The Oral Pathology Top Seven List

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The Oral Pathology Top Seven List

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Case #7

Denture-Related Hyperplasia
the mandibular cuspid. It is frequently bilateral and typically appears as a small, pink papule that measures less than 5 mm in diameter (Fig. 12-10). Retrocusp papillae are quite common, having been reported in 25% to 99% of children and young adults. The prevalence in older adults drops to 6% to 19%, suggesting that the retrocusp papilla represents a normal anatomic variation that disappears with age.

**Histopathologic Features**

Microscopic examination of the giant cell fibroma reveals a mass of vascular fibrous connective tissue, which is usually loosely arranged (Fig. 12-11). The hallmark is the presence of numerous large, stellate fibroblasts within the superficial connective tissue. These cells may contain several nuclei. Frequently, the surface of the lesion is pebbly. The covering epithelium often is thin and atrophic, although the rete ridges may appear narrow and elongated.

**Treatment and Prognosis**

The giant cell fibroma is treated by conservative surgical excision. Recurrence is rare. Because of their characteristic appearance, retrocusp papillae should be recognized clinically and do not need to be excised.

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**EPULISFISSURATUM (INFLAMMATORY FIBROUS HYPERPLASIA; DENTURE INJURY TUMOR; DENTURE EPULIS)**

The epulis fissuratum is a tumorlike hyperplasia of fibrous connective tissue that develops in association with the flange of an ill-fitting complete or partial denture. Although the simple term epulis sometimes is used synonymously for epulis fissuratum, epulis is actually a generic term that can be applied to any tumor of the gingiva or alveolar mucosa. Therefore, some authors have advocated not using this term,
preferring to call these lesions *inflammatory fibrous hyperplasia* or other descriptive names. However, the term *epulis fissuratum* is still widely used today and is well understood by virtually all clinicians. Other examples of epulides include the *giant cell epulis* (peripheral giant cell granuloma) (see page 485), *ossifying fibroid epulis* (peripheral ossifying fibroma) (see page 487), and *congenital epulis* (see page 503).

**Clinical Features**

The epulis fissuratum typically appears as a single or multiple fold or folds of hyperplastic tissue in the alveolar vestibule (Figs. 12-12 and 12-13). Most often, there are two folds of tissue, and the flange of the associated denture fits conveniently into the fissure between the folds. The redundant tissue is usually firm and fibrous, although some lesions appear erythematous and ulcerated, similar to the appearance of a pyogenic granuloma. Occasional examples of epulis fissuratum demonstrate surface areas of inflammatory papillary hyperplasia (see page 478). The size of the lesion can vary from localized hyperplasias less than 1 cm in size to massive lesions that involve most of the length of the vestibule. The epulis fissuratum usually develops on the facial aspect of the alveolar ridge, although occasional lesions are seen lingual to the mandibular alveolar ridge (Fig. 12-14).

The epulis fissuratum most often occurs in middle-aged and older adults, as would be expected with a denture-related lesion. It may occur on either the maxilla or mandible. The anterior portion of the jaws is affected much more frequently than the posterior region.
more often than the posterior areas. There is a pronounced female predilection; most studies show that two-thirds to three-fourths of all cases submitted for biopsy occur in women.

Another similar but less common fibrous hyperplasia, often called a fibroepithelial polyp or leaflike denture fibroma, occurs on the hard palate beneath a maxillary denture. This characteristic lesion is a flattened pink mass that is attached to the palate by a narrow stalk (Fig. 12-15). Usually, the flattened mass is closely applied to the palate and sits in a slightly cupped-out depression. However, it is easily lifted up with a probe, which demonstrates its pedunculated nature. The edge of the lesion often is serrated and resembles a leaf.

Histopathologic Features

Microscopic examination of the epulis fissuratum reveals hyperplasia of the fibrous connective tissue. Often multiple folds and grooves occur where the denture impinges on the tissue (Fig. 12-16). The overlying epithelium is frequently hyperparakeratotic and demonstrates irregular hyperplasia of the rete ridges. In some instances, the epithelium shows inflammatory papillary hyperplasia (see page 478) or pseudoepitheliomatous (pseudocarcinomatous) hyperplasia. Focal areas of ulceration are not unusual, especially at the base of the grooves between the folds. A variable chronic inflammatory infiltrate is present; sometimes, it may include eosinophils or show lymphoid follicles. If minor salivary glands are included in the specimen, then they usually show chronic sialadenitis.

In rare instances, the formation of osteoid or chondroid is observed. This unusual-appearing process, known as osseous and chondromatous metaplasia, is a reactive phenomenon caused by chronic irritation by the ill-fitting denture (see page 292). The irregular nature of this bone or cartilage can be microscopically disturbing, and the pathologist should not mistake it for a sarcoma.

The denture-related fibroepithelial polyp has a narrow core of dense fibrous connective tissue covered by stratified squamous epithelium. Like the epulis fissuratum, the overlying epithelium may be hyperplastic.

Treatment and Prognosis

The treatment of the epulis fissuratum or fibroepithelial polyp consists of surgical removal, with microscopic...
CHAPTER 12
Soft Tissue Tumors

478

Papillary surface. Many cases are associated with denture stomatitis.

**INFLAMMATORY PAPILLARY HYPERPLASIA (DENTURE PAPILLOMATOSIS)**

Inflammatory papillary hyperplasia is a reactive tissue growth that usually, although not always, develops beneath a denture. Some investigators classify this lesion as part of the spectrum of denture stomatitis (see page 194). Although the exact pathogenesis is unknown, the condition most often appears to be related to the following:

- An ill-fitting denture
- Poor denture hygiene
- Wearing the denture 24 hours a day

Approximately 20% of patients who wear their dentures 24 hours a day have inflammatory papillary hyperplasia. Candida organisms also have been suggested as a cause, but any possible role appears uncertain.

