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Mucosal Pain Disorders of the Head and Neck

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Painful disease processes that affect the mucous membranes of the upper aerodigestive tract are predominantly inflammatory in nature and include viral and bacterial infections, hypersensitivity reactions, and immunopathologic disorders. In most instances, a diagnosis can be rendered on the basis of clinical findings. Importantly, the diffuse desquamative or bullous diseases are not always easy to differentiate from one another without the benefit of histopathologic and immunofluorescence studies. The most common diseases to cause pain are aphthous stomatitis, herpes simplex infections, viral pharyngitis, allergic and bacterial sinusitis, and oral erosive lichen planus.

VIRAL VESICULAR MUCOSITIS

There are three groups of viruses that are capable of causing painful vesicular eruptions of the upper air passage mucosa; two are herpes group viruses, herpes simplex (HSV) types 1 and 2 and varicella-zoster virus (VZV), whereas the third is a coxsackievirus. Owing to the neural tropism of the two herpesviridiae, recurrent disease is common; coxsackieviruses, on the other hand, do not remain latent as an integrated genome akin to HSV 1 and 2 and VZV.

Herpes Simplex Virus, Types 1 and 2

For many years, clinicians and virologists assumed that HSV 1 was limited to the skin and oral cavity whereas HSV 2 showed tropism for genitoanal mucosa. Recent investigations have disclosed that HSV

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1 is the predominant virus in the head and neck area and HSV 2 is predominant in the genital region, yet either virus can infect both locations. Indeed, sexually active young adults who frequently engage in orogenital sex show a higher prevalence of HSV 2 than HSV 1 in the oral regions. Similarly, homosexuals show a much higher prevalence of oral HSV 2 compared to heterosexuals. Regardless of the viral genotype, the lesions induced by both HSV types 1 and 2 are clinically indistinguishable.

Twenty years ago, data indicated that HSV 1 causing a primary infection of the oral cavity and lips occurred in less than 1 per cent of the population. Enigmatically, 15 to 20 per cent of adults have a history of recurrent herpes labialis, and nearly 98 per cent of the population over age 21 years harbors antibodies to type 1 HSV. Regardless, primary herpes of the oral cavity remains rare. Most instances of primary herpes are subclinical in which the virus gains entry to the host, induces an immune response, and is either inactivated or gains entry into a neuron. Neuronal virions, by retrograde transport, find their way to the trigeminal ganglion where they uncoat and integrate their genome into the host's ganglion cell DNA. They remain latent and sequestered from specific serum antibodies for months or years. Alternatively, if the latent virus is awakened by such stimuli to sensory nerves as trauma of excessive actinic radiation, the viral genome may reassemble, pass through the nerve axon, and be released into the overlying keratinocytes where they propagate. Once the viral particles are released from lysed cells, they are neutralized by antibody, complement-mediated inflammatory reactions ensue, and the lesion resolves in less than 2 weeks.

Primary Herpetic Gingivostomatitis

Primary herpes can be caused by HSV 1 or HSV 2. Classically, the patient is febrile and exhibits lymphadenopathy and lethargy. The chief complaint is oral pain characterized as acute, raw, or burning. While children are predominantly affected, infection among adolescents and young adults is by no means rare. On physical examination, a characteristic pattern of involvement is observed. (Fig. 1) The lips are covered with vesicles and ulcers. These vesicles may cluster and eventually form bullae; however, during the onset, the lesions are clearly vesicular, measuring less than 5 mm in diameter. Similar lesions are encountered on the tongue, buccal mucosa, soft palate, and oropharynx. The pathognomonic clinical sign for primary infection is the concomitant appearance of a gingivitis as well as an extragingival stomatitis. Vesicular stomatitis with gingivitis, elevated temperature, and lymphadenopathy are classic features of primary herpetic gingivostomatitis, regardless of HSV genotype. Within 1 to 2 days most vesicles have ruptured, leaving focal ulcerations. By the fifth day, lesions begin to crust and viral particles are no longer being shed. Healing takes place from 10 to 14 days without residual scarring.

Systemic or locally applied acyclovir does not significantly hasten healing; medications are useful, however, in the immunocompro-

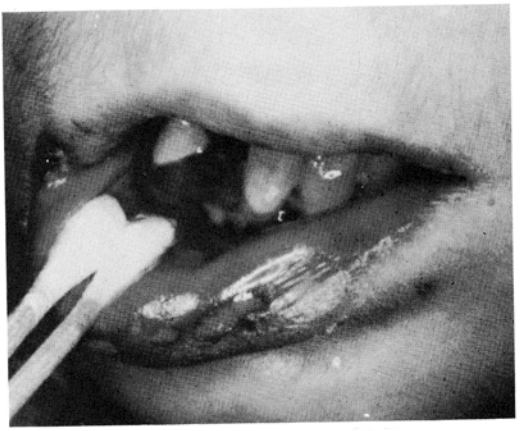

Figure 1. Primary herpetic gingivostomatitis.

mised patient. Palliative care consists of analogesics, antipyretics, and analgesic mouth rinses to ease oral pain. In infants, cherry viscous lidocaine is effective and may be applied via a pacifier. In adults, mixtures of diphenhydramine or promethazine elixir or syrup mixed with equal parts Kaopectate provide a soothing rinse; 1 per cent lidocaine may be added to the rinse as well.

Recurrent Herpes Labialis

Herpes labialis is the most common form of HSV infection among humans, occurring in approximately 15 per cent of the population. The common cold sore represents reactivation of latent ganglionic herpes. The lesions are painful, clustered vesicles located on the vermilion border, skin of the lips, and occasionally the skin encircling the nares (Fig. 2). Most patients note a prodromal paresthesia a few hours prior to onset of the vesicular eruption, a symptom that probably heralds the emergence of the virus from sensory nerve endings. Healing occurs within 10 to 14 days without scarification.

L-Lysine has been investigated for its prophylactic properties in the prevention of herpes labialis and is generally not effective. Topical 5 per cent acyclovir ointment is of minor benefit, yet may accelerate healing by 1 to 2 days. Although most patients experience only two or three recurrences each year, some develop severe, frequent recurrences that can be prevented by prescribing 600 to 1000 mg of systemic acyclovir oral tablets daily.

Recurrent Intraoral Herpes

Unilateral intraoral pain of the hard palate is the most common symptom in recurrent herpes of the oral mucosa. Clinically the palatal gingiva adjacent to the premolar and molar teeth is stippled with tiny vesicles that cluster in a group and tend to ulcerate rapidly (Fig. 3). As with herpes labialis, intraoral recurrent lesions are transported to

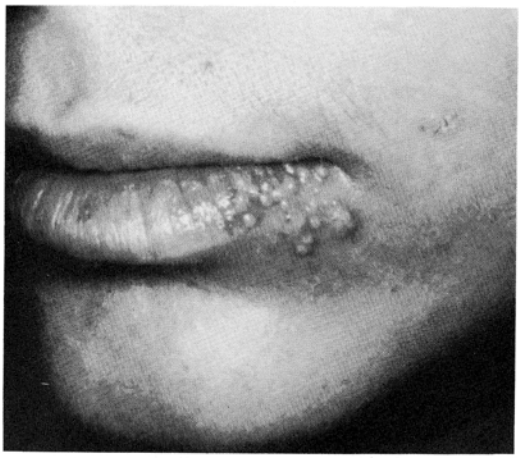

Figure 2. Secondary, recurrent herpes labialis.

the mucosal site of involvement via sensory nerves, in this case, the greater palatine nerve. The vesicles rapidly ulcerate and heal within 10 days; they are infectious for the first 4 days. Topical lidocaine ointment can be applied during the painful phase and may be alternated with application of 5 per cent acyclovir cream.

Complications

Health professionals rendering care to individuals with head and neck herpetic lesions are susceptible to infection. Dental care providers are prone to contract ocular herpes when employing aerosol

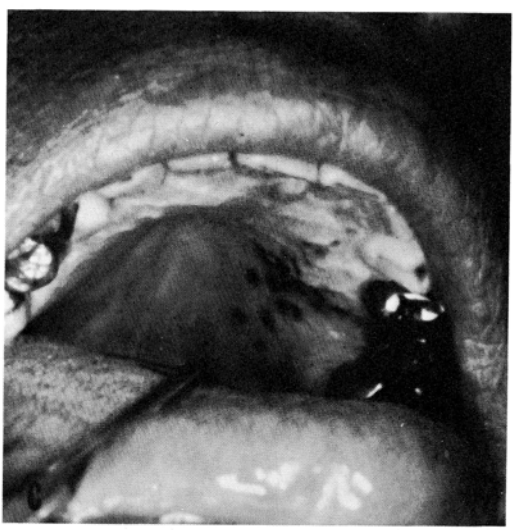

Figure 3. Secondary, recurrent palatal herpes.

rotary instruments while working on patients with active oral or labial lesions. Herpetic witlow, a cutaneous infection of the digits is also an occupational hazard in dentistry and otolaryngology. The use of latex examination gloves eliminates such risks. Herpetic encephalitis can be a fatal consequence of viremia among immunocompromised patients. Lastly, it should be recognized that oral herpetic lesions that persist longer than 1 month may be indicative of an underlying human immunodeficiency virus infection.

Varicella-Zoster Virus

Varicella-zoster virus (VZV) is a herpes group virus that, unlike HSV 1 and 2, causes primary infection in over 98 per cent of the population; alternatively, recurrent disease affects less than 1 per cent. Akin to HSV, VZV is both epidermotropic and neurotropic. Primary infection results in a cutaneous eruption with keratinocyte lysis and vesicle formation commonly known as chicken pox.

Secondary Zoster (Shingles)

In the head and neck region, activation of latent trigeminal ganglion VZV will follow the distribution of the first, second, or third division of cranial nerve or a combination of two or even all three divisions. The vesicles will be unilaterally distributed over the skin and mucous membranes with abrupt, dramatic midline termination. VZV involvement of the ninth cranial nerve is extremely rare. The lesions in shingles or zoster are exquisitely painful, with acute and throbbing pain that is both superfical and visceral. The disease may persist for over 3 weeks. Narcotic analgesics may be necessary to control pain, and systemically administered oral acyclovir, 600 to 1000 mg per day, should be initiated as soon as possible.

Vesicular Otitis Externa (Ramsay-Hunt Syndrome)

The sensory fibers of cranial nerve VII have their cell bodies in the geniculate ganglion. Reactivation of VZV in this region results in earache within the external canal with referred pain into the TMJ or throat. Accompaniments may include vertigo, sensorineural hearing loss, dysgeusia, hypogeusia, and decreased lacrimal and salivary secretion. Clinical examination discloses a vesicular eruption on focal areas of the external ear skin with extension into the external auditory meatus, sparing the tympanic membranes. When a concomitant ipsilateral seventh nerve paralysis is observed, the condition is referred to as the Ramsay-Hunt syndrome. Orally administered acyclovir results in early resolution or may have no beneficial affects.

Complications

The primary complication of VZV infection is persistent pain, long after the cutaneous and mucosal eruptions have healed, the so-called postherpetic neuralgia. VZV is a neurotropic virus that is capable of

causing axonal demyelinization; this pathologic feature may account for or contribute to the generation of pain symptoms.

Coxsackieviruses

There are three diseases of the upper air passages that are caused by various members of Group A coxsackieviruses (CV): herpangina, hand, foot, and mouth disease, and lymphonodular pharyngitis. Unlike HSV and VZV, the CVs are enteroviridiae that do not show any neurotropism and therefore do not become dormant or latent. Rather, the infections are primary and do not recur at a later date after the appearance of neutralizing antibody.

Herpangina

Vesicular lesions of the soft palate and fauces (oropharyngitis) represent the characteristic lesions of herpangina (Fig. 4). Often there are only five to ten clustered vesicles; nevertheless, the patient generally complains of throat pain, expressing a "raw" soreness. Malaise and fever are present. The vesicles rupture within 1 to 2 days, and resolution can be expected in 10 days.

Hand, Foot, and Mouth Disease

Some strains of coxsackie A cause both oral and cutaneous eruptions. The oral lesions are not unlike those seen in primary herpetic gingivostomatitis in that panoral involvement is the rule. The mucosa, but not the vermilion, of the lips is always involved; most children will not be able to masticate hard foods because of pain. The *sine qua*

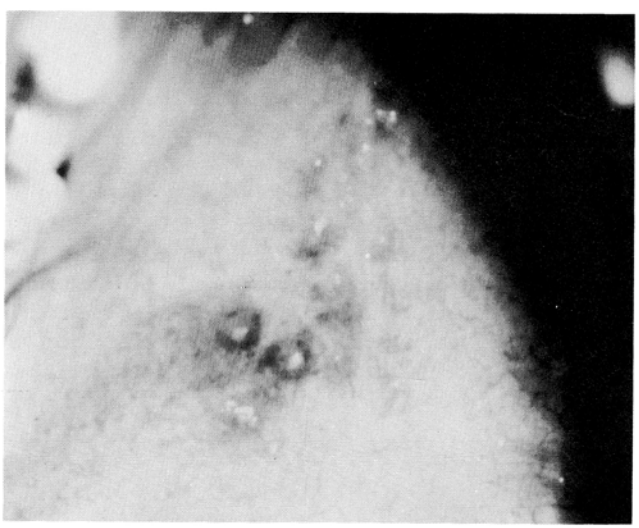

Figure 4. Coxsackievirus infection, herpangina.

non of this infection is vesicular dermatitis of the extremities without trunk involvement. The vesicles are most numerous on the skin of the hands and feet with only occasional lesions on the forearms and lower legs. There have been no studies to explain this peculiar, yet diagnostic, distribution of lesions. The disease runs its course in 10 to 12 days.

Lymphonodular Pharyngitis

Sore mouth and throat are the chief complaints in this disease; lymphadenopathy, fever, and tiredness are frequently accompaniments. Among the viral diseases of the upper air passages, lymphonodular pharyngitis is the most unique in regard to its clinical appearance. Dispersed throughout the oropharynx are orange-yellow, 3 to 5 mm papules; vesiculation is lacking. Indeed the papules resemble adenoids, even though they are located on the soft palate and fauces. Sore throat symptoms are not severe, and the disease lasts 7 to 10 days.

The management of coxsackievirus oropharyngeal infections is similar to that for herpetic lesions. In general, mouth rinses and gargle solutions containing antihistiminic elixirs mixed 50/50 with Kaopectate are quite soothing.

Viral Pharyngitis (Common Cold)

The common cold with its attendant sore throat does not require a great deal of consideration here because it is a common cause of throat pain. Suffice it to say that the disease is not caused by any single viral agent. Strains of rhinovirus are the more common causative agents, followed by coronaviruses, parainfluenza viruses, respiratory syncytial virus, and adenoviruses. The throat is either diffusely erythematous or telangiectatic with tonsillitis and adenoiditis of varying degrees. The patient is frequently febrile and lethargic and exhibits cervical lymphadenopathy. The infection may, of course, descend to cause tracheobronchitis. Appropriate therapy remains a challenge, as no effective antiviral agents for these pathogens are currently available.

Epstein-Barr Virus

Infectious mononucleosis is caused by a herpesgroup virus, the Epstein-Barr virus (EBV). Viral receptors are present on B lymphocytes and oropharyngeal keratinocytes. Whereas most instances of EBV infection are subclinical, infectious mononucleosis represents the acute clinical infection with this virus. The chief complaint is lethargy or malaise accompanied by generalized lymphadenopathy (cervical disease being most evident), fever, and sore throat. Frequently soft palate petechiae are observed, probably as a consequence of active sucking or clicking of a pruritic or sore uvula. A positive monospot assay supports the diagnosis; however, a heterophile anti-

body titer is more specific. Systemic administration of acyclovir, 600 mg daily, may reduce the symptoms.

MUCOSAL BACTERIAL INFECTIONS

Bacterial infections of the mucosal soft tissues of the head and neck are uncommon in the oral cavity with the exception of odontogenic and periodontal infections. While stomatitis is most often viral, infectious diseases of the remaining upper aerodigestive tract are primarily bacterial, and acute infection with pyogenic microorganisms is invariably attended by pain symptoms, often severe in character.

Stomatitis

Bacterial infections of the oral cavity include chronic inflammatory periodontal disease and dental caries, the latter having the potential to progress and spread to the adjacent marrow spaces, sinuses, and tissue spaces of the head and neck. Superficial mucosal infections have been reported to occur with beta-hemolytic streptococci and gonococci, both being extremely rare and verifiable by swab culture.

Pharyngitis/Tonsilitis

Pharyngitis caused by viral infection, usually the common cold or coxsackieviruses, has been described previously. Bacterial infections are more often encounted in the oropharynx than in the oral cavity, with beta-hemolytic streptococci being the major culprits. Throat pain is often severe and is accompanied by elevated temperature, cervical adenopathy, and mucosal erythema, oftentimes striking. Ulceration with a gray-white pseudomembrane is occasionally encountered yet is more characteristic of *Corynebacterium diptheriae* infection. The palatine tonsils and adenoids are enlarged, sometimes markedly so. In pharyngitis caused by beta-hemolytic streptococci, the antistreptolysin 0 titers will be elevated, and throat swabs will yield positive cultures. Although penicillin is the treatment of choice, cephalosporins and ampicillin are effective; analgesic medication may also be advisable. Since organisms other that streptococci can initiate clinically similar features, all such cases should be cultured and subjected to antibiotic sensitivity analysis. Serious complications can progress from a peritonsillar abscess including space infections, cellulitis of the parapharyngeal tissues, endocarditis, nephritis, and brain abscess.

Laryngitis

Infections of the larynx may involve the epiglottis, the larynx proper, or be localized to the true vocal cords. Acute epiglottitis is seen mainly in children younger than 7 years of age and is most often caused by *Haemophilus influenzae* type B. Clinically, a swollen, fiery red epiglottis is observed at the base of the tongue with airway ob-

struction. Nasotracheal intubation is needed; ampicillin or chloramphenicol should be administered intravenously followed by supportive care and correction of any acid-base electrolyte imbalances.

Most instances of laryngitis are accompanyied by tracheobronchitis and are viral in origin (parainfluenza types 1 to 4). Bacterial organisms may also be responsible including *Haemophilus influenzae*, streptococci, staphylococci, and pneumococci. Symptoms include a croupy cough, hoarseness, inspiratory stridor, and mild sore throat. Airway obstruction can become a complication and must be treated as a medical emergency. Other specific forms of laryngitis including syphylitic laryngitis, tuberculous laryngitis, scleroma (*Klebsiella rhinoscleromatis*, and diphtheritic laryngitis are characterized by hoarseness without pain.

Rhinitis/Sinusitis

Chronic cocaine usage will cause septal ulcerations that progress to osseous destructive perforations. Such lesions can be extremely painful. Alternatively, rhinitis may be unexplained (vasomotor rhinitis), or allergic or infectious in origin. Such infectious agents as *Mycobacteria* and deep fungi are rare and manifest as painless granulomatous tumefactions. Infection with *Pseudomonas mallei, Klebsiella rhinoscleromatis*, and *Rhinosporidium seebri* result in granulomatous nodules of the lining mucosa, rhinorrhea, and pain symptoms. Necrotizing granulomas associated with osteodestructive lesions such as malignant polymorphic reticulosis, lethal midline granuloma, and necrotizing sialometaplasia can frequently cause pain although all are rare, show tumefaction with ulceration, and can be diagnosed by histopathologic examination. Most cases of rhinitis are, however, a consequence of allergic, viral, or bacterial disease. It is axiomatic that rhinitis of infectious origin can result in spread of infection to the paranasal sinuses.

Acute, painful sinusitis is invariably of bacterial origin. The pain is severe, and a sensation of extreme pressure is experienced in the antral, frontal, or orbital areas, depending on which sinus cavity is involved. Maxillary sinusitis can be secondary to spread of infection from the nasal cavity or from the dentition; in the latter, a necrotic tooth will be uncovered. Those infections unrelated to spread from odontogenic sources are generally found to be associated with *Haemophilus influenzae*, streptococci, staphylococci, anaerobic streptococci, or *Bacteroides*. A mucopurulent exudate from the nasal cavity is generally evident. Sinus radiographs will disclose soft tissue hyperplasia of the sinus lining or an air-fluid interface. Any nasal discharge should be submitted to the clinical laboratory for smear, culture, and sensitivity testing.

Treatment consists of antibiotics (amoxicillin or ampicillin being the first line of therapy) in conjunction with nasal decongestant sprays. Should infection fail to resolve, sinus drainage should be pursued surgically.

Untreated acute sinusitus may progess to chronic bacterial si-

nusitis. Chronic nasal discharge and obstruction may be the only symptoms although a low grade pain complaint may be reported. Increased pressure and pain will usually be elicted when the patient lowers the head. Sinus radiographs, tomograms, and CT scans will disclose antral clouding, membrane thickening, and sinus wall cortical osteosclerosis. Initially, conservative antibiotic therapy should be instituted.

FUNGAL INFECTIONS

Candida albicans

Candida albicans, other related *Candida* species, and *Geotrichium* are common inhabitants of the oral and oropharyngeal mucosa. These superficial fungi rarely cause disease in healthy patients. When the normal oral microflora is suppressed owing to antibiotic therapy, *Candida* organisms may proliferate with resultant pseudomembranous candidiasis. This disease is characterized by the presence of curdled milk-like papules on the mucous membranes and is asymptomatic. Although less prevalent, the atrophic form of candidiasis can cause symptoms of pain and burning. Atrophic candidiasis presents as multifocal, diffuse erythematous lesions of the oral, oropharyngeal, and esophageal mucosa. Often atrophic candidiasis is encountered underneath ill-fitting dental prostheses, particularly in the palate. The diagnosis can be confirmed by cytologic smear, stained with periodic-acid–Schiff. Treatment consists of prescribing topical nystatin or chlortrimazole oral troches, four times daily. Oral ketaconazole, 100 mg per day is also effective. Another form of candidiasis, angular cheilitis, affects the labial commissures with cracked, painful fissures (Fig. 5). Application of topical nystatin cream over a 10-day period will generally suffice; however, the disease will recur in the event that any intermaxillary vertical dimension problem remains uncorrected.

Phycomycetes

While *Nocardia* may cause infection of the maxillary sinus, mucormycosis and aspergillosis are the more common causes of mycotic sinusitis. Most instances occur in patients with advanced type I diabetes mellitus or arise in immunocompromised patients. While aspergillosis is rarely associated with fatality, diffuse pain, or osseous destruction, mucormycosis can result in sinus opacification, sinus wall destruction, and extension into the oral cavity by palatal ulceration. Waters sinus radiographs will disclose diffuse opacification with antral wall erosions. Significantly, the disease may progress superiorly to involve the ethmoidal sinus and can then procede to cause intracranial disease with involvement of cranial nerves III, IV, and VI resulting in blindness and ophthalmoplegia. Biopsy will disclose the presence of diffuse necrosis and numerous hyphae are demonstrable. Aggressive therapy is necessary owing to the potential lethal complications.

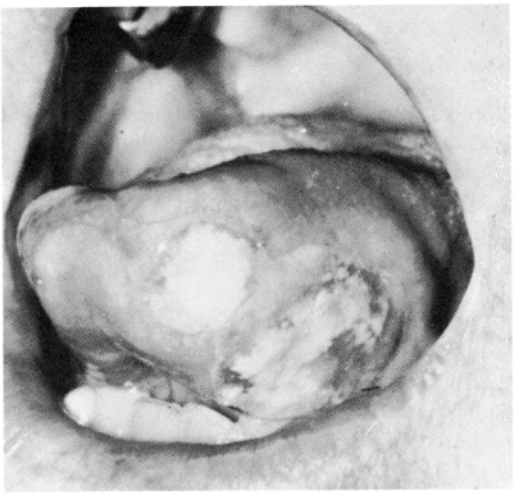

Figure 5. Agranulocytic tongue ulcers.

The sinuses must be surgically débrided and systemic amphotericin B therapy should be initiated.

ALLERGIC MUCOSITIS

Environmental allergens may contact nasal, oral, or pharyngeal mucosa with subsequent mucositis. Clinically, the nasal mucous membranes are erythematous and edematous. Allergic rhinitis will result in nasal obstruction, dull pain, and because of edematous closure of the ostia, sinusitis may ensue. Although a wide variety of pollen and grass allergens will induce rhinitis and sinusitis, oral and pharyngeal allergies are uncommon yet may occur in response to such antigens as foodstuff agents, mouthwashes, chewing gum, and even dental restorative materials. Allergic mucositis may be IgE-mediated or T cell–mediated. Allergic rhinitis is readily diagnosed by obtaining nasal washings or smears; numerous eosinophils are observed microscopically. Alternatively, cell-mediated, contact hypersensitivity is not accompanied by eosinophilia. The lesions are usually red and are more often encountered in the oral cavity or oropharynx. Biospy will generally disclose a submucosal lymphocytic infiltrate.

Acute, humoral (IgE)-mediated mucositis is managed by prescription of antihistamines and nasal decongestant sprays, although progession to sinusitis may require nasal lavage. Delayed hypersensitivity reactions are managed by prescription of systemic or topical steroid preparations. In all instances of hypersensitivity mucositis, attempts should be made to search out and eliminate the incriminating allergen. For immediate hypersensitity reactions, desensitization procedures with the appropriate antigen(s) can be instituted.

ULCERATIVE MUCOSITIS

Traumatic Ulcers

Traumatically induced ulcerations are most commonly encountered in the oral cavity and nasal septum. Oral and nasal traumatic ulcers are focal, usually oval in shape, and manifest a grayish-white pseudomembrane. The pain is often sharp; yet, in long-standing ulcers the patient may complain of a dull rawness. In general, the etiologic agent is readily identifiable.

Minor Recurrent Aphthous Stomatitis

The canker sore is probably the most common cause of oral and oropharyngeal pain, affecting approximately 15 per cent of the population. The severity of symptoms will, of course, depend on the number of lesions present. Minor aphthae appear as round ulcers with a gray-white pseudomembrane surrounded by an erythematous halo. The ulcers are small, usually about 5 mm in diameter. As a rule, the lesions are not encountered on the palate or gingiva; rather, they show a predilection for movable tissues such as lips, buccal mucosa, tongue, and soft palate. (Fig. 6) The pain begins to wane after 5 or 6 days and healing without scarring occurs within 10 to 14 days. The lesions may then recur from time to time, and recurrent episodes are variable from one patient to the next. Some individuals are plagued with monthly recurrences. The frequency is highest among children and adolescents, becoming less of a problem with advancing age. While many clinicians assume that such lesions are herpetic, the etiology remains unknown; virologic studies have failed to reveal a causative agent. Immunologic abnormalities in T lymphocyte subsets have

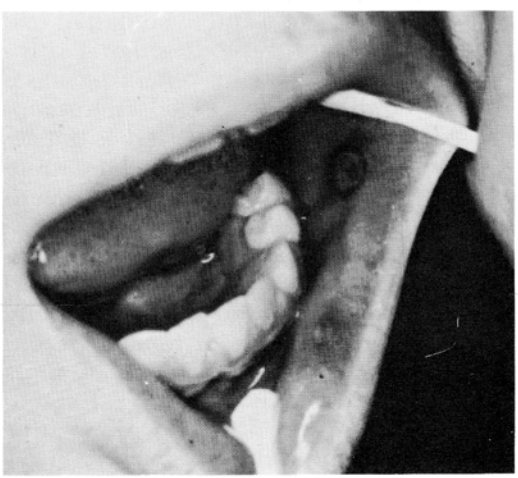

Figure 6. Minor recurrent aphthous stomatitis.

been encountered, indicating that recurrent aphthous stomatitis may be the result of an episodic immunoregulatory balance.

Recurrent oral ulcers with clinical features identical to those of recurrent aphthous stomatitis are encountered in patients with gluten enteropathy, Behçet's syndrome, and cyclic neutropenia. In the former, patients will present with the symptoms of streatorrhea; in Behçet's syndrome, oral ulcers are accompanied by genital ulcers, arthritis, and cutaneous lesions; in the latter, oral ulcers appear on a monthly cycle commensurate with transitory neutropenia.

Major Recurrent Aphthous Stomatitis

Major aphthae affect young adults. Unlike the more common minor variant, the major form is characterized by the presence of large, irregular ulcerations varying in size from 1 to 2 cm in diameter. (Fig. 7) The ulcers are recurrent, persist for 3 to 5 weeks, and while one crop is healing, another is evolving. Any given patient may have two or three ulcers concomitantly. While the lesions can affect any oral site, they are most often observed on the faucel pillars, soft palate, lips, and buccal mucosa. There is a male predilection and, classically, the ulcers heal with residual scarring, a feature that accounts for another designation for this form of ulcerative stomatitis, recurrent scarring aphthae. (Synonyms include Sutton's disease and periadenitis mucosa necrotica recurrens.) These lesions constitute the most painful disease to affect the oral and oropharyngeal mucosa. The pain is severe and constant. Most individuals suffering from this disorder cannot masticate foods and often must resort to soft diets.

Minor aphthae can be treated by a 2- to 3-second application of silver nitrate or, in the case of multiple ulcers, topical steroids, tet-

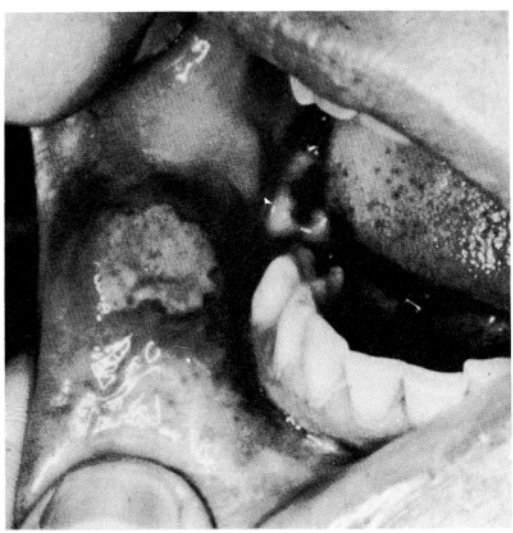

Figure 7. Major recurrent aphthous stomatitis.

racycline rinses, and antihistaminic rinses will speed resolution or palliate pain symptoms. Major recurrent aphthous stomatitis lesions will resolve with 40 mg prednisone daily for 2 weeks only to return in the future when retreatment is required.

EROSIVE, BULLOUS, AND DESQUAMATIVE DISEASES

Erosive, bullous, and desquamative diseases are immunopathologic disorders, representing autoimmune diseases or allergic reactions of either B- (humoral) or T- cell mediated pathogenic responses. In each disorder, a specific immunopathic defect can be identified, involving various cell or cell product proteins or glycoproteins involved in adhesion. Once the adhesive elements have been damaged, bullae, erosions, or desquamations ensue.

Erosive Lichen Planus

Lichen planus (LP) is an inflammatory dermatologic disease of unknown origin, although the histopathologic features are suggestive of a delayed, cell-mediated, immunologic disorder; a causative antigen has not been uncovered. The antigenic stimulus is undoubtedly located in the epithelium, perhaps in the lowermost strata and may be exogenous or, alternatively, could conceivably be an autoantigen. The oral and oropharyngeal mucous membranes are frequently involved in this dermatologic disease (Fig. 8). Whereas the disease affects 0.5 to 1.0 per cent of the population, patients with oral LP may or may not show concomitant cutaneous disease. the more common form of oral lichen planus is the asymptomatic, reticulated variant. A feeling of rawness or burning pain, often severe, is associated with the erosive form of the disease. The erosive lesions are usually confined to the buccal mucosa and gingiva.

Clinically, diffuse erythema is encountered, yet invariably, there are associated white lesions. The white component surrounds the erythematous, erosive zones, and typically evinces interconnective white lines referred to as stria of Wikham. Microscopically, the erosive regions show an attenuated cornified layer, and the spinous layer is thin as well. The basal cell layer is disrupted and the basement membrane is thickened. Lying in juxtaposition to the basilar layer is a zonal lymphocytic infiltrate in the submucosal connective tissue. The disrupted basal layer evolves into a junctional separation. Immunofluorescent studies disclose basement membrane fluorescence with antisera to fibrinogen without immunoglobulin binding and immunophenotyping of the lymphocytic infiltrate in LIP reveals a T cell population.

Drug- induced cutaneous LP is well documented. The chief pharmacologic and environmental antigens include antimalarial quinidine drugs, photographic processing chemicals, certain antihypertensive agents, gold, and infrequently, a variety of other drugs. Usually, however, no antigen is identifiable. Severe oral erosive LP may require

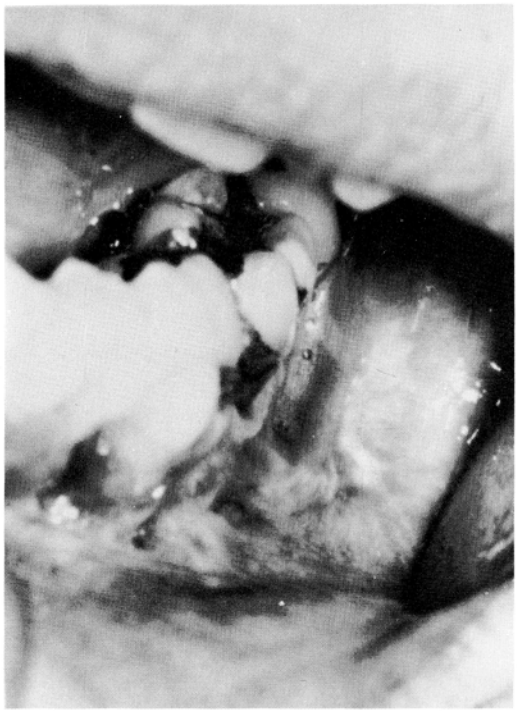

Figure 8. Erosive lichen planus.

short-term corticosteroids, 20 to 40 mg of prednisone each day for 7 to 10 days, tapering the dosage for the last 3 days. Milder forms can be managed with 0.05 per cent topical fluocinonide ointment. The erosive form usually requires intermittent topical steroid therapy every 1 to 2 months. Complete remission, without later recurrence, is witnesed in fewer than 20 per cent of patients with oral disease.

Benign Mucous Membrane Pemphigoid

Occurring primarily in women over the age of 45 years, benign mucous membrane pemphigoid (BMMP) is perhaps the second most common erosive/bullous head and neck mucosal disease. Also known as ocular pemphigus, cicatricial pemphigoid, and gingivosis, this desquamative disorder is restricted to mucous membranes of the oropharynx, particularly the soft palate, gingiva, anterior nasal cavity, and both bulbar and palpebral conjuntivae, with attending pain and spontaneous oral or nasal bleeds. The lesions of the gingiva are rather characteristic, showing a superficial slough of epithelium over a diffuse erythematous base. (Fig. 9) Gentle rubbing with gauze will induce Nikolsky's sign. Examination of the anterior chamber of the nasal cavity discloses diffuse erythema of both the septum and lateral walls. The ocular lesions consist of gelatinous plaques, well-defined bullae, corneal erosions, or, in long-standing lesions, symblepharon. Blind-

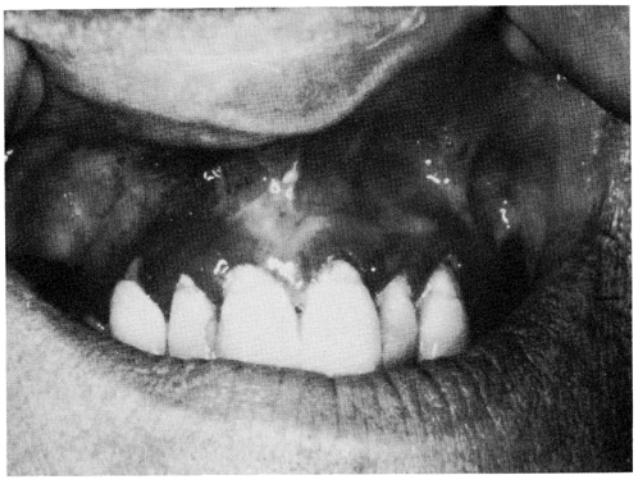

Figure 9. Benign mucous membrane pemphigoid.

ness may eventuate from this external ocular disease. All three mucous membranes are not concomitantly affected in every patient.

The diagnosis is based on microscopic and immunofluorescent findings. Microscopically, the lesion is identical to that encountered in the cutaneous disease, bullous pemphigoid (BP). A junctional cell separation characterized by a subepithelial cleavage is encountered and, invariably, an intense mixed mononuclear inflammatory cell infiltrate is evident. Direct immunofluorescent findings include BMZ deposition of complement fraction 3 and IgG or IgM. Unlike bullous pemphigoid, indirect fluorescence is rarely observed. Recent studies have indicated that the antigen in BMMP differs from that of BP. The BMMP antigen appears to reside in the lamina lucida region of the BMZ.

Therapeutically, being an autoimmune disorder, BMMP responds to immunosuppressive drugs. In most instances, it is advisable to initiate therapy with systemic prednisone, 40 mg daily, tapering the dosage after 10 days to 20 mg a day for 2 days, then to 10 mg daily for 2 days, then to 5 mg daily for 2 days. Systemic therapy will generally eliminate or minimize the mucous membrane lesions. Recurrences can then be managed with topical fluocinonide, applied 4 to 6 times each day for 10-day periods.

Pemphigus Vulgaris

While usually considered a cutaneous disease, pemphigus vulgaris (PV) involves the oral cavity and oropharynx and the oropharyngeal lesions precede skin disease in 25 to 50 per cent of the cases. Unlike the turgid bullae observed on the skin, mucosal bullae present as white gelatinous plaques with an irregular outline accompanied by an erythematous border. Desquamation is observed and Nikolsky's

sign is readily elicited by swabbing the mucosa with a cotton-tipped applicator. These desquamative lesions are generally quite painful; the patient complains of a burning mouth or a sore throat. The lesions can occur anywhere but are most frequently noted on the soft palate and buccal mucosae. As noted earlier, cutaneous bullae may be absent and the chief complaint is often oral pain.

PV is an autoimmune disease. The patient generates autoantibodies to a 30 kD and a 12 kD protein that represents a normal constituent of the interepithelial attachment apparatus. The antibodies bind the intercellular region of stratified squamous epithelium; most research studies conclude that complement fixation plays a role in the acantholytic process. The diagnosis is secured by biopsy, which discloses an intraepithelial bulla located in the suprabasilar region. Immunofluorescence studies will aid in confirmation as antiintercellular space fluorescence is observed employing FITC-conjugated antihuman class immunoglobulins. The disease is managed by systemic steroid therapy. Massive dose regimens have actually resulted in remission of this potentially fatal disease. Topical steroid preparations are rarely employed as the disease will eventually progress to affect the skin. Alternatively, and rarely, some cases appear to remain confined to the oral cavity.

Erythema Multiforme

Another disease that affects both the upper air passage mucous membranes, other mucous membranes and the skin is erythema multiforme (EM). The more common variety is EM minor, in which the disease is limited to the skin, oral cavity, or both. The cutaneous lesions may be bullous or assume an iris configuration. The oral lesions are classic. No other bullous disease affecting the head and neck mucous membranes causes diffuse hemorrhagic desquamation of both upper and lower lip vermilions. Intraorally, multifocal erosions, ulcerations, and foci of erythema are observed, culminating in severe orolabial pain symptoms (Fig. 10). It is not uncommon to encounter minor EM of the oral cavity in the absence of skin lesions. The more severe form is referred to as EM major or the Stevens-Johnson syndrome, which is characterized by ocular, oral, nasal, genital, and cutaneous bullae, erosions, and iris lesions.

There are no pathognomonic features for EM microscopically, yet biopsy should be performed to rule out other bullous diseases. Immunofluorescent staining of involved tissue discloses the presence of complement fraction 3 in the walls of submucosal vessels. Whereas some cases of EM are of unknown etiology, many represent an allergic reaction to sulfa drugs. Another form of EM arises subsequent to recurrent herpes labialis or genitalis. Postherpetic EM is usually recurrent, and the lesions may persist for 2 to 3 weeks.

Erythema multiforme secondary to drug therapy may be fatal. It is important to immediately eliminate the drug and initiate systemic prednisone therapy, 40 to 60 mg per day for a period of 7 to 10 days,

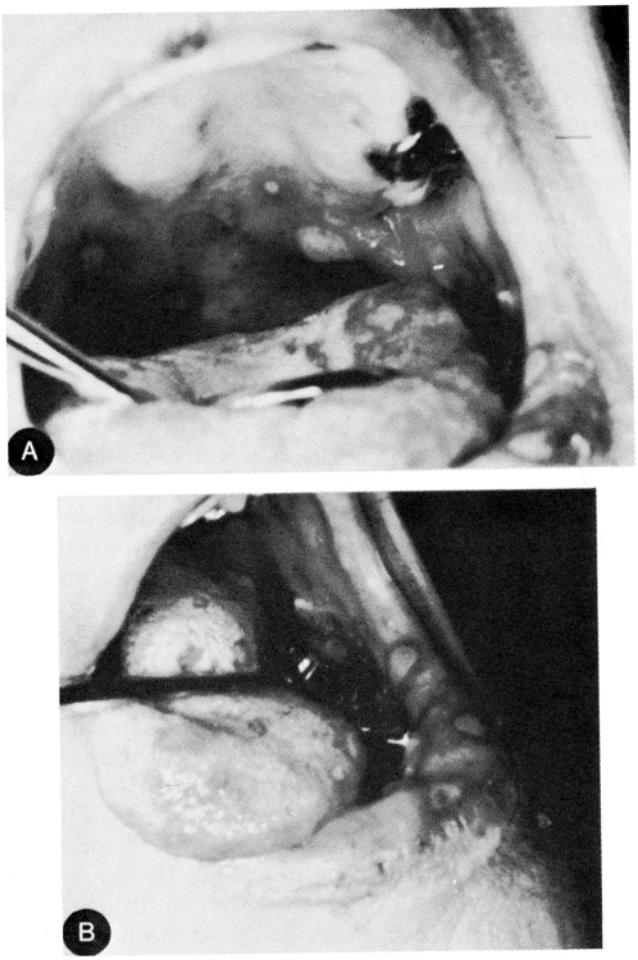

Figure 10. A and B, Erythema multiforme secondary to sulfonylurea.

slowly tapering the dose thereafter. Postherpetic EM episodes may be prevented by placing the patient on daily acyclovir.

REFERENCES

1. Antoon JW, Miller RL: Aphthous ulcers—a review of the literature on etiology, pathogenesis, diagnosis, and treatment. J AM Dent Assoc 101:803, 1980
2. Axell T, Rundquist L: Oral lichen planus—a demographic study. Community Dent Oral Epidemiol 15:52, 1987
3. Blacklely B, Friedman I, Wright I: Herpes zoster virus associated with facial palsy and auditory nerve symptoms: A case report with histopathological findings. Acta Otolaryngol 63:533, 1967

4. Blitzer A, et al: Patient survival factors in paranasal sinus mucomycosis. Laryngoscope 90:635, 1980
5. Blozis GG, Robinson JE: Oral tissue changes caused by radiation therapy and their management. Dent Clin Noth Am 12:543, 1968
6. Buchner A: Hand, foot, and mouth disease. Oral Surg 41D:333, 1976
7. Cawson RA: Denture sore mouth and angular cheilitis. Br Dent J 115:441, 1963
8. Chapnick JS, Bach MC: Bacterial and fungal infections of the maxillary sinus. Otolaryngol Clin North Am 9:43, 1976
9. Cherry JD, Hahn CL: Herpangina: The etiologic spectrum. Pediatrics 36:632, 1965
10. Coslet RS: The psychological factor in the etiology of acute necrotizing gingivitis. Dent Hyg 53:257, 1979
11. Daniels TE, Quadra-White C: Direct immunofluorescence in oral mucosal disease: A diagnostic analysis of 130 cases. Oral Surg 51:38, 1981
12. Deeb ZE, Yenson AC, DeFries HO: Acute epiglottitis in the adult. Laryngoscope 95:289, 1985
13. Eversole LR: Allergic stomatits. J Oral Med Oct/Dec:34, 1979
14. Ferguson MM, Wray D, Carmichael HA, et al: Coeliac disease associated with recurrent aphthae. Gut 2:223, 1980
15. Goldman L, Farrington J: Stomatitis with glossitis following oral therapy with penicillin tablets. Arch Dermatol 57:399, 1958
16. Huff JC, Weston WL, Tonnesen MG: Erythema multiforme: A critical review of characteristics, diagnostic criteria, and causes. J Am Acad Dermatol 8:763, 1983
17. Laskaris G, Sklavounou A, Stratigos J: Bullous pemphigoid, cicatricial pemphigoid and pemphigus vulgaris. A comparative clinical survey of 278 cases. Oral Surg Oral Med Oral Pathol 54:656, 1982
18. Lehner T: Pathology of recurrent oral ulceration and oral ulceration in Behçet's syndrome: Light, electron and fluorescence microscopy. J Pathol 97:481, 1969
19. Lennette EH, Magoffin RL: Virologic and immunologic aspects of major oral ulcerations. J Am Dent Assoc 87:1055, 1973
20. Lever WF: Oral lesions in pemphigus. Am J Orthod Oral Surg 28:569, 1942
21. Lever WF, Schaumberg-Lever G: Treatment of pemphigus vulgaris. Results obtained in 84 patients between 1961 and 1982. Arch Dermatol 120:44, 1984
22. Lorentzer WH: Angular cheilitis. Northwest Dent 60:10, 1981
23. Lozada F: Prednisone and azathioprine in the treatment of patients with vesiculoerosive oral diseases. Oral Surg 52:257, 1981
24. Lozada F, Silverman S: Erythema multiforme: Clinical and natural history in fifty patients. Oral Surg 46:628, 1978
25. Lozada F, Silverman S: Topically applied fluocinonide in an adhesive base in the treatment of oral vesiculo-erosive diseases. Arch Dermatol 116:898, 1980
26. Molin L: Oral acyclovir prevents herpes simplex virus-associated erythema multiforme. Brit J Dermatol 116:109, 1987
27. Myelsson A, Brorson JE: The correlation between bacteriologic findings in the nose and maxillary sinus in acute maxillary sinusitis. Laryngoscope 83:2003, 1973
28. Nally FF, Ross IH: Herpes zoster of the oral and facial structures. Report of five cases and discussion. Oral Surg 32:221, 1971
29. Paradise JL, et al: Efficacy of tonsillectomy for recurrent throat infection in severely affected children: Results of parallel randomized and nonrandomized clinical trials. N Engl J Med 310:674, 1984
30. Phelan JA, Slatzman BR, Friedland GH, et al: Oral findings in patients with acquired immunodeficiency syndrome. Oral Surg Oral Med Oral Pathol 64:50, 1987
31. Rogers RS, Sams WM, Shorter RG: Lymphocytotoxicity in recurrent aphthous stomatitis—lymphocytotoxicity for oral epithelial cells in recurrent aphthous stomatitis and Behçet syndrome. Arch Dermatol 109:361, 1974
32. Scully C, El-Korn M: Lichen planus: Review and update on pathogenesis. J Oral Pathol 14:431, 1985
33. Ship II: Epidemiologic aspects of recurrent aphthous ulcerations. Oral Surg Oral Med Oral Pathol 33:400, 1972
34. Shklar G, McCarthy PL: Oral lesions of mucous membrane pemphigoid; a study of 85 cases. Arch Otolaryngol 93:354, 1971

35. Silverman S Sr, Gorsky M, Lozada-Nur F, et al: Oral mucous membrane pemphigoid. Oral Surg Oral Med Oral Pathol 61:233, 1986
36. Spruance SL, Wenerstrom G: Pathogenesis of recurrent herpes simplex labialis: Implications for antiviral treatment. Oral Surg Oral Med Oral Pathol 58:667, 1984
37. Steigman AJ, Lipton MM, Braspennickx H: Acute lymphonodular pharyngitis: A newly described condition due to coxsackie A virus. J Pediatr 61:331, 1963
38. Weathers DR, Griffin JW: Intraoral ulcerations of recurrent herpes simplex and recurrent aphthae: Two distinct clinical entities. J Am Dent Assoc 81:81, 1970
39. Weichselbaum PK, Derbes VJ: Chronic scarring aphthous ulcers of the mouth. Suppressive action of prednisone. Oral Surg 10:370, 1957
40. Wray D: Gluten-sensitive recurrent aphthous stomatitis. Dig Dis Sci 26:737, 1981

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