. 5**C) caused by topical analgesic can erode the cheek mucosa. The cheek exhibits white lesions such as lichen planus (see **Fig. 6**A) or less obvious hidden lesions representing invasive SCC (see **Fig. 6**B and C). The nonkeratinized (unattached) gingiva is a common site for aphthous ulcerative lesions (see **Fig. 2**A). Herpes virus type 1 in immune competent hosts commonly infects the keratinized (attached) gingiva. Pyogenic granuloma (lobular capillary hemangioma) (see **Fig. 2**B) and peripheral giant cell reparative granuloma (see **Fig. 2**C) can also be seen on the keratinized (attached) gingiva. The Stensen duct exits the buccal mucosa near the second maxillary molar and should be assessed for parotid flow by milking the parotid gland. Fordyce spots are small, painless, pale yellow ectopic sebaceous glands common to the posterior oral cavity and do not require biopsy. Examine the entire buccal mucosa from the labial commissure back to the anterior tonsillar pillar, then gently pinch the buccal mucosa between your fingers and thumb and feel for hidden masses.

Tongue

The dorsal tongue is examined when the tongue is protruded. Asymmetry in movement, irregularities, and color changes should be noted. The tongue usually deviates to the side of a hypoglossal nerve injury. The tongue is grasped with a 2×2 gauze sponge and drawn carefully forward. Black hairy tongue (lingua villosa nigra) (**Fig. 7**A) occurs as filiform papillae become elongated from abnormal desquamation. This can occur from a liquid diet, tobacco use, or after drinking bismuth subsalicylate (Pepto-Bismol). Absence of filiform papillae in the central tongue will produce medium rhomboid glossitis (see **Fig. 7**B). Neither of these conditions requires a biopsy. Dorsal
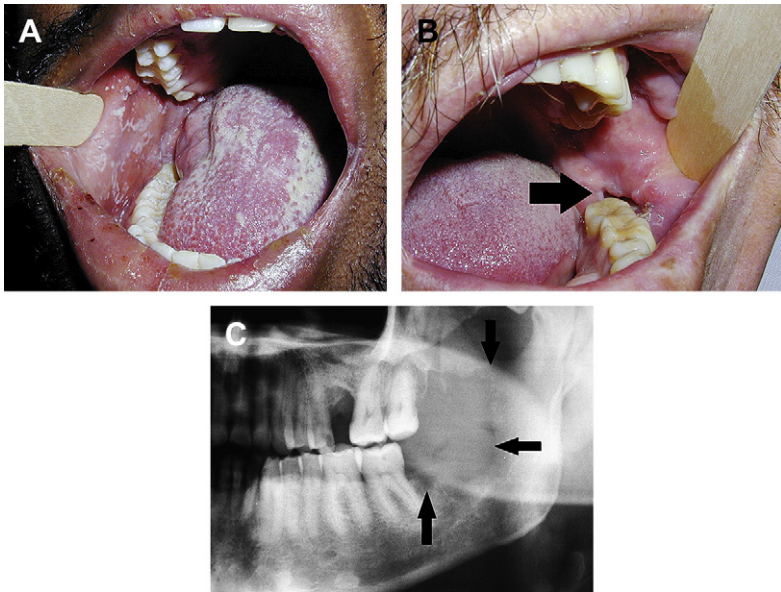
Fig. 6. (*A*) 26-year-old man with weight loss and oral lesions consistent with lichen planus. Note enlarged fungiform papillae on the anterior tongue. (*B*) 46-year-old male with no risk factors presents with an inconspicuous buccal sulcus hole (*large arrow*). (*C*) Pantographic film of patient in (*B*) with black arrows showing areas of bony invasion of the body and ramus by SCC.
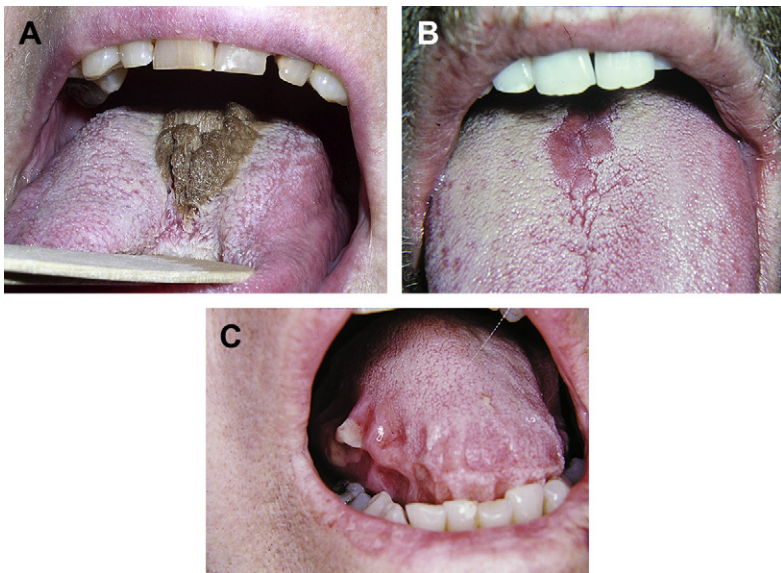

Fig. 7. (*A*) Elongated and pigmented filiform papillae consistent with black or brown hairy tongue. (*B*) Medium rhomboid glossitis, which responded to antifungal therapy. (*C*) Patient with multiple myeloma with macroglossia and dental indentations of the tongue and biopsies consistent with amyloid.

tongue atrophy can be the result of nutritional deficiencies (vitamin B_{12}, folate) or associated with oral manifestations of mucocutaneous disease. Tongue enlargement can suggest systemic disease as in the case of primary amyloidosis (see **Fig. 7**C). The lateral tongue surface is examined by extending the tongue and rotating it. Here there are few papillae and its mucosa is more erythematous. Posteriorly the folate papillae and lingual tonsil can be seen. The lingual tonsil is part of the Waldeyer ring of tonsil tissue and may appear enlarged and abnormal in the presence of infection. The lateral tongue and FOM are common sites for SCC, therefore any suspicious red or white lesion here should be considered for biopsy (**Fig. 8**). The ventral tongue has prominent vasculature and salivary duct openings. The Bartholin ducts arise from the sublingual gland and open in a soft tissue fold known as the plica sublingualis. The Wharton ducts from the submandibular gland open next to the lingual frenulum near the midline. Obstruction of the sublingual mucous ducts produces a bluish FOM with cystic-like swelling or ranula (**Fig. 9**A). Wharton duct obstruction from salivary stones (sialolithiasis) produces inflammation (sialodochitis) in the FOM (see **Fig. 9**B). Both may require surgical intervention.