**Clinical Features**

Inflammatory papillary hyperplasia usually occurs on the hard palate beneath a denture base (Figs. 12-17 and 12-18). Early lesions may involve only the palatal vault, although advanced cases cover most of the palate. Less frequently, this hyperplasia develops on the edentulous mandibular alveolar ridge or on the surface of an epulis fissuratum. On rare occasions, the condition occurs on the palate of a patient without a denture, especially in people who habitually breathe through their mouth or have a high palatal vault. Candida-associated palatal papillary hyperplasia also has been reported in dentate patients with human immunodeficiency virus (HIV) infection.

Inflammatory papillary hyperplasia is usually asymptomatic. The mucosa is erythematous and has a pebbly or papillary surface. Many cases are associated with denture stomatitis.

**Histoopathologic Features**

The mucosa in inflammatory papillary hyperplasia exhibits numerous papillary growths on the surface that are covered by hyperplastic, stratified squamous epithelium (Fig. 12-19). In advanced cases, this hyperplasia is pseudoepitheliomatous in appearance, and the pathologist should not mistake it for carcinoma (Fig. 12-20). The connective tissue can vary from loose and edematous to densely collagenized. A chronic inflammatory cell infiltrate is usually seen, which consists of lymphocytes and plasma cells. Less frequently, polymorphonuclear leukocytes are also present. If underlying salivary glands are present, then they often show sclerosing sialadenitis.

**Treatment and Prognosis**

For very early lesions of inflammatory papillary hyperplasia, removal of the denture may allow the erythema and edema
CHAPTER 12
Soft Tissue Tumors

Fig. 12-20 Inflammatory Papillary Hyperplasia. Higher-power view showing pseudoepitheliomatous hyperplasia of the epithelium. This epithelium has a bland appearance that should not be mistaken for carcinoma.

to subside, and the tissues may resume a more normal appearance. The condition also may show improvement after topical or systemic antifungal therapy. For more advanced and collagenized lesions, many clinicians prefer to excise the hyperplastic tissue before fabricating a new denture. Various surgical methods have been used, including the following:

- Partial-thickness or full-thickness surgical blade excision
- Girettage
- Electroosurgery
- Gyosurgery
- Lasersurgery

After surgery, the existing denture can be lined with a temporary tissue conditioner that acts as a palatal dressing and promotes greater comfort. After healing, the patient should be encouraged to leave the new denture out at night and to keep it clean.

FIBROUS HISTIOCYTOMA

Fibrous histiocytomas are a diverse group of tumors that exhibit fibroblastic and histiocytic differentiation, although the cell of origin is uncertain. Because of the variable nature of these lesions, an array of terms has been used for them, including dermatofibroma, sclerosing hemangioma, fibroxanthoma, and nodular subepidermal fibrosis. Unlike other fibrous growths discussed previously in this chapter, the fibrous histiocytoma is generally considered to represent a true neoplasm.

Clinical Features

The fibrous histiocytoma can develop almost anywhere in the body. The most common site is the skin of the extremities, where the lesion is called a dermatofibroma. Tumors of the oral and perioral regions are rare, and it is likely that many previously reported examples would be reclassified today as solitary fibrous tumors (see next topic). Rare intra-bony lesions of the jaws also have been reported. Oral fibrous histiocytomas tend to occur in middle-aged and older adults; cutaneous examples are most frequent in young adults. The tumor is usually a painless nodular mass and can vary in size from a few millimeters to several centimeters in diameter (Fig. 12-21). Deeper tumors tend to be larger.

Histopathologic Features

Microscopically, the fibrous histiocytoma is characterized by a cellular proliferation of spindle-shaped fibroblastic cells with vesicular nuclei (Figs. 12-22 and 12-23). The margins of the tumor often are not sharply defined. The tumor cells are arranged in short, intersecting fascicles, known as a storiform pattern because of its resemblance to the irregular, whorled appearance of a straw mat. Rounded histiocyte-like cells, lipid-containing xanthoma cells, or multinucleated giant cells can be seen occasionally, as may scattered lymphocytes. The stroma may demonstrate areas of myxoid change or focal hyalinization.
The Oral Pathology Top Seven List

Brad W. Neville, DDS

Case #6

Sialolithiasis
lesions of patients with multiple “mucus retention cysts” also show prominent oncocytic metaplasia of the epithelial lining.

**Treatment and Prognosis**

Isolated salivary duct cysts are treated by conservative surgical excision. For cysts in the major glands, partial or total removal of the gland may be necessary. The lesion should not recur.

For rare patients who develop multifocal salivary ductal ectasia (“mucus retention cysts”), local excision may be performed for the more problematic swellings; however, surgical management does not appear feasible or advisable for all of the lesions, which may number as many as 100. In one reported case, systemic erythromycin and chlorhexidine mouth rinses were helpful in relieving pain and reducing drainage of pus. Sialagogue medications also may be helpful in stimulating salivary flow, thereby preventing the accumulation of inspissated mucus within the dilated excretory ducts.

**SIALOLITHIASIS (SALIVARY CALCULI; SALIVARY STONES)**

Sialoliths are calcified structures that develop within the salivary ductal system. Researchers believe that they arise from deposition of calcium salts around a nidus of debris within the duct lumen. This debris may include inspissated mucus, bacteria, ductal epithelial cells, or foreign bodies. The cause of sialoliths is unclear, but their formation can be promoted by chronic sialadenitis and partial obstruction. Their development typically is not related to any systemic derangement in calcium and phosphorus metabolism.

**Clinical and Radiographic Features**

Sialoliths most often develop within the ductal system of the submandibular gland, which accounts for about 80% of cases; the formation of stones within the parotid gland system is distinctly less frequent. The long, tortuous, upward path of the submandibular (Wharton) duct and the thicker, mucoid secretions of this gland may be responsible for its greater tendency to form salivary calculi. Sialoliths also can form within the minor salivary glands, most often within the glands of the upper lip or buccal mucosa. Salivary stones can occur at almost any age, but they are most common in young and middle-aged adults.

Major gland sialoliths most frequently cause episodic pain or swelling of the affected gland, especially at mealtime. The severity of the symptoms varies, depending on the degree of obstruction and the amount of resultant back-pressure produced within the gland. If the stone is located toward the terminal portion of the duct, then a hard mass may be palpated beneath the mucosa (Fig. 11-13).

Sialoliths typically appear as radiopaque masses on radiographic examination. However, not all stones are visible on standard radiographs (perhaps because of the degree of calcification of some lesions). They may be disguised anywhere along the length of the duct or within the gland itself (Fig. 11-14). Stones in the terminal portion of the submandibular duct are best demonstrated with an occlusal radiograph. On panoramic or periapical radiographs, the calcification may appear superimposed on the mandible and care must be exercised not to confuse it with an intrabony lesion (Fig. 11-15). Multiple parotid stones radiographically can mimic calcified parotid lymph nodes, such as might occur in tuberculosis. Sialography, ultrasound, and CT scanning may be helpful additional imaging studies for sialoliths. Diagnostic sialendoscopy also can be a valuable tool in the evaluation and diagnosis of ductal obstructions. In this technique, a miniaturized endoscope is inserted into the duct orifice, allowing visualization of the ductal system for any stones, strictures, or adhesions.

Minor gland sialoliths often are asymptomatic but may produce local swelling or tenderness of the affected gland (Fig. 11-16). A small radiopacity often can be demonstrated with a soft tissue radiograph.

**Histopathologic Features**

On gross examination, sialoliths appear as hard masses that are round, oval, or cylindrical. They are typically yellow,
often demonstrates squamous, oncocytic, or mucous cell metaplasia. Periductal inflammation is also evident. The ductal obstruction frequently is associated with an acute or chronic sialadenitis of the feeding gland.

**Treatment and Prognosis**

Small sialoliths of the major glands sometimes can be treated conservatively by gentle massage of the gland in an
Recurrent or persistent ductal obstruction (most commonly caused by sialoliths) can lead to a chronic sialadenitis. Periodic swelling and pain occur within the affected gland, usually developing at mealtime when salivary flow is stimulated. Sialography often demonstrates sialectasia (ductal dilatation) proximal to the area of obstruction (Fig. 11-20). In chronic parotitis, Stensen duct may show a characteristic sialographic pattern known as “sausaging,” which reflects a combination of dilatation plus ductal strictures from scar formation. Chronic sialadenitis also can occur in the minor glands, possibly as a result of blockage of ductal flow or local trauma.

**SIALADENITIS**

Inflammation of the salivary glands (sialadenitis) can arise from various infectious and noninfectious causes. The most common viral infection is mumps (see page 238), although a number of other viruses also can involve the salivary glands, including Coxsackie A, ECHO, choriomeningitis, parainfluenza, human immunodeficiency virus (HIV), and cytomegalovirus (CMV) (in neonates). Most bacterial infections arise as a result of ductal obstruction or decreased salivary flow, allowing retrograde spread of bacteria throughout the ductal system. Blockage of the duct can be caused by sialolithiasis (see page 427), congenital strictures, or compression by an adjacent tumor. Decreased flow can result from dehydration, debilitation, or medications that inhibit secretions.

One of the more common causes of sialadenitis is recent surgery (especially abdominal surgery), after which an acute parotitis (surgical mumps) may arise because the patient has been kept without food or fluids (NPO) and has received atropine during the surgical procedure. Other medications that produce xerostomia as a side effect also can predispose patients to such an infection. Most community-acquired cases of acute bacterial sialadenitis are caused by *Staphylococcus aureus* or streptococcal species. Hospital-acquired infections are also most frequently associated with *S. aureus*, but they also may be caused by a variety of other species, including *Eikenella corrodens*, *Escherichia coli*, *Fusobacterium*, *Haemophilus influenzae*, *Klebsiella*, *Prevotella*, *Proteus*, and *Pseudomonas*. Noninfectious causes of salivary inflammation include Sjögren syndrome (see page 434), sarcoidosis (see page 310), radiation therapy (see page 266), and various allergens.

**Clinical and Radiographic Features**

Acute bacterial sialadenitis is most common in the parotid gland and is bilateral in 10% to 25% of cases. The affected gland is swollen and painful, and the overlying skin may be warm and erythematous (Fig. 11-18). An associated low-grade fever and trismus may be present. A purulent discharge often is observed from the duct orifice when the gland is massaged (Fig. 11-19).

Recurrent or persistent ductal obstruction (most commonly caused by sialoliths) can lead to a chronic sialadenitis. Periodic swelling and pain occur within the affected gland, usually developing at mealtime when salivary flow is stimulated. Sialography often demonstrates sialectasia (ductal dilatation) proximal to the area of obstruction (Fig. 11-20). In chronic parotitis, Stensen duct may show a characteristic sialographic pattern known as “sausaging,” which reflects a combination of dilatation plus ductal strictures from scar formation. Chronic sialadenitis also can occur in the minor glands, possibly as a result of blockage of ductal flow or local trauma.

**Juvenile recurrent parotitis** is the most common inflammatory salivary disorder of children in the United States and the second most common such disorder worldwide (following mumps). It is characterized by recurring episodes of unilateral or bilateral, non-suppurative parotid swelling, usually beginning between the ages of 3 and 6 years. The exact cause is unknown, although congenital duct malformations, genetic factors, immunologic disorders, and dental malocclusion have been suggested as possible contributing factors. Although multiple recurrences often develop, the condition usually resolves around the time of puberty.
The Oral Pathology Top Seven List

Brad W. Neville, DDS

Case #5

Pernicious Anemia
with endoscopy or esophageal barium contrast radiographic studies usually show the presence of abnormal bands of tissue in the esophagus, called esophageal webs. Another sign is an alteration of the growth pattern of the nails, which results in a spoon-shaped configuration (koilonychia). The nails may also be brittle.

Symptoms of anemia may prompt patients with Plummer-Vinson syndrome to seek medical care. Fatigue, shortness of breath, and weakness are characteristic symptoms.

Laboratory Findings
Hematologic studies show a hypochromic microcytic anemia that is consistent with an iron-deficiency anemia.

Histopathologic Features
A biopsy specimen of involved mucosa from a patient with Plummer-Vinson syndrome typically shows epithelial atrophy with varying degrees of submucosal chronic inflammation. In advanced cases, evidence of epithelial atypia or dysplasia may be seen.

Treatment and Prognosis
Treatment of Plummer-Vinson syndrome is primarily directed at correcting the iron-deficiency anemia by means of dietary iron supplementation. This therapy usually resolves the anemia, relieves the glossodynia, and may reduce the severity of the esophageal symptoms. Occasionally, esophageal dilation is necessary to help improve the symptoms of dysphagia. Patients with Plummer-Vinson syndrome should be evaluated periodically for oral, hypopharyngeal, and esophageal cancer because a 5% to 50% prevalence of upper aerodigestive tract malignancy has been reported in affected persons.

\* Pernicious Anemia

Pernicious anemia is an uncommon condition that occurs with greatest frequency among older patients of Northern European heritage, although recent studies have identified the disease in black and Hispanic populations as well. Asian populations seem to be affected much less frequently. The disease is a megaloblastic anemia caused by poor absorption of cobalamin (vitamin B\textsubscript{12}, extrinsic factor). Intrinsic factor, which is produced by the parietal cells of the stomach lining, is needed for vitamin-B\textsubscript{12} absorption. Normally, when cobalamin is ingested, it binds to intrinsic factor in the duodenum. Because the lining cells of the intestine preferentially take up the cobalamin-intrinsic factor complex, significant amounts of the vitamin cannot be absorbed unless both components are present.

In the case of pernicious anemia, most patients lack intrinsic factor because of an autoimmune destruction of the parietal cells of the stomach; this results in decreased absorption of cobalamin. Antibodies directed against intrinsic factor are also found in the serum of these patients. Vitamin B\textsubscript{12} deficiency may occur for other reasons, and although the resulting signs and symptoms may be identical to those of pernicious anemia, these should be considered as distinctly different deficiency disorders. For example, a decreased ability to absorb cobalamin may also occur after gastrointestinal bypass operations. In addition, because cobalamin is primarily derived from animal sources, some strict vegetarians (vegans) may develop vitamin B\textsubscript{12} deficiency.

Because cobalamin is necessary for normal nucleic acid synthesis, anything that disrupts the absorption of the vitamin causes problems, especially for cells that are multiplying rapidly and, therefore, synthesizing large amounts of nucleic acids. The cells that are most mitotically active are affected to the greatest degree, especially the hematopoietic cells and the gastrointestinal lining epithelial cells.

Clinical Features

With respect to systemic complaints, patients with pernicious anemia often report fatigue, weakness, shortness of breath, headache, and feeling faint. Such symptoms are associated with most anemias and probably reflect the reduced oxygen-carrying capacity of the blood. Vitamin B\textsubscript{12} also functions to maintain myelin throughout the nervous system; therefore, with reduced levels of the vitamin, many patients report paresthesia, tingling, or numbness of the extremities. Difficulty in walking and diminished vibratory and positional sense may be present. Psychiatric symptoms of memory loss, irritability, depression, and dementia have also been described.

Oral symptoms often consist of a burning sensation of the tongue, lips, buccal mucosa, or other mucosal sites. Clinical examination may show focal patchy areas of oral mucosal erythema and atrophy (Fig. 17-17), or the process may be more diffuse, depending on the severity and duration of the condition. The tongue may be affected in as many as 50% to 60% of patients with pernicious anemia, but it may not show as much involvement as other areas of the oral mucosa in some instances. The atrophy and erythema may be easier to appreciate on the dorsal tongue than at other sites, however.

Histopathologic Features

Histopathologic examination of an erythematous portion of the oral mucosa shows marked epithelial atrophy with loss of rete ridges, an increased nuclear-to-cytoplasmic ratio of the surface epithelial cells, and prominent nucleoli (Fig. 17-18). This pattern can be misinterpreted as epithelial dysplasia at times, although the nuclei in pernicious anemia typically are pale staining and show peripheral chromatin clumping. A patchy diffuse chronic inflammatory cell infiltrate is usually noted in the underlying connective tissue.
the elimination of painful injections. One recent systematic literature review has identified what appears to be an increased risk of gastric carcinoma, with pernicious anemia patients being seven times more likely to develop this tumor compared to the general population. Both vitamin B<sub>12</sub> deficiency and folate deficiency will cause megaloblastic anemia, and it is important to distinguish between the two problems. Treatment of vitamin B<sub>12</sub> deficiency with folate will resolve the anemia and the oral mucosal atrophy, but reduced myelin production will continue, resulting in further CNS damage.

**PITUITARY DWARFISM**

Pituitary dwarfism is a relatively rare condition that results from either the diminished production of growth hormone by the anterior pituitary gland, abnormalities of the growth hormone molecule, or a reduced capacity of the tissues to respond to growth hormone. Affected patients are typically much shorter than normal, although their body proportions are generally appropriate.

Several conditions may cause short stature, and a careful evaluation of the patient must be performed to rule out other possible causes, such as the following:

1. Intrinsic defects in the patient’s tissues (e.g., certain skeletal dysplasias, chromosomal abnormalities, and idiopathic short stature)
2. Alterations in the environment of the growing tissues (e.g., malnutrition, hypothyroidism, and diabetes mellitus)

If a lack of growth hormone is detected, the cause should be determined. Sometimes the fault lies with the pituitary gland itself (e.g., aplasia or hypoplasia). In other instances, the problem may be related to destruction of the pituitary or hypothalamus by tumors, therapeutic radiation, or infection.

If the hypothalamus is affected, a deficiency in growth hormone–releasing hormone, which is produced by the hypothalamus, results in a deficiency of growth hormone. Often deficiencies in other hormones, such as thyroid...

**Laboratory Findings**

Hematologic evaluation of vitamin B<sub>12</sub> deficiency shows a macrocytic anemia and reduced serum cobalamin levels. The Schilling test for pernicious anemia has been used to determine the pathogenesis of the cobalamin deficiency by comparing absorption and excretion rates of radiolabeled cobalamin. However, this study is rather complicated to perform, and is now considered to be obsolete. The presence of serum antibodies directed against intrinsic factor is quite specific for pernicious anemia.

**Treatment and Prognosis**

Once the diagnosis of pernicious anemia is established, treatment traditionally has consisted of monthly intramuscular injections of cyanocobalamin. The condition responds rapidly once therapy is initiated, with reports of clearing of oral lesions within 5 days. High-dose oral cobalamin therapy has also been shown to be an equally effective treatment, however, with advantages being its cost-effectiveness and the elimination of painful injections.
The Oral Pathology Top Seven List

Brad W. Neville, DDS

Case #4

Cinnamon Stomatitis
The antigen can be placed on the mucosa in a mixture with Orabase or in a rubber cup that is fixed to the mucosa.

**Treatment and Prognosis**

In mild cases of acute contact stomatitis, removal of the suspected allergen is all that is required. In more severe cases, antihistamine therapy, which is combined with topical anesthetics, usually is beneficial. Chronic reactions respond to removal of the antigenic source and application of a topical corticosteroid gel or oral suspension.

When attempting to discontinue the source of a diffuse allergic mucositis, use of plain baking soda or toothpaste that is free of flavoring or preservatives is recommended. The patient also should be instructed to avoid mouthwash, gum, mints, chocolate, cinnamon-containing products, carbonated drinks, and excessively salty, spicy, or acidic foods. If an association cannot be found, then cutaneous patch testing may provide helpful information.

**PERIORAL DERMATITIS (PERIORIFICAL DERMATITIS)**

Perioral dermatitis does not refer to every rash that occurs around the mouth but is specific for a unique inflammatory skin disease that involves the cutaneous surfaces surrounding the facial orifices. Because the disorder also often involves the paranasal and periorbital skin, periorificial dermatitis is the most appropriate designation. Although the process is idiopathic, the dermatitis is associated strongly with uncritical use of potent topical corticosteroids on the facial skin. F luorinated toothpaste and overuse of heavy facial cosmetics, creams, and moisturizers also are implicated in many patients. Weaker correlations have been seen with systemic corticosteroids, corticosteroid inhalers, and nasal corticosteroids. Heavy exposure to ultraviolet light, heat, and wind appears to worsen the dermatitis. Some of these substances may initially induce an irritant or allergic contact dermatitis, whereas others are thought to produce inappropriate occlusion of the skin surface with subsequent proliferation of skin flora.

**Clinical Features**

Perioral dermatitis appears with persistent erythematous papules, papulovesicles, and papulopustules that involve the skin surrounding the vermilion border of the upper and lower lips. In addition, involvement of the perinasal skin is seen in approximately 40% of affected patients, and 25% have periorbital dermatitis (Fig. 9-36). Classically, there is a zone of spared skin immediately adjacent to the vermilion border. Pruritus and burning are variable. The vast majority of the cases are diagnosed in women between the ages of 20 to 45 years, lending further support to the association with cosmetic use. In spite of this, the process does occur in men and in children of either sex.

**Histopathologic Features**

Biopsy of perioral dermatitis demonstrates a variable pattern. In many cases there is a chronic lymphohistiocytic dermatitis that often exhibits spongiosis of the hair follicles. In other patients a rosacea-like pattern is noted in which there is perifollicular granulomatous inflammation. On occasion, this histopathologic pattern has been misdiagnosed as sarcoidosis.

**Treatment and Prognosis**

Most cases resolve with “zero therapy,” which includes discontinuation of corticosteroids, cosmetics, and facial creams. Discontinuation of potent topical corticosteroid use often is followed by a period of exacerbation, which can be minimized by substitution of a less potent corticosteroid before total cessation. Oral tetracycline is considered the therapeutic gold standard for perioral dermatitis but must be avoided during childhood and pregnancy. In addition, a shortage of tetracycline in the United States has made its use problematic. No strong evidence has been presented to demonstrate that doxycycline or minocycline is equivalent or superior to tetracycline. Luckily, perioral dermatitis also responds well to topical pimecrolimus or topical erythromycin. Weaker therapeutic recommendations include topical metronidazole, clindamycin, tetracycline, adapalene, or azelaic acid, plus systemic erythromycin or isotretinoin. The pathosis typically demonstrates significant improvement within several weeks and total resolution in a few months. Recurrence is uncommon.

**CONTACT STOMATITIS FROM ARTIFICIAL CINNAMON FLAVORING**

Mucosal abnormalities secondary to the use of artificially flavored cinnamon products are fairly common, but the
range of changes was not recognized widely until the late 1980s. Cinnamon oil is used as a flavoring agent in confectionery, ice cream, soft drinks, alcoholic beverages, processed meats, gum, candy, toothpaste, breath fresheners, mouthwashes, and even dental floss. Concentrations of the flavoring are up to 100 times that in the natural spice. The reactions are documented most commonly in those products associated with prolonged or frequent contact, such as candy, chewing gum, and toothpaste. The anticalculus components of tar tar-control toothpastes have a strong bitter flavor and require a significant concentration of flavoring agents including cinnamon to hide the taste, resulting in a greater chance these formulations will cause oral mucosal lesions. Although much less common, reactions to cinnamon in its natural spice form have been documented.

**Clinical Features**

The clinical presentations of contact stomatitis vary somewhat, according to the medium of delivery. Toothpaste results in a more diffuse pattern; the signs associated with chewing gum and candy are more localized. Pain and burning are common symptoms in all cases.

The gingiva is the most frequent site affected by toothpaste, often resembling plasma cell gingivitis (see page 145); enlargement, edema, and erythema are common. Sloughing of the superficial oral epithelium without creation of an erosion is seen commonly. Erythematous mucositis, occasionally combined with erosion, has been reported on the buccal mucosa and tongue. Exfoliative cheilitis and circumoral dermatitis also may occur.

Reactions from chewing gum and candy are more localized and typically do not affect the lip vermilion or perioral skin. Most of the lesions appear on the buccal mucosa and lateral borders of the tongue. Buccal mucosal lesions often are oblong patches that are aligned along the occlusal plane (Fig. 9-37). Individual lesions have an erythematous base but often are predominantly white as a result of hyperkeratosis of the surface epithelium. Ulceration within the lesions may occur. Hyperkeratotic examples often exhibit a ragged surface and occasionally may resemble the pattern seen in morsicatio (see page 259). Lingual involvement may become extensive and spread to the dorsal surface (Fig. 9-38). Significant thickening of the surface epithelium can occur and may raise clinical concern for oral hairy leukoplakia (OHL) (see page 242) or carcinoma (Fig. 9-39).

**Histopathologic Features**

Usually, the epithelium in contact stomatitis from artificial cinnamon flavoring is acanthotic, often with elongated rete ridges and thinning of the suprapapillary plates. Hyperkeratosis and extensive neutrophilic exocytosis may be present. The superficial lamina propria demonstrates a heavy inflammatory cell infiltrate that consists predominantly of lymphocytes that may be intermixed with plasma cells, histiocytes, or eosinophils. This infiltrate often obscures the epithelium and connective tissue interface (Fig. 9-40). A characteristic feature in localized cases caused by gum, mints, or candies is the frequent presence of an obvious perivascular inflammatory infiltrate that extends well below the interface zone (Fig. 9-41).
reappear, usually within 24 hours. On occasion, resolution is more gradual and the patient may benefit from short-term use of a topical corticosteroid.

**LICHENOID CONTACT REACTION FROM DENTAL RESTORATIVE MATERIALS**

Dental amalgam has been in active use for over 180 years and has proven to be a durable and relatively inexpensive material that remains one of the most commonly placed dental restorations. Because of an associated low-level release of mercury from these fillings (an amount significantly less than the daily contribution from food and non-dental sources), its use has been blamed for a wide variety of health concerns. Due to the controversy, a number of controlled studies were performed, showing no association between the presence of dental amalgams and systemic disease. Two oral pathoses, burning mouth syndrome and orofacial granulomatosis, also have been correlated with the presence of amalgams by some investigators, but no conclusive evidence exists to associate these disorders with the dental restorative material. The primary adverse effects that are well documented include acute and chronic hypersensitivity reactions.

Dental amalgams contain mercury, silver, tin, and copper, with some variations also including zinc, indium, palladium, or platinum. The vast majority of hypersensitivity reactions to dental restorative materials are to dental amalgam, usually associated with the mercury content. Reactions have been seen much less frequently to other dental restorations containing materials such as gold, beryllium, chromium, cobalt, or composite resins.

Although rare acute reactions to mercury may be seen following placement of amalgam, the vast majority of adverse alterations represent chronic type IV hypersensitivity reactions that are seen most commonly associated with older and corroded amalgams. It is believed the metal ions released by corrosion haptenize with oral keratinocyte surface proteins and initiate a cell-mediated autoimmune response directed at the basal cell layer of the epithelium. Some investigators have called these chronic alterations “galvanic lesions,” but neither clinical nor experimental studies support the electrogalvanic hypothesis of origin.

These chronic contact reactions appear clinically and histopathologically similar to lichen planus (see page 729) but demonstrate a different mucosal distribution. When patients with true oral lichen planus are examined, the lesions migrate and exhibit no direct correlation to contact with dental materials. In addition, patients with lichen planus do not demonstrate a significantly increased positive patch testing to dental restorative materials and exhibit minimal-to-no clinical improvement on removal of their amalgams.

However, there is a subgroup of patients whose lichenoid lesions do not migrate and usually involve only the mucosa adjacent to a dental metal. On patch testing, the vast majority of patients with lichenoid lesions of this type exhibit a positive reaction to the dental restorative material. The diagnosis of galvanic lesions is based on the clinical appearance and the history of mercury exposure in the oral environment. The histopathologic features are not specific, but they are sufficient to raise a high index of suspicion in an oral and maxillofacial pathologist who is familiar with the pattern. Use of dental amalgam should be investigated in every patient with an atypical pattern of gingivitis. Diet-related examples often are the most difficult to diagnose and may necessitate cutaneous allergy patch testing or a diet diary to isolate the cause.

**Treatment and Prognosis**

Typically, the signs and symptoms disappear within 1 week after the discontinuation of the cinnamon product. If the patient resumes intake of the product, the lesions reappear, usually within 24 hours. On occasion, resolution is more gradual and the patient may benefit from short-term use of a topical corticosteroid.
The Oral Pathology Top Seven List

Brad W. Neville, DDS

Case #3

Neurofibromatosis Type I
Clinical and Radiographic Features

The diagnostic criteria for NF1 are summarized in Box 12-1. Patients have multiple neurofibromas that can occur anywhere in the body but are most common on the skin. The clinical appearance can vary from small papules to larger soft nodules to massive, pendulous masses (elephantiasis neuromatosa) on the skin (Figs. 12-64 and 12-65). The plexiform variant of neurofibroma, which feels like a “bag of worms,” is considered pathognomonic for NF1. The tumors may be present at birth, but they often begin to appear during puberty and may continue to develop slowly throughout adulthood. Accelerated growth may be seen during pregnancy. There is a wide variability in the expression of the disease. Some patients have only a few neurofibromas; others have literally hundreds or thousands of tumors. However, two-thirds of patients have relatively mild disease.

Another highly characteristic feature is the presence of café au lait (coffee with milk) pigmentation on the skin (Fig. 12-66). These spots occur as yellow-tan to dark-brown...
macules that vary in diameter from 1 to 2 mm to several centimeters. In NF1, this pigmentation typically has a smooth edge (“coast of California”), in contrast to the irregular border (“coast of Maine”) of the café au lait spots that may occur with polyostotic fibrous dysplasia (see page 593). The pigmentation usually is present at birth or it may develop during the first year of life. Freckling of the axilla (Crowe sign) or of other intertriginous zones is also a highly suggestive sign.

Lisch nodules, translucent brown-pigmented spots on the iris, are found in nearly all affected individuals. The most common general medical problem is hyper tension, which may develop secondary to coarctation of the aorta, pheochromocytoma, or renal artery stenosis. Other possible abnormalities include CNS tumors, macrocephaly, mental deficiency, seizures, short stature, and scoliosis.

Studies indicate that oral manifestations may occur in as many as 72% to 92% of cases, especially if a detailed clinical and radiographic examination is performed. The most commonly described finding is enlargement of the fungiform papillae, which has been reported in up to 50% of patients; however, the specificity of this finding for neurofibromatosis is unknown. Only about 25% to 37% of patients will develop actual intraoral neurofibromas (Fig. 12-67). Radiographic findings may include enlargement of the mandibular foramen, enlargement or branching of the mandibular canal, increased bone density, concavity of the medial surface of the ramus, and increase in dimension of the coronoid notch. Cephalometric analysis often shows a short length of the mandible, maxilla, and cranial base.

Several unusual clinical variants of NF1 have been described. On occasion, the condition can include unilateral enlargement that mimics hemifacial hyperplasia (see page 35). In addition, several patients with NF1 have been described with associated Noonan syndrome or with central giant cell granulomas of the jaw.

Treatment and Prognosis

There is no specific therapy for NF1, and treatment often is directed toward prevention or management of complications. Facial neurofibromas can be removed for cosmetic purposes. Carbon dioxide (CO₂) laser and dermabrasion have been used successfully for extensive lesions. NF1 patients with prominent hemifacial enlargement may require more significant cosmetic remodeling surgery.

One of the most feared complications is the development of cancer, most often a malignant peripheral nerve sheath tumor (neurofibrosarcoma; malignant schwannoma), which has been reported to occur in about 5% of cases. These tumors are most common on the trunk and extremities, although head and neck involvement is occasionally seen (Figs. 12-68 to 12-70). The 5-year survival rate for malignant peripheral nerve sheath tumors associated with NF1 is 35% to 54%. Other malignancies also have been associated with NF1, including CNS tumors, pheochromocytoma, leukemia, rhabdomyosarcoma, and Wilms tumor. The average lifespan of individuals with NF1 is 8 to 15 years.
that he most likely had a rare condition known as Proteus syndrome. Because patients with NF1 may fear acquiring a similar clinical appearance, they should be reassured that they have a different condition. The phrase “Elephant Man disease” is incorrect and misleading, and it should be avoided. Genetic counseling is extremely important for all patients with neurofibromatosis.

◆ MULTIPLE ENDOCRINE NEOPLASIA TYPE 2B

The multiple endocrine neoplasia (MEN) syndromes are a group of rare autosomal dominant conditions characterized by tumors or hyperplasias of the neuroendocrine tissues (see Table 12-1, page 493). MEN type 1 is caused by mutations of the \textit{MEN1} gene located on chromosome 11. Affected individuals can develop a variety of tumors of the parathyroid glands, pancreatic islets, anterior pituitary gland, and adrenal cortex. MEN type 2 encompasses a family of disorders (familial medullary thyroid carcinoma [MTC] syndrome, MEN type 2A, and MEN type 2B) that are characterized by the development of MTC. These three conditions are caused by mutations at various sites of the RET proto-oncogene on chromosome 10. Patients with familial MTC syndrome develop MTC but are not at increased risk for other neuroendocrine tumors. Patients with MEN type 2A are at increased risk for MTC (over 95% of patients), adrenal pheochromocytomas (50% of patients), and primary hyperparathyroidism (20% to 30% of patients).

Over 95% of cases of MEN type 2B are caused by a germline mutation at codon 918 (M918T) of the RET proto-oncogene, although a few examples have been described with a mutation at codon 883 (A883F). In addition to MTC and pheochromocytomas, patients develop mucosal neuromas that especially involve the oral mucous membranes. Because oral manifestations are prominent...
The Oral Pathology Top Seven List

Brad W. Neville, DDS

Case #2

Multiple Endocrine Neoplasia Type 2B
that he most likely had a rare condition known as Proteus syndrome. Because patients with NF1 may fear acquiring a similar clinical appearance, they should be reassured that they have a different condition. The phrase “Elephant Man disease” is incorrect and misleading, and it should be avoided. Genetic counseling is extremely important for all patients with neurofibromatosis.

◆ MULTIPLE ENDOCRINE NEOPLASIA TYPE 2B

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Over 95% of cases of MEN type 2B are caused by a germline mutation at codon 918 (M918T) of the \( \text{RET} \) proto-oncogene, although a few examples have been described with a mutation at codon 883 (A883F). In addition to MTC and pheochromocytomas, patients develop mucosal neuromas that especially involve the oral mucous membranes. Because oral manifestations are prominent...
**Chapter 12**

**Soft Tissue Tumors**

498

abdominal distention, megacolon, constipation, and diarrhea. The most significant aspect of this condition is the development of MTC, which occurs in virtually all cases. This aggressive tumor arises from the parafollicular cells (C cells) of the thyroid gland, which are responsible for calcitonin production. MTC silently develops early in life and, without prophylactic thyroidectomy before 1 year of age, most patients will develop metastatic tumor during childhood or adolescence.

**Laboratory Values**

If MTC is present, then serum or urinary levels of calcitonin are elevated. An increase in calcitonin levels may herald the onset of the tumor, and calcitonin also can be monitored to detect local recurrences or metastases after treatment. Pheochromocytomas may result in increased levels of urinary vanillylmandelic acid (VMA) and increased epinephrine-to-norepinephrine ratios.

**Histopathologic Features**

The mucosal neuromas are characterized by marked hyperplasia of nerve bundles in an otherwise normal or loose connective tissue background (Figs. 12-73 and 12-74). Prominent thickening of the perineurium is typically seen.

**Treatment and Prognosis**

The prognosis for patients with MEN type 2B centers on early recognition of the oral features. Because of the extremely poor prognosis for MTC, the thyroid gland should be removed as soon as possible—preferably within the first year of life. The average age of death from this neoplasm is 21 years. It has been suggested that patients with the A883F mutation of the RET proto-oncogene may develop a less aggressive form of MTC than patients with the M918T mutation. Patients also should be observed for the development of pheochromocytomas because they may
result in a life-threatening hypertensive crisis, especially if surgery with general anesthesia is performed.

**MELANOTIC NEUROECTODERMAL TUMOR OF INFANCY**

The melanotic neuroectodermal tumor of infancy is a rare pigmented neoplasm that usually occurs during the first year of life. It is generally accepted that this lesion is of neural crest origin. In the past, however, a number of tissues were suggested as possible sources of this tumor. These included odontogenic epithelium and retina, which resulted in various older terms for this entity, such as pigmented ameloblastoma, retinal anlage tumor, and melanotic progonoma. Because these names are inaccurate, however, they should no longer be used.

**Clinical and Radiographic Features**

Melanotic neuroectodermal tumor of infancy almost always develops in young children during the first year of life; only 9% of cases are diagnosed after the age of 12 months. There is a striking predilection for the maxilla, which accounts for 69% of reported cases. Less frequently reported sites include the skull (11%), epididymis and testis (9%), mandible (6%), and brain (4%). A slight male predominance has been noted.

The lesion is most common in the anterior region of the maxilla, where it classically appears as a rapidly expanding mass that is frequently blue or black (Fig. 12-75). The tumor often destroys the underlying bone and may be associated with displacement of the developing teeth (Fig. 12-76). In some instances, there may be an associated osteogenic reaction, which exhibits a “sun ray” radiographic pattern that can be mistaken for osteosarcoma.

**Laboratory Values**

High urinary levels of vanillylmandelic acid (VMA) often are found in patients with melanotic neuroectodermal tumor of infancy. These levels may return to normal once...
The Oral Pathology Top Seven List
Brad W. Neville, DDS

Case #1

Pyostomatitis Vegetans
Pyostomatitis vegetans is a relatively rare condition that has a controversial history. It has been associated in the past with diseases such as pemphigus or pyodermatitis vegetans. Most investigators today, however, believe that pyostomatitis vegetans is an unusual oral expression of inflammatory bowel disease, particularly ulcerative colitis or Crohn disease. The pathogenesis of the condition, like that of inflammatory bowel disease, is poorly understood. A few patients with pyostomatitis vegetans have also been noted to have one of several concurrent liver abnormalities.

**Clinical Features**

Patients with pyostomatitis vegetans exhibit characteristic yellowish, slightly elevated, linear, serpentine pustules set on an erythematous oral mucosa. These lesions are seen on the buccal mucosa, appearing as yellow-white pustules. Oral discomfort is variable but can be surprisingly minimal in some patients. This variation in symptoms may be related to the number of pustules that have ruptured to form ulcerations. The oral lesions may appear concurrently with the bowel symptoms, or they may precede the intestinal involvement.

**Histopathologic Features**

A biopsy specimen of an oral lesion of pyostomatitis vegetans usually shows marked edema, causing an acantholytic appearance of the involved epithelium. This may be the result of the accumulation of numerous eosinophils within the spinous layer, often forming intraepithelial abscesses. Subepithelial eosinophilic abscesses have been used successfully to manage refractory oral ulcers of Crohn disease.
CHAPTER 17  Oral Manifestations of Systemic Diseases

reported in some instances. The underlying connective tissue usually supports a dense mixed infiltrate of inflammatory cells that consists of eosinophils, neutrophils, and lymphocytes. Perivascular inflammation may also be present.

**Treatment and Prognosis**

Usually, the intestinal signs and symptoms of inflammatory bowel disease are of most concern for patients with pyostomatitis vegetans. Medical management of the bowel disease with sulfasalazine or systemic corticosteroids also produces clearing of the oral lesions (see Fig. 17-45). Often the oral lesions clear within days after systemic corticosteroid therapy has begun, and they may recur if the medication is withdrawn. If the bowel symptoms are relatively mild, then the oral lesions have been reported to respond to topical therapy with some of the more potent corticosteroid preparations.

**UREMIC STOMATITIS**

Patients who have either acute or chronic renal failure typically show markedly elevated levels of urea and other nitrogenous wastes in the bloodstream. **Uremic stomatitis** represents a relatively uncommon complication of renal failure. In two series that included 562 patients with renal failure, only eight examples of this oral mucosal condition were documented. Nevertheless, for the patients in whom uremic stomatitis develops, this can be a painful disorder. The cause of the oral lesions is unclear, but some investigators suggest that urase, an enzyme produced by the oral microbiota, may degrade urea secreted in the saliva. This degradation results in the liberation of free ammonia, which presumably damages the oral mucosa.

**Clinical Features**

Most cases of uremic stomatitis have been reported in patients with acute renal failure. The onset may be abrupt, with white plaques distributed predominantly on the buccal mucosa, tongue, and floor of the mouth (Fig. 17-47). Patients may complain of unpleasant taste, oral pain, or a burning sensation with the lesions, and the clinician may detect an odor of ammonia or urine on the patient’s breath. The clinical appearance occasionally has been known to mimic oral hairy leukoplakia.

**Treatment and Prognosis**

In some instances, uremic stomatitis may clear within a few days after renal dialysis, although such resolution may take place over 2 to 3 weeks. In other instances, treatment with a mildly acidic mouth rinse, such as diluted hydrogen peroxide, seems to clear the oral lesions. For control of pain while the lesions heal, patients may be given palliative therapy with ice chips or a topical anesthetic, such as viscous lidocaine or dyclonine hydrochloride. Although renal failure itself is life threatening, at least one example of a uremic