Clinicopathologic conference cases presented at the Annual Meeting of the American Academy of Oral and Maxillofacial Pathology, June 14-19, 2013

CLINICOPATHOLOGIC CONFERENCE CASE 1: INCIDENTAL FINDING ON LEFT POSTERIOR TONGUE

TM Gibson, BD Martin, University of Missouri—Kansas City, School of Dentistry, Kansas City, MO, USA; David Grant Medical Center, Travis Air Force Base, CA, USA

Clinical Presentation: An asymptomatic 67-year-old Indian man presented for routine dental care. His medical history was significant only for insulin-dependent diabetes and remote cerebrovascular accident. The patient denied history of cigarette smoking, betel nut use, and alcohol consumption.

On initial examination, a sessile, uniformly elevated plaque of the left postero-lateral tongue was observed, measuring approximately 2.5 × 2 cm (Figure 1-1, A). The lesion exhibited a yellowish hue and a subtle verrucous architecture. The area was nontender to palpation. The entirety of the well-delineated lesion’s anterior border was visible within the oral cavity.

In addition to the aforementioned lesion, the clinical examination also found a large unrelated homogenous white plaque of the left lateral tongue. A biopsy was taken of the leukoplakia, which was diagnosed as hyperparakeratosis without dysplasia.

Differential Diagnosis: The list of differential diagnoses for epithelial lesions affecting the posterior tongue is quite broad. Considerations including potentially malignant conditions, neoplastic conditions, and developmental anomalies were entertained.

Any well-defined plaque of the postero-lateral tongue, a high-risk site, with associated architectural and color change, should be investigated to rule out an epithelial process such as oral epithelial dysplasia (OED) or oral squamous cell carcinoma (OSCC). OED, a potentially malignant condition, typically presents as an asymptomatic erythroplakia or leukoplakia.1,2 Architectural alterations range from nearly imperceptible in early lesions to a papillary or nodular appearance in later-stage lesions. As alterations in color, texture, ulceration, and firmness are observed, they raise the index of suspicion that the preneoplastic OED has transformed into OSCC.3 OED cannot be completely excluded clinically, but the lack of ulceration induration argues against OSCC.

Oral mucosal lymphangioma is a hamartomatous tumor of lymphatic tissue.4 This benign proliferation is usually diagnosed at a young age, with 50% occurring congenitally and the remainder typically discovered by the third year of life.5,6 Nearly 75% of all lymphangiomas are found in the head and neck, with oral lesions most often arising on the anterior two-thirds of the tongue.5,8 There is no gender predilection.7 Lymphangiomas of the tongue can be situated deep or superficially, with the more superficial lesions presenting as a pebbly or cluster-like accumulation of translucent to red-purple vesicles. These changes are commonly described as having a “frog egg” or “ tapioca pudding” appearance. Although the tongue is a common location for oral lesions most often arising on the anterior two-thirds of the tongue, there is no gender predilection.7,8 In contrast to our patient’s lesions, oral linear epidermal nevi (OLEN) present during childhood and typically stabilize during adolescence. Clinically they appear as verrucous papules and plaques and follow a linear distribution. Unlike the skin lesions, which are usually pigmented, OLEN tend to range from normal to yellow-white. Although oral involvement is rare, the tongue is the most common location, and solitary oral lesions have been reported.7,10

Acanthosis nigricans (AN) is an acquired cutaneous alteration associated with a number of systemic conditions including gastrointestinal adenocarcinoma and insulin-resistant diabetes mellitus.7,10 Because of these associations, AN is generally observed in older patients. Oral involvement occurs in 15% to 40% of cases, with the higher end of the spectrum associated with malignancy.11 Oral involvement presents as finely papillary surface alterations that generally lack pigment as seen in the

Fig. 1-1. A, Clinical mirror image of patient’s left tongue demonstrates a 2.5 × 2-cm well-delineated plaque with a yellow hue and subtle verrucous architecture. Located anteriorly on the lateral border of the tongue is a homogenous leukoplakia. B, Clinical image of patient’s left tongue 1 week after biopsy. Biopsy was taken from the center of the leukoplakia and the anterosuperior margin of the well-delineated plaque with a yellow hue.
cutaneous lesions. The tongue is a common location. To help manage his diabetes mellitus, he was taking metformin at the time of diagnosis. Interestingly, metformin is used to manage AN associated with insulin resistance, and thus argues against this being diabetes-associated AN.