Floor of Mouth

The FOM is the horseshoe-shaped area between the ventral tongue and the mandibular alveolar ridge, extending to the insertion of the anterior tonsillar pillar into the tongue. It is best seen anteriorly by elevating the tongue to the roof of the mouth. Posterior examination requires elevating the tongue medially and superiorly with a mirror or tongue blade. The FOM, submandibular gland, sublingual gland, and level I lymph nodes are evaluated by bimanual palpation. Torus mandibularis (see **Fig. 9**C) are common benign exostosis found in the FOM that complicate denture fabrication
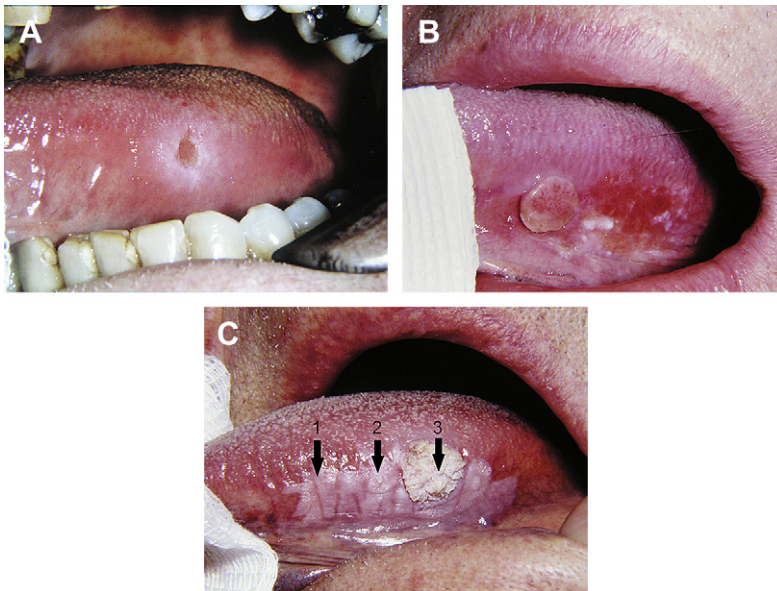

Fig. 8. SCC of the lateral tongue. (*A*) Benign-appearing nonhealing ulcer of the lateral tongue which was consistent with SCC. (*B*) Lateral tongue with a suspicious posterior erythroplakia that was mild dysplasia; the anterior sessile mass was positive for SCC. (*C*) Three lesions on the lateral tongue that represent leukoplakia (*1 arrow*), invasive SCC (*2 arrow*) and verrucous carcinoma (*3 arrow*).
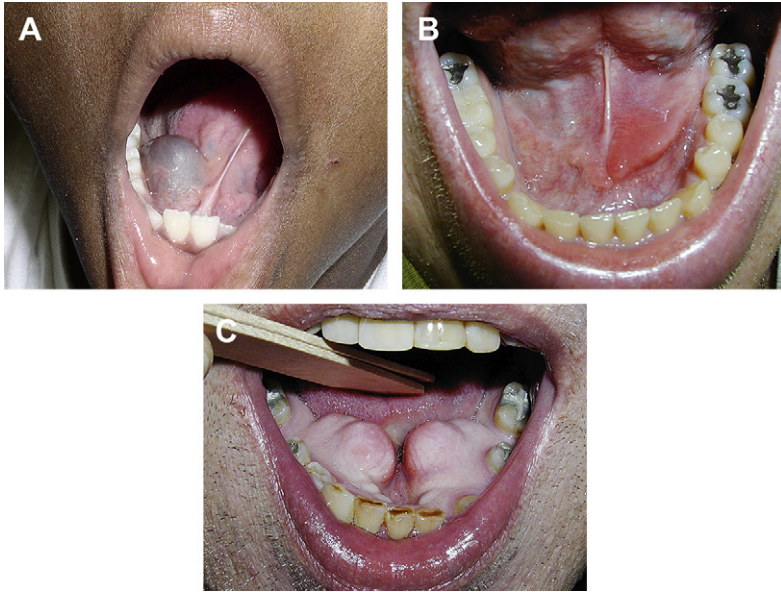
Fig. 9. (*A*) Sublingual duct obstruction in right FOM consistent with ranula formation. (*B*) Left Warthon duct obstruction and inflammation form sialolithiasis. (*C*) This patient presents with anterior FOM boney exostosis or torus mandibularis.

but are otherwise left untreated. Invasive SCC of the FOM (**Fig. 10**A) is common in patients with alcohol and tobacco risk factors. Extra time should be spent evaluating the lateral tongue and FOM because of their hidden nature and risk for cancer especially in the patient with risk factors.

Hard Palate

The hard palate is viewed by tipping the patient's head back. The minor salivary glands here are sites for neoplasia and should be carefully inspected (see **Fig. 10**B). Common benign palatal lesions include torus palatinus (see **Fig. 10**C), stomatitis nicotina or smoker's palate, and oral candidiasis. Dentures may cause a common red velvety erythema or papillary hyperplasia, a benign condition not considered erythroplakia. Upper denture edges can produce tissue redundancy known as epulis fissuratum. An ill-fitting denture is associated with oral cancer[8] and removing the denture during palate examination can help identify suspicious growth (**Fig. 11**A). Hard palate injury may undergo a benign reparative hyperplasia known as necrotizing sialometaplasia (see **Fig. 11**B). The histologic features of these ulcers, known as pseudoepitheliomatous hyperplasia, can imitate carcinoma but are benign. Pseudoepitheliomatous hyperplasia may also be seen in granular cell tumor of the tongue and North American blastomycosis of the larynx.

The Oropharynx

The oropharyngeal examination includes the soft palate, palatine tonsils, posterior and lateral pharyngeal walls, and base of the tongue. This examination is a continuation of the oral cavity examination and the 2 are often completed simultaneously. The oropharynx is the site of human papilloma virus (HPV) infection possibly because of a weakness at the embryonic junction between the oral ectoderm and pharyngeal
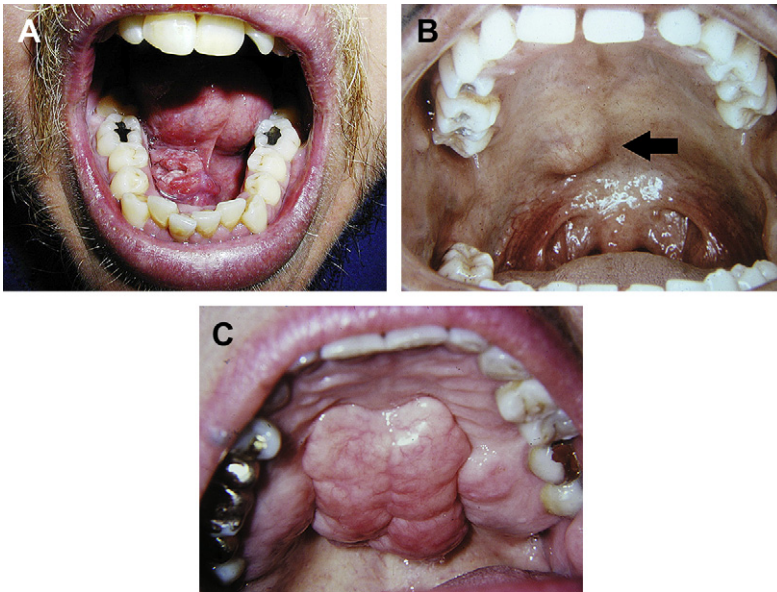
Fig. 10. (*A*) Anterior right FOM ulcerative SCC in a patient with oral cancer risk factors. (*B*) Right palatal mass (*arrow*) consistent with a minor salivary gland pleomorphic adenoma. (*C*) This patient has a large midpalatal exostosis or torus palatinus and adjacent maxillary alveolar exostosis.
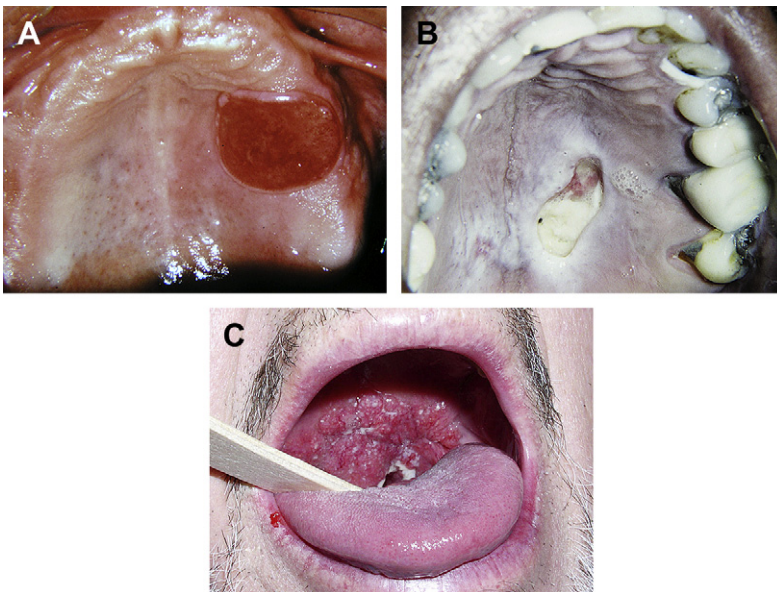

Fig. 11. (*A*) Left maxillary alveolar ridge SCC in a patient who had an ill-fitting denture. (*B*) Left palatal ulcer with pseudoepitheliomatous hyperplasia on biopsy and a diagnosis of necrotizing sialometaplasia. The lesion resolved without treatment. (*C*) Hard and soft palate SCC; biopsies were positive for high-risk HPV.

endoderm, an area known as the buccopharyngeal membrane. Recent increases in oropharyngeal cancer are related to HPV-16 and -18 infections in this area (see **Fig. 11**C).

Palatine Tonsil and Soft Palate

The tonsil, soft palate, and oropharyngeal examination requires depression of the posterior tongue, usually by asking the patient to say "Ahhh," or by mirror or tongue blade retraction. The tonsils and the tonsillar pillars and tonsillar fossa should be evaluated for symmetry and soft tissues abnormalities. Palpation of the palatine tonsil should be considered in cancer evaluation. The soft palate and uvula should be evaluated for masses or mucosal abnormalities. The uvula should be midline or this could represent vagal nerve palsy or peritonsillar space infection or parapharyngeal space mass.

Posterior and Lateral Oropharyngeal Wall

The posterior and lateral oropharyngeal walls can be seen with tongue depression with a tongue blade and soft palate elevation by saying "Ahhh." For adequate evaluation of this region, flexible nasopharyngoscopy should be considered.

Base of Tongue

Inspect the base of the tongue using a laryngeal mirror or flexible nasopharyngoscopy. Visualization is aided by pulling on the tongue with a 2×2 gauze sponge. Administration of 10% benzocaine spray to the tongue base will help reduce pain and gagging. Palpate the dorsum and lateral margins and lingual tonsils with a gloved finger. Masses at the tongue base vary. Some lesions include benign disease such as osseous choristoma (**Fig. 12**A), granular cell myoblastoma (see **Fig. 12**B), or a mucous retention cyst arising in the vallecula (see **Fig. 12**C).

Hypopharynx and Larynx

A thorough inspection of the hypopharynx and larynx is a critical component of the oral, head and neck cancer examination in patients with dysphagia, hoarseness, globus, or who have risk factors for hypopharyngeal or laryngeal cancer. A systematic evaluation for mucosal malignancy of the tongue base, vallecula, epiglottis, larynx, postcricoid and pyriform sinus areas is accomplished with a laryngeal mirror, flexible nasopharyngoscope, or a laryngeal stroboscope.

Nasopharynx

Examination of the nasopharynx can be done through an oral or nasal approach. The patient opens widely and breathes through the mouth, which causes the soft palate to rise. A tongue blade depresses the middle portion of the tongue. A small warmed nasopharyngeal mirror is extended over the tongue blade and into the oropharynx pointing upward. Ask the patient to now breathe through the nose to allow the soft palate to draw forward so that the examiner can see the nasopharyngeal region reflecting in the mirror. Inspect the posterior choanae and posterior part of the nasal septum. Inspect the turbinates and note the mucosa on the upper surface of the soft palate. Slowly rotate the mirror to visualize Eustachian tube openings, the pharyngeal tonsil, and walls of the nasopharynx. Look for masses, ulcerations, or discolorations. If your patient is unable to tolerate this procedure, consider a topical anesthetic or proceed to flexible nasopharyngoscopy.
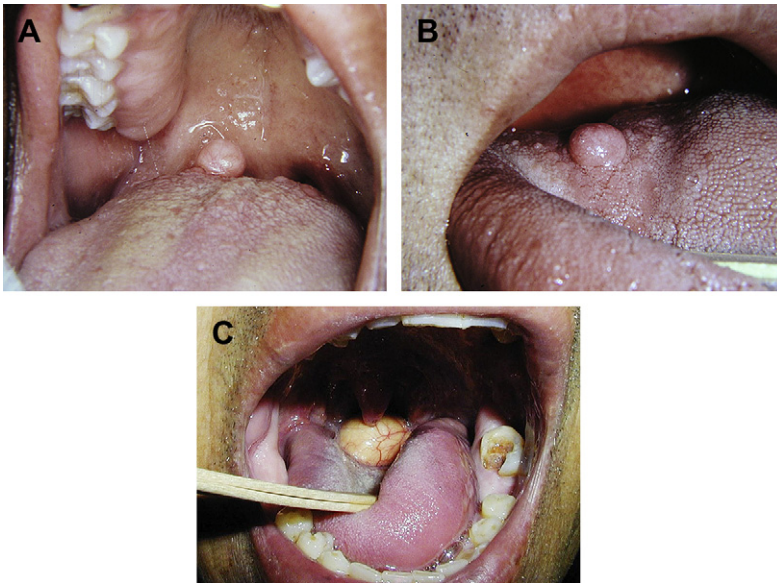
Fig. 12. Posterior tongue and tongue base lesions. (*A*) Osseous choristoma. (*B*) Granular cell myoblastoma. (*C*) Large mucous retention cyst arising from the vallecula producing dysphagia and sleep disturbance.

FLEXIBLE NASOPHARYNGOSCOPY

The flexible nasopharyngoscope has become an essential instrument for detecting head and neck cancers. The nasal cavity, nasopharynx, a portion of the oropharynx, hypopharynx, and larynx can all be thoroughly inspected using this scope. Following topical nasal vasoconstriction and anesthetic sprays, the nasopharyngoscope is carefully passed transnasally into the nasopharynx. The nasal cavity and nasopharynx are evaluated for mucosal lesions, masses, or structural abnormalities. The scope is gently advanced down into the oropharynx and hypopharynx. Examine all of the laryngeal structures as you would for the mirror examination. Then slowly remove the scope.

MIRROR EXAMINATION

Traditionally the laryngeal mirror has been the instrument of choice for examining the hypopharynx and larynx. Ask the patient to sit up straight and slightly protrude the chin upward and forward. Next have the patient open widely and protrude the tongue. Grasp the tip of the tongue with gauze and gently pull it forward. The patient should be concentrating on breathing in and out through the mouth. Carefully insert a warmed laryngeal mirror into the oropharynx, using the back of the mirror to elevate the soft palate. If the patient cannot tolerate this maneuver without gagging, consider 10% benzocaine topical anesthetic spray. Once the mirror is in place, the tongue base, vallecula, pharyngeal walls, and pyriform sinuses are evaluated for abnormalities. The epiglottis shape, position, and mucosal surfaces are closely inspected for abnormalities. The larynx and vocal cords are brought into view by having the patient say a high-pitched "e." Examine the arytenoids, aryepiglottic folds, false vocal cords, and true vocal cords for abnormalities. Assess the mobility of the true vocal cords by having the patient breath in (abduction) and phonate (adduction). If the mirror

examination is insufficient and the patient is at high risk for laryngeal or hypopharyng-eal cancer, a flexible nasopharyngoscope should be used to complete the examination.

SCREENING AND DIAGNOSTIC TESTING

There are limitations of any screening test or diagnostic test. Tests discriminate between the presence or absence of disease or a predictor of disease. The frequency with which a test indicates the presence of a disease is the sensitivity; specificity is the frequency with which a test indicates the absence of the disease.[9] A test that identifies a disease 90% of the time has a sensitivity of 90% and a 10% false-negative rate. A test that identifies the absence of disease 80% of the time has a specificity of 80% and has a 20% false-positive rate. The significance of choosing a test with a certain sensi-tivity or specificity corresponds to the accuracy of the test result.

Screening is looking for cancer before the patient has symptoms; finding a cancer at the early stage makes it easier to treat and improves outcome. Unfortunately by the time the oral symptoms appear cancer may be metastatic. Screening examinations in high-risk patients have shifted from the alcohol and tobacco abuser to those who have multiple partners or who participate in high-risk sexual activities or patients who have previously had oral cancer.

Risk factors for oral cancer include using tobacco products (cigarettes, cigar, pipes, smokeless, and chewing tobacco), heavy alcohol use, betel nut chewing, human papillomavirus infection (HPV-16 and HPV-18), sunlight exposure (lower lip) and being male. Most oral cancers occur in people older than 45 years, more often in blacks than in whites. Even though the total number of new cases and deaths from oral cancer has decreased slowly in the past 20 years, the number of new cases of oral cancer (espe-cially of the tongue) has been increasing in adults less than 40 years of age.

Clinical Oral Examination

The clinical oral examination (COE) is considered a screening test with sensitivity ranging from 60% to 97%. A meta-analysis showed an overall sensitivity of 85% (95% CI 0.73, 0.92) and specificity of 97% (95% CI 0.93, 0.98) indicating a satisfactory test performance for an oral examination.[10] The visual detection of premalignant oral lesions has remained problematic, in contrast to skin lesions such as melanoma, where visual screening has been shown to have sensitivity and specificity of 93% and 98%.[11] One explanation for this discrepancy is that precancerous and early cancerous lesions are often subtle and rarely demonstrate the clinical characteristics observed in advanced cases: ulceration, indurations, pain, or associated cervical lymphadenopathy.[12] Besides their clinical subtlety, premalignant lesions are highly heterogeneous in their presentation and may mimic a variety of common benign or reactive conditions. Furthermore, there is a growing realization that some premalig-nant and early cancerous lesions are not readily detectable to the naked eye. There-fore, additional screening aids for oral cancer are needed.[10]

Toluidine Blue Test

The toluidine blue test (tolonium chloride) is a blue cationic (basic) dye used in histology. Alkaline solutions of the dye bind to nucleic acids and proteins in oral lesions but not normal mucosa. One percent acetic acid, a mucolytic agent is applied or rinsed first. Next a small amount of 1% toluidine blue solution is applied to the lesion and surrounding oral mucosa. The patient rinses with water and any tissue that stains is positive and a biopsy should be taken immediately.[13] Toluidine blue staining

identifies high-risk primary oral premalignant lesions that may be treated before they progress to invasive carcinoma.[14]

Light Visualization Technology

Distinguishing premalignant and malignant lesions from benign mucosa may be difficult by simple observation and resulting delay could mean a poorer prognosis. Noninvasive technology that highlights oral premalignant and malignant lesions in a highly sensitive and specific manner could help clinicians in early diagnosis and treatment of these conditions. Several light visualization technologies (ViziLite, MicroLux, Orascoptic, and VELscope) have been approved by the US Food and Drug Administration for real-time cancer screening. Special light absorption and reflection properties makes healthy tissue and abnormal tissue appear differently. Dental reimbursement code CDT-5 D0431 is used here for oral cancer screening procedures that apply to the adjunctive light screening devices. Medical reimbursement code 2009 ICD-9-CM V76.42 is used for screening for malignant neoplasms of the oral cavity and CPT 82397 is used specifically for a chemiluminescent assay. Intraoral chemiluminescent visualization uses the emission of white light from a chemical source. ViziLite Plus (Zila Pharmaceuticals, Phoenix, AZ, USA) uses a low-energy, blue-white, light stick that reflects off abnormal cells after a 30-second acetic acid rinse. The light enhances visualization of hyperkeratosis as acetowhite lesions, which are seen as a white glow on the epithelial surface. TBlue a toluidine blue-based dye, can be used in conjunction with ViziLite to increase accuracy. A multicenter study by Epstein and colleagues[15] in 2006 reported that the effect of chemiluminescent light on visualization of mucosal lesions did not seem to improve visualization of red lesions, but red lesions with white had enhanced brightness and sharpness.

MicroLux/DL (AdDent Inc, Danbury, CT, USA) and Orascoptic systems (a Kerr Company, Middleton, WI, USA) use a diffused, blue-white, light-emitting diode (LED) light source. The patient rinses with acetic acid for 60 seconds and then the examiner looks for acetowhite lesions. In a study of 50 patients, McIntosh and colleagues[16] in 2009 showed MicroLux/DL had a sensitivity of 77.8% and a specificity of 70.7%, with a positive predictive value of 36.8%. He concluded that although MicroLux/DL seems useful at enhancing lesion visibility, it was a poor discriminator for inflammatory, traumatic, and malignant lesions.

Intraoral direct fluorescence visualization involves a hand-held device that emits a cone of blue light that excites various molecules within the mucosa. The light energy is absorbed and re-emitted as a visible fluorescence. Abnormal tissues attenuate the light and appear dark brown to black.[12,17,18] VELscope (LED Dental, White Rock, BC, Canada) emits a blue light into the oral cavity that penetrates the stratified squamous epithelium, inducing fluorescence in normal cells. Dysplastic and malignant cells will interrupt the light and cause a loss of fluorescence, delineating a dark area of abnormality. Poh and colleagues[12] describe dark areas of cancer (**Fig. 13**) and premalignancy compared with normal tissue using direct fluorescence visualization. More studies must be performed to evaluate the role of the VELscope in screening. Lingen concluded, "There is currently no hard data to support the contention that these technologies can help the clinician to identify premalignant lesions before they are detectable by COE alone. Nevertheless, studies to determine their utility in this setting are anticipated in the near future."[10]

Brush Cytology

OralCDx Laboratories, Inc (Suffern, NY) produces OralCDx Brush Test, a noninvasive oral brush biopsy kit made up of a sterile biopsy brush, 2 fixative packages, a glass
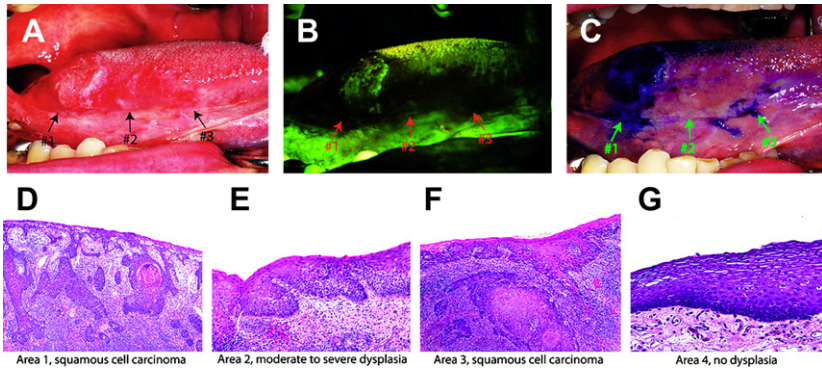
Fig. 13. Clinical characterization and corresponding histology within an oral cancer field at right lateral tongue of a 52-year-old male former smoker. (*A*) White light image of a clinically visible nodular lesion (#1) and an ill-defined change (#2 and #3) anterior to the nodular tumor area. (*B*) The same field under a fluorescence visualization (FV) device showed an area of dark brown change of FV loss at the nodular lesion (#1) and an additional area (#2 and #3), 25 mm anterior to the nodular area (#1). (*C*) Uptake of toluidine blue in areas #1 and #3 but absent in area #2. (*D–G*) Photomicrographs showed varying degrees of histology change of the field: (*D*) (#1) invasive SCC, (*E*) (#2) moderate to severe dysplasia, (*F*) (#3) invasive SCC, and (*G*) (#4) no dysplasia at the surgical boundary, 10 mm away from FV boundary (hematoxylin-eosin staining, original magnification, 40×). (*Reproduced from* Tsui IFL, Garnis C, Poh CF. A dynamic oral cancer field: unraveling the underlying biology and its clinical implication. Am J Surg Pathol 2009;33(11):1732–8; with permission.)

slide and slide holder, a prepaid mailer box, a test requisition form, billing and reimbursement information. It requires no topical or local anesthetic. The circular brush is applied to the suspicious area and rotated 5 to 10 times. The material is transferred to a glass slide, preserved, and dried. The slide is then mailed to a laboratory where a pathologist examines the cells to determine the final diagnosis. In a prospective, randomized, controlled study, Hohlweg-Majert evaluated the advantage of computer-assisted analysis of the oral brush biopsy compared with synchronous scalpel biopsy in the early detection of oral lesions. The sensitivity for the detection of abnormal cells by means of OralCDx was 52%, specificity 29%, and the positive predictive value 63%. According to these findings, the use of oral brush biopsy as a standardized, minimally invasive method of screening oral lesions should be reconsidered.[19]

Given the lack of evidence on the effectiveness of adjunctive cancer detection techniques, clinical examination and histopathologic confirmation with biopsy remain the gold standard for the detection of oral cancer. More randomized controlled studies are needed to confirm the positive cost-benefit relationship and the true usefulness of these new diagnostic methods in oral mucosal pathology.[20]

Biomarkers

Biomarkers are biologic molecules that are indicators of a physiologic state and also of change during a disease process. Their usefulness in oral squamous cell carcinoma (OSCC) is the ability to provide early detection and monitor progression in this patient population. Genomics and proteomics have been the source of recent study. Genomics is the discipline of mapping and sequencing genes and studying their function and relationships. Proteomics is a blend of protein and genome and is the study of the full set of proteins in a cell type or tissue, and the changes under various

conditions. Both proteomic[21] and genomic[22] approaches are currently being used to characterize diagnostic biomarkers in saliva. Saliva baseline protein and mRNA expression levels are needed to interpret changes that may indicate disease states. In the past, several molecular markers have been used to detect OSCC with varying degrees of specificity and sensitivity. DNA markers include TP53, microsatellite instability, the presence of papillomavirus, and Epstein-Barr virus genomic sequences.[23] It is known that mRNA is not always translated into protein[24] and the amount of protein produced for a given amount of mRNA depends on the gene it is transcribed from and on the current physiologic state of the cell. Proteomics confirms the presence of the protein and provides a direct measure of the quantity present. Saliva was once considered a hostile environment to find cancer markers because of the decomposing bacteria and cellular debris. Recently the human salivary proteome has been completely identified as 1166 proteins. It is thought that by screening for a combination of biomarkers, the sensitivity and specificity of cancer detection will be enhanced compared with screening for single tumor markers.[21] Using salivary proteomics, Hu and colleagues[25] in 2008 identified 5 candidate biomarkers in patients with OSCC and the combined use of these biomarkers yielded a receiver operating characteristic value of 93%, sensitivity of 90%, and specificity of 83% in detecting OSCC. Current saliva-based technology is making new headway in salivary transcriptome,[26] salivary soluble CD44,[27] salivary proteomics,[25] and microRNA (miRNA).[28] Blood biomarker research in oral cancer screening includes identification of specific mRNA[29] and interleukin-6.[30] Microfluidics and micro- and nanoelectromechanical systems (MEMS and NEMS) such as the hand-held Oral Fluid NanoSensor Test (OFNASET by GeneFluidics, Inc, Monterey Park, CA, USA) is being developed for saliva-based diagnostics. The routine measurement of proteins, DNA, mRNA, electrolytes, and small molecules in saliva using MEMS/NEMS is envisioned.[31] As the technologies required for biomarker identification and detection advance, the functional value of saliva as a diagnostic fluid will become more important for the improvement of oral health.

DIAGNOSTIC TESTING
Laboratory

Anemia
The World Health Organization defines the normal hemoglobin threshold ranges from 11 g/dL in children to 13 g/dL in adult men. Modern counters measure red blood cell (RBC) count, hemoglobin concentration, mean corpuscular volume (MCV), and RBC distribution width, and are used to calculate hematocrit, mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC), which are then compared with values adjusted for age and sex. Microcytic anemia (MCV <80) such as iron-deficiency anemia can cause glossitis, angular cheilitis or stomatitis, or dysphagia from esophageal webs (Plummer-Vinson syndrome). Macrocytic anemia (MCV >100) can result from vitamin B_{12} and folate deficiency.

Neutrophilia
Neutrophilia is an absolute neutrophil count greater than 7500 cells/mm^3. Physiologic causes include exercise and stress; infectious causes include bacterial, fungal, or viral infections. Inflammatory causes include surgery, burn injury, myocardial infarction, or pulmonary embolus. Metabolic disorders (diabetic ketoacidosis, uremia, and eclampsia) include acute hemorrhage or hemolysis. Myloproliferative diseases such as myelocytic leukemia cause abnormal neutrophils. Drugs (steroids, epinephrine, or lithium), malignant tumors, or hereditary neutrophilia may produce increases in the total neutrophil count.

Neutropenia

Neutropenia is a decrease in the absolute number of neutrophils to less than 1500 cells/mm^3. Major causes include drugs in chemotherapy, such as cyclophosphamide, 5-fluorouracil, azidothymidine, other drugs, such as phenothiazines, sulfonamides, and phenytoin, some infections, hematologic diseases, and autoimmune disorders.

Leukemia

Diagnosis is based on a CBC and bone marrow evaluation. The disease is a bone marrow cancer, acute or chronic, of the lymphocytic cell line (acute and chronic lymphocytic leukemia) or myelogenous cell lines (acute and chronic myelogenous leukemia). Platelet counts from 25,000 mm^3 to 60,000 mm^3 are at sufficiently low levels to result in spontaneous bleeding. Most patients have white blood cell (WBC) counts of greater than 10,000 mm^3. Common head and neck manifestations are cervical lymphadenopathy, laryngeal pain, gingival bleeding, oral ulceration, and gingival enlargement (Fig. 14B). Fever was the most common symptom in patients with all types of leukemia.[32]

Diabetes mellitus

Diabetes mellitus is associated with several oral disorders including gingivitis, peridontitis, salivary dysfunction, dental caries, oral mucosal diseases (lichen planus, recurrent aphthous stomatitis), candidiasis, xerostomia, burning mouth, and taste and neurosensory disorders.[33] The current preferred screening tests are limited to fasting plasma glucose (FPG), random plasma glucose (RPG), oral glucose tolerance test (OGTT), and glycosylated hemoglobin (HbA$_{1C}$).[34] The sensitivity and specificity
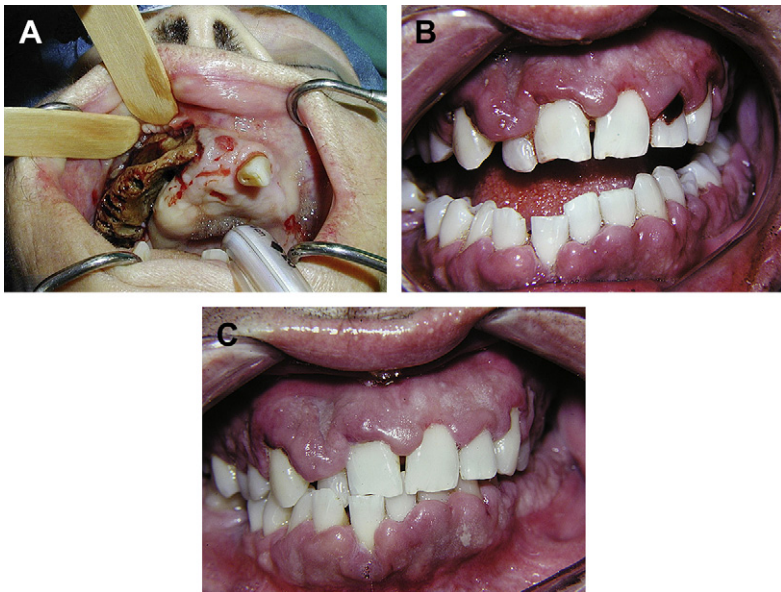
Fig. 14. (*A*) Patient taking intravenous bisphosphonate for metastatic breast cancer developed bisphosphonate-associated osteonecrosis after right upper molar extraction and required maxillectomy to keep necrosis from advancing into the orbit. (*B*) Patient with acute myelomonocytic leukemia with gingival hypertrophy before oral hygiene. (*C*) Improvement in gingival inflammation in same patient 48 hours after dental prophylaxis and initial chemotherapy.

relates to the glucose concentration. An FPG of greater than 110 mg/dL has sensitivity of 85.2% and specificity of 88.5%. An RPG of 130 mg/dL or greater has a balanced sensitivity (63%) and specificity (87%), based on diagnosis by OGTT. The OGTT, although inconvenient and rarely used, remains the gold standard for diagnosis of diabetes with 100% specificity. HbA_{1C} testing can be done in both fasting and nonfasting states and represents glucose control for a period of months rather than a single point value. When participants had both an HbA_{1C} greater than 6.1% and an FPG of 110 mg/dL or greater, the HbA_{1C} sensitivity was 71.6% and specificity 95.7%.[34]

Vitamin B₁₂ and folate deficiency

Vitamin B_{12} and folate are B complex vitamins that are necessary for normal RBC formation, tissue and cellular repair, and DNA synthesis. Children do not have as extensive hepatic reserves of vitamin B_{12} and folate as adults and have rapidly progressing symptoms. A deficiency in either vitamin B_{12} or folate can lead to macrocytic anemia, with weakness, light-headedness, and shortness of breath. A vitamin B_{12} deficiency can result in varying degrees of neuropathy with tingling and numbness in the hands and feet and mental changes that range from confusion and irritability to severe dementia. Patients may also have impaired sense of smell, syncope, and may have an increased risk of myocardial infarction and stroke.

HIV

The HIV virus is detected by a screening enzyme-linked immunosorbent assay (ELISA) test, which is confirmed by a Western blot test. Tests can be done on blood, urine, and saliva. A large study on HIV testing in 752 US laboratories reported a sensitivity of 99.7% and specificity of 98.5% for enzyme immunoassay.[35] Viral load is a quantitative RNA viral test using polymerase chain reaction (PCR); the value is between 50 and 1,000,000 copies/mL, and less than 50 copies/mL is considered undetectable.

CD4 counts between 500 and 1500 per milliliter of blood are considered normal; counts less than 200 are considered AIDS.

Hepatitis

Hepatitis is inflammation of the liver from several causes. The viral hepatitis panel includes A, B and C viruses. Viral hepatitis B and C pose serious risks to health care workers; hepatitis B is discussed here. Testing for hepatitis B virus (HBV) is directed toward antibodies produced in response to HBV infection (anti-HBc, anti-HBs, IgM anti-HBc, IgG anti-HBc, anti-HBe); antigens produced by the virus (HbsAg, HBeAg), and viral DNA detection (HBV-DNA). Susceptible patients have no antigens or antibodies. Patients with acute infection have surface antigen, core and IgM antibodies but no surface antibody. Patients with chronic infection have surface antigen, core antibodies but no IgM and no surface antibody. Anyone with surface antigen (HbsAg) present is infective. Anyone with surface antibody (anti-HBs) present is immune (**Table 3**).

Coagulopathy

The best screening test for coagulopathy is a good history.[36] Initial laboratory evaluation includes CBC, platelets, peripheral blood smear, prothrombin time (PT) and partial thromboplastin time (PTT). Normal platelets range from 150,000 to 450,000 cells/μL. Thrombocytopenia can be detected from a CBC; a peripheral smear can help rule out pseudothrombocytopenia and identify abnormal platelets.[37] Traditionally, platelet function was measured by bleeding time, however the Platelet Function Analyzer-100 (Dade Behring Inc, Newark, DE, USA) has been shown to be superior in detecting von Willebrand disease, with a sensitivity of 89% and a specificity of

Table 3		
Interpretation of hepatitis B serology		
Tests	**Results**	**Interpretation**
HBsAg	Negative	Susceptible
Anti-HBc	Negative	
Anti-HBs	Negative	
HBsAg	Negative	Immune because of natural infection
Anti-HBc	Positive	
Anti-HBs	Positive	
HBsAg	Negative	Immune because of hepatitis B vaccination
Anti-HBc	Negative	
Anti-HBs	Positive	
HBsAg	Positive	Acutely infected
Anti-HBc	Positive	
IgM anti-HBc	Positive	
Anti-HBs	Negative	
HBsAg	Positive	Chronically infected
Anti-HBc	Positive	
IgM anti-HBc	Negative	
Anti-HBs	Negative	

90%.[38,39] PT is 10 to 12 seconds and measures extrinsic pathway factor VII and common pathway factors V, X, prothrombin and fibrinogen. Vitamin K is required for the synthesis of the critical factors of these pathways; liver disease and warfarin prolong the PT. The PT is now expressed in the international normalized ratio, a ratio of the patient's prothrombin time divided by a reference control. The activated PTT measures the intrinsic and common pathways (all factors except VII and XIII). PTT is altered in hemophilia A (factor VIII deficiency) and B (factor IX deficiency), and with use of the anticoagulant heparin.[1] An excellent discussion on coagulation factor inhibitor (blocking antibodies) vessel wall disorders (scurvy) and other disorders may be found in *Burket's Oral Medicine*.[1] Several new platelet function analyzers have been developed recently for screening for platelet function abnormalities and monitoring antiplatelet therapy; most have been designed as point-of-care instruments that are rapid, simple to use, and easy to interpret. These include modified thromboelastography, VerifyNow, Plateletworks, impact cone and plate(let) analyzer, and vasodilator-stimulated phosphoprotein phosphorylation assay. These newer technologies have yet to be extensively studied; therefore, their precision, reliability, and clinical usefulness remain unproved.[40]

CBC

CBC measures the cells that circulate in the bloodstream: WBCs (leukocytes), RBCs (erythrocytes), and platelets (thrombocytes). The WBC count is generally between 4300 and 10,800 cells/mL. The differential can be helpful to determine bacterial (neutrophil), viral (lymphocyte), or parasitic (eosinophil) infection; basophils and monocytes can also be helpful in identifying many disease states. The RBCs are evaluated for the amount of hemoglobin in grams/deciliter (low in anemia) and the packed cell volume or the hematocrit. The RBC indices, MCV, MCH, and MCHC, are useful in determining causes for anemia and other diseases such as thalassemia. Platelet disorders are congenital or acquired and are classified into quantitative and qualitative platelet disorders.[1]

CULTURE STUDIES

Gram staining is performed on the specimen at the time of culture. Although infections can be caused by aerobic or anaerobic bacteria or a mixture of both, brain, dental, and lung infections have a high probability of being caused by anaerobic bacteria. Anaerobic organisms have a characteristic appearance. *Bacteroides* are irregular-shaped gram-negative rods, *Fusobacterium* are pale gram-negative spindle-shaped rods, and *Clostridium* are large gram-positive rods that form spores. Anaerobes can live only in the absence of oxygen and are destroyed when exposed to the atmosphere in a matter of seconds. These cultures should be placed in an oxygen-free environment at 35°C (95°F) for at least 48 hours before the culture plates are examined for growth. Aerobic, fungal and *Mycobacterium* cultures are commonly performed in infections of the head and neck and require oxygen to grow; therefore a special environment during culture is not necessary. The oral cavity has indigenous aerobic and anaerobic flora, aerobic gram-negative rods, and fungi. The anaerobic organisms of oropharyngeal flora are pathogenic. The presence of aerobic gram-negative rods and fungi generally represent colonization and antibiotic coverage need not routinely be directed at these organisms. On the other hand, the antibacterial spectrum of an agent used for head and neck prophylaxis should include coverage for pathogenic oral flora, namely the gram-positive aerobic cocci (especially streptococci) and anaerobic bacteria.[41] *Mycobacterium* does not retain stain because of high lipid content in its wall, and is neither gram-positive nor gram-negative; a Ziehl-Neelsen stain (acid-fast) is required. Fungal specimens can be evaluated clinically by mixing with 10% potassium hydroxide and examining under magnification for the presence of fungal elements. Fungal cultures are then inoculated on to Sabouraud dextrose agar (SDA) with antibiotics for fungal culture and observed for 3 weeks. Fungi are identified from rate of growth, color, texture, pigmentation of fungal colony, and their morphologic features on microscopy. Viral swab specimens from the head and neck are placed in viral transport medium at 2 to 8°C. Diagnostic laboratory testing for virus infections are confirmed by cell culture, which causes cell changes specific for the type of virus involved. Acute viral infections are detection with virus-specific IgM antibodies in blood, which is produced for weeks. Chronic or previous viral infections are detected by virus-specific IgG antibodies, which are produced indefinitely. Viral antibody and antigens can be detected by ELISA. Viral nucleic acids (DNA, RNA) can be detected with PCR or by nucleic acid hybridization with virus-specific probes. Other techniques of viral detection include electron microscopy and hemagglutination assay.

PATHOLOGY
Fine-needle Aspiration

Fine-needle aspiration (FNA) cytology for an abnormal neck mass is reliable and inexpensive. A 23-gauge needle on a 10-mL disposable syringe is inserted into the questionable mass and cells are aspirated with negative pressure using multiple passes. A smear is made on a glass slide, which is then placed in 95% ethyl alcohol and followed by the Papanicolaou staining technique. The success depends on the accuracy of sampling and on the skill and experience of the tissue pathologist who will be examining the cells. Repeat aspiration is suggested and excision biopsy is occasionally considered. Frable and Frable[42] in 1982 reviewed 567 patients with neck masses and found the sensitivity and specificity of FNA to be 85% to 90%. Stevens and colleagues[43] showed pooled estimates of FNA for thyroid nodules to have sensitivity of 94% and specificity of 81%. This means that about 10% will have false-negative

results and approximately 20% will be falsely positive. Ultrasound and computed tomography (CT) guidance can increase the accuracy of the FNA.[44] Aspirate results are based on 1 of the 4 types: 1, inadequate/insufficient; 2, benign; 3, atypical/indeterminate (suspicious of malignancy); 4, malignant.

Punch Biopsy

A punch biopsy ranges from 1 to 8 mm in diameter. The appropriate diameter for most inflammatory skin conditions is 4 mm. Ideally the biopsy should include the full thickness of skin and subcutaneous fat to fully identify the disease process. Smaller punched incisions often require only silver nitrate cautery and are left to heal without suturing.

Biopsy

Suspicious mucosal lesions that persist more than 3 weeks after removal of local irritants such as traumatic oral conditions, infection, or inflammation should undergo biopsy. The oral biopsy remains the gold standard for diagnosing a premalignant lesion or invasive carcinoma. If the biopsy results in dysplasia (low to high grade) the patient is at risk for progression to cancer and requires long-term monitoring and medical or surgical treatment. A clinical photograph of the lesion before biopsy is important as it documents the size, characteristics, and location of the original lesion. Future considerations for re-excision for malignancy, additional margins, or for directing accurate radiotherapy are improved with photographic documentation. The incisional or excisional biopsy procedure is done in the office under local anesthesia. A core biopsy is another method of tissue diagnosis that is used instead of FNA biopsy, or vice versa. The core biopsy preserves the cellular relationship of the tumor, which can help in diagnosis. Core biopsy is a more invasive procedure than FNA, as it involves making a small incision (cut) in the skin. A 14-gauge Vim-Silverman needle or the 16-gauge automated Biopty needle is passed through the incision and several narrow samples of the tissue are taken. Ultrasound guidance may be needed to locate the lump or area to be sampled. Core biopsy is also done under local anesthetic.

RADIOLOGY

Medical radiology of the head and neck includes the plain film, CT generally for bone assessment, magnetic resonance imaging for soft tissue evaluation, positron emission tomography initially used for head and neck cancer surveillance, now being used to improve accuracy of head and neck staging in newly diagnosed cancer,[45] barium swallow for functional swallow and aspiration evaluations, radionuclide imaging generally for thyroid and lymphatic assessment, and ultrasound for soft tissue evaluation and localization for FNA biopsies. Robitschek and colleagues[44] showed significant improvement in FNA sensitivity in the head and neck when using ultrasound.

Dental radiology includes the periapical film (PAX) to visualize periapical pathology, bitewing films to identify occlusal and interpromimal dental caries, occlusal films most commonly to identify submandibular sialolithiasis, the panorex (panoramic radiograph or orthopantomogram) is a two-dimensional view of the bones and dentition of the upper and lower dental arches. Cone-beam computed tomography is a recent addition to the dental practice, a helical three-dimensional CT scan for hard tissue imaging with high diagnostic quality and lower radiation doses than conventional CT scans.[46]

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