Verruciform xanthoma (VX) is a benign hyperplastic condition most often affecting the oral mucosa, although skin and genitalia may be involved. The cause is unknown but may be reactive or immune related. VX generally arises in the fifth and sixth decades, slightly more often in men. Intraorally it presents most often on the gingiva and alveolar mucosa. VX tends to be sessile, slightly elevated with subtle papillary surface alterations, well-delineated, and ranging in color from red to yellow. Most oral lesions are 2 cm or smaller, although lesions up to 4 cm have been reported. The overall clinical presentation of this plaque of the posterolateral tongue was most consistent with a diagnosis of VX.

**Diagnosis and Management:** The patient subsequently had an incisional biopsy performed of the anterior leukoplakic lesion and the posterior papillary sessile lesion with a yellowish hue (see Figure 1-1, B). The histopathology of the lesion revealed papillary parakeratinized oral epithelium with elongated rete ridges and parakeratin plugging of the crypts located between the epithelial projections (Figures 1-2 and 1-3). In the connective tissue papillae were large macrophages with granular cytoplasm and round nuclei (Figure 1-4). These macrophages have been shown to contain lipids and are often referred to as xanthoma cells. The accumulation of lipid contributes to the yellowish clinical appearance.

The final diagnosis was verruciform xanthoma. Although lesional tissue of the verruciform xanthoma remains, no further treatment is planned. Malignant transformation of verruciform xanthoma has not been reported. The leukoplakic area will continue to be followed clinically.

**Discussion:** Verruciform xanthoma is a hyperplastic mucocutaneous condition first described in the oral cavity by Shafer in 1971. It most often occurs on the masticatory mucosa surfaces, with the gingiva being the most frequent site of occurrence. The penis, scrotum, and vulva have been reported as extraoral locations. It is not uncommon for a VX to be clinically mistaken for a squamous papilloma, condyloma acuminatum, or even a squamous cell carcinoma. Verruciform xanthomas are more often found in middle-aged adults, with a slight male predilection.

A definitive etiology for verruciform xanthoma has yet to be defined. The human papillomavirus has been implicated, but only a few cases have been positive for human papillomavirus and a viral pathogenesis has yet to be established. The most
prevalent and accepted theory is that verruciform xanthoma occurs as a result of an inflammatory response to localized epithelial damage or trauma or an unusual reaction. VX may be seen in association with conditions involving epithelial disturbances, such as lichen planus, lupus erythematosus, epidermolysis bullosa, epithelial dysplasia, squamous cell carcinoma, pemphigus vulgaris, warty dyskeratoma, and graft-vs-host disease.

Verruciform xanthomas are not associated with diabetes, lipoprotein metabolism, hyperlipidemia, or any other metabolic disorder. Xanthomatous infiltrates of the skin are usually associated with lipoprotein metabolism disorders. This does not pertain to verruciform xanthomas of the skin; lipid metabolism is usually normal. 13

References


CLINICOPATHOLOGIC CONFERENCE CASE 2: A MAN WITH PROGRESSIVE ALVEOLAR BONE LOSS AND SPONTANEOUS TOOTH EXFOLIATION BC Jham, R Hill, M Mulholland, PC Edwards, Midwestern University, College of Dental Medicine, Downers Grove, IL, USA; Private Practice, Periodontics, Bay City, MI, USA; Private Practice, Oral and Maxillofacial Surgery, Bay City, MI, USA; Indiana University, School of Dentistry, Indianapolis, IN, USA

Clinical Presentation: A 46-year-old man was seen with a 2-year history of increasing maxillary anterior and left premolar tooth mobility. On interview, the patient reported frequent purulent, foul tasting drainage from the immediate area that was unresponsive to conventional periodontal therapy. Medical history included hypertension, treated with Losartan (50 mg/d) for the past 3 years.

Clinical examination found multiple well-defined punctate lesions on the attached maxillary gingiva, each measuring between 0.1 and 0.3 cm; they were red, and several had a surrounding white halo, creating a target-like appearance (Figure 2-1, A, B). In addition, a single, well-defined, white, linear area of exposed bone with irregular borders, measuring approximately 10 mm, was present on the gingival mucosa adjacent to the left maxillary central incisor. A. Right side. B. Left side.

Fig. 2-1. Multiple well-defined punctate lesions are noted. A single, well-defined area of exposed bone is present on the gingival mucosa adjacent to the left maxillary central incisor. A. Right side. B. Left side.
Differential Diagnosis: Given the clinical presentation of extensive bone loss, periodontal disease (PD) was the first consideration. Periodontal disease is a chronic inflammatory disease that involves the periodontium and gradually destroys the alveolar bone. Chronic periodontitis is the most common form of PD, representing the primary cause of tooth loss in adults over 35 years of age. In the current case, the patient’s gingival tissues appeared uninfamed, with small amounts of plaque and calculus, which would not favor a diagnosis of periodontal disease. Also, chronic periodontitis typically develops over a period of years to decades. However, certain diseases can modify the course and behavior of chronic periodontitis. In this context, poorly controlled diabetic individuals show an exaggerated inflammatory response to the bacterial challenge of periodontal disease, increasing the severity of periodontal disease and potentially accelerating bone and tooth loss. However, even in periodontal disease associated with diabetes mellitus, some degree of gingival inflammation would be expected. Also, the absence of bleeding and the presence of minimal plaque did not favor this diagnosis.

Patients with neutropenia present with a variety of oral manifestations, including gingivitis and periodontitis. Deep periodontal pockets, generalized bone loss, and advanced tooth mobility have been reported. However, a decrease in host defenses and a history of infections elsewhere in the body would be expected in a patient with severe neutropenia. Chronic leukemias can affect middle-aged adults and lead to mucosal ulceration and gingival enlargement. Osseous changes have also been described. However, gingival and bony infiltration by leukemic cells is more common in acute forms of the disease. Intense bleeding, which was absent in the current case, is also commonly noted.

The evolution period favored a benign or low-grade malignant neoplasm, whereas the aggressive pattern of bone destruction was more characteristic of a malignant process. However, more localized change would be expected, in contrast to the more generalized (2 quadrants) presentation noted in this case. Thus, systemic malignancies, including lymphoma, multiple myeloma, and metastases, were also considered in the differential diagnosis.

Langerhans cell histiocytosis (LCH) can mimic periodontal disease. The intraoral presentation of LCH classically includes punched-out necrotic ulcers with considerable amounts of associated granulation tissue, tissue necrosis, marked bone loss, and loosening of teeth. The current case showed some features consistent with LCH. However, LCH is more commonly a disease of the late teens to early adulthood. Also, the radiographic presentation of LCH is classically that of multiple punched-out radiolucent lesions, often exhibiting a “teeth floating in the air” radiographic presentation.

One of the most striking features of the present case was the fact that the left secondary maxillary premolar had self-exfoliated. In children, a number of diseases are known to cause early exfoliation of deciduous teeth, including Papillon-Lefèvre syndrome, hypophosphatasia, Chédiak-Higashi syndrome, and leukocyte adhesion deficiency. Exfoliation of permanent teeth has been reported in the context of bone osteonecrosis associated with trigenital herpes zoster. Also, as previously mentioned, painless exfoliation of teeth could ensue secondary to necrosis of the bone. Findings inconsistent with herpes zoster in this case included the multiple-year duration, the absence of obvious surface epithelial necrosis, the lack of classic clinical symptoms such as pain, and the observation that the process clearly crossed the midline.

**Diagnosis and management:** An incisional biopsy was performed, revealing fragments of surface epithelium containing a subsurface proliferation of hyperplastic stratified squamous epithelium demonstrating marked hyperortho- and hyperparakeratinization (Figure 2-3, A). Lesional tissue harvested from...
within the bone consisted of ribbons of hyperkeratinized epithelium surrounding numerous fragments of necrotic bone. This neoplastic epithelium lacked the classic cytologic features of malignancy, absent significant cellular or nuclear pleomorphism or mitotic activity, a feature that characterizes the deceptively bland features of the entity.

The final diagnosis, based on the clinical, radiographic, and histologic presentation, was carcinoma cuniculatum. **Discussion:** Carcinoma cuniculatum (CC) is a rare, distinct clinicopathologic variant of squamous cell carcinoma (SCC), first described in 1954. CC was originally believed to involve exclusively the skin of the sole of the foot, but involvement of other sites is now accepted. The etiology of CC is unknown, although tobacco and alcohol use have been suggested as possible predisposing factors. Trauma has also been suggested as a possible etiologic factor, although there is no evidence to support this. The possibility of an association with human papillomavirus infection has also been raised, but this remains doubtful.

There is disagreement over whether there is a sex predilection, with some studies reporting the lesion as more common in men, whereas others indicate an equal distribution between the sexes. CC appears to primarily affect older adults, with a mean age of approximately 50 years, and a more recent investigation suggesting a mean age of 67 years. However, CC can affect patients over a wide age range, from 7 years to 92 years.

Clinically, CC presents initially as a slow-growing mass. The 2-year evolution of the current case is in agreement with the literature, which documents periods ranging from 1 to 24 months (mean, 8.5 months) before diagnosis. The most common clinical presentation is that of an indurated, occasionally painful, surface ulcer. However, signs and symptoms vary and may include swelling, white patches, bleeding, and exudation. Of the cases occurring in the oral cavity, 78% involved the alveolar gingiva or palate, with burrowing into the underlying bone representing a defining feature. Bony involvement often leads to loosening of teeth. Radiographically, radiolucent lesions with ill-defined margins and resorption of adjacent cancellous and cortical bone may be observed in more advanced lesions.

Macroscopically, CC shows both exophytic and endophytic growth patterns. Cords and ribbons of heavily keratinized epithelium penetrate deeply into the underlying tissue and bone, creating ramified sinuses and crypts similar to rabbit burrows (cuniculus, hence the name cuniculatum). The keratin-filled crypts tend to discharge a yellowish, foul-smelling secretion. Microscopically, CC is defined by its characteristic infiltrative pattern of deep proliferation of stratified squamous epithelium forming keratin cores and keratin-filled crypts that are characteristically devoid of significant atypia. The diagnosis is challenging because of the rarity of this lesion and lack of familiarity with the condition by many clinicians and pathologists. The histopathologic differential diagnosis includes verrucous carcinoma, which generally does not present with the prominent infiltrative invasion into bone, and well-differentiated SCC. In fact, CC is often mistakenly considered to represent a variant of verrucous carcinoma. Lesions demonstrating heavy orthokeratinization, as in the current case, may be potentially misdiagnosed as an orthokeratinizing odontogenic cyst, particularly if the clinical and radiographic features are overlooked.

**Fig. 2-3.** A, Low-magnification photomicrograph of the biopsy specimen demonstrates normal surface epithelium overlying strands of markedly hyperkeratinized epithelium that is burrowing into the underlying connective tissue (hematoxylin-eosin). B, The maxillary bone is replaced by ribbons of epithelium demonstrating prominent keratinization and forming keratin-filled crypts (hematoxylin-eosin). C, The epithelial ribbons are deceptively bland looking, with no significant cellular pleomorphism and minimal mitotic activity. This epithelium surrounds a fragment of nonviable bone (hematoxylin-eosin).
CC is a locally aggressive tumor, and the preferred treatment is en bloc resection with the goal of achieving tumor-free margins.21,24 Chemotherapy and radiotherapy have been used in a few cases, but their benefit is controversial.21,27

Prognosis is favorable, as CC is rarely associated with regional or distant metastasis.24 Although recurrence is not expected,29,24 when it does occur, pathologic transformation into conventional SCC is sometimes noted, resulting in a more aggressive clinical presentation.21

As is clearly highlighted in the current case, a definitive diagnosis of carcinoma cuniculatum is dependent on correlating the classic, but usually bland, cytology of the lesion with the clinical and radiographic findings.

References

CLINICOPATHOLOGIC CONFERENCE CASE 3: A 75-YEAR-OLD MAN WITH PROGRESSIVE RIGHT-SIDED HEARING LOSS AND DIZZINESS

N Said-Al-Naief, A Pourian, J Cure, R Lopez, Loma Linda University, School of Dentistry, Loma Linda, CA, USA; University of Iowa, School of Dentistry, Iowa City, IA, USA; University of Alabama, School of Medicine, Birmingham, AL, USA; Charlotte Radiology PA, Charlotte, NC, USA

Clinical Presentation: A 57-year-old man presented to the otolaryngology—head and neck surgery department by referral from a Veterans Affairs hospital for further evaluation of dizziness and lightheaded unsteadiness. This was accompanied by vague, nonspecific right-sided temporal bone and temporomandibular discomfort. He also had had progressive hearing loss since 1973 but denied any otologic or any other head and neck symptoms. Thorough head and neck evaluation found intact
cranial nerves II to XII except for decreased hearing on the right side. His vision was also normal. Review of his medical history found hypertension and diabetes mellitus. He was on insulin, omeprazole, citalopram, metoprolol, metformin, potassium, enalapril, and meclizine. He also reported the surgical removal of a right heel spur several years ago with uneventful healing. The physical examination was within normal limits. Examination of the oral cavity and oropharynx demonstrated no abnormalities, and examination of the neck found no palpable lymphadenopathy, thyromegaly, or masses noted. Similarly, the examination of the external auditory canals was clean, and the tympanic membranes appeared translucent and mobile. There were no middle ear effusions, and the nasal passages were clear. However, he underwent an audiogram, which found a profound right sensorineural hearing loss. He does not use any tobacco products and does not drink alcohol. Additionally, there were no known drug allergies to report. Family history was positive for hypertension and diabetes mellitus, and he had a half-brother who was diagnosed with a brain tumor, but he did not recall the exact type.

Axial computed tomography (CT) without contrast found marked endosteal scalloping of the right posterior petrous bone centered over the retro labyrinthine area, and a slightly enlarged adjacent vestibular aqueduct with respect of mastoid (Figure 3-1). At magnetic resonance imaging, a 3-cm, expansile, well-circumscribed mass could be seen arising from the right petrous bone with an exophytic component extending into the cerebellopontine angle. The mass appeared heterogeneous on both T1- and T2-weighted images, with focal high signal intensities, possibly owing to subacute hemorrhages. The lesion encroached on the vestibular aqueduct. On T1, the majority of the lesion was isointense with the cerebellum, with a nodular area of hyper-intensity, which may represent blood- or protein-filled cysts (Figure 3-2). The lesion is mostly hyperintense on T2, with intensity equal to that of the surrounding cerebrospinal fluid, except for a focal nodule centrally (Figure 3-3).

**Differential Diagnosis:** Considering the radiographic and histomorphologic pattern combined, a thorough clinical,
Meningiomas may be confused with ELSTs, especially compared with those seen as a result of secondary extension from especially those arising in temporal bone and ear, are rare cerebellopontine angle. 1-3 Primary extracranial meningiomas, considered characteristic.1,5 Histologically, schwannomas are Widening of the fallopian canal in the temporal bone is also considered characteristic.1,5 Histologically, schwannomas are spindle cell neoplasms with the palisaded nuclear cell patterns and haphazardly arranged patterns known as Antoni A (Verocay bodies) and Antoni B patterns, respectively. The tumor also characteristically stains positively with anti S-100 protein antibodies and collagen IV immunohistochemistry (IHC) stains, among other peripheral nerve sheath IHC staining markers.

Meningioma is the second most common tumor found in the cerebellopontine angle.1,3 Primary extracranial meningiomas, especially those arising in temporal bone and ear, are rarely compared with those seen as a result of secondary extension from an intracranial tumor, constituting fewer than 1% of all meningiomas.2 Meningiomas may be confused with ELSTs, especially when arising in the posterior aspect of petrous bone, at the jugular foramen; however, unlike ELSTs, meningiomas tend to extend to the path of least resistance, grow along dural planes, and have slow-growing pushing or scalloped margins. They are typically associated with hyperostosis of the bone in juxtaposed position to the tumor.4 Furthermore, homogeneous enhancement is identified on T1-weighted scans with contrast compared with the heterogeneous pattern seen in ELSTs and T2-weighted imaging of meningiomas; the hypointense uniform features reflect the cellular density of the tumor. Middle ear meningiomas are more common in women during the fifth decade of life, and symptoms may also overlap with those of ELST, in which patients typically report loss of hearing and equilibrium, headaches, obstruction, and cranial nerve involvement. Meningioma may have various histomorphologic patterns, especially the meningothelial type (which has lobules of tumor cells with indistinct borders and round to oval nuclear contours) and the psammomatous variants (which display similar histomorphologic features as seen in the meningothelial, with the addition of concentric lamellar calcific deposits called psammoma bodies). Immunohistochemistry staining is not particularly helpful in distinguishing ELST from meningioma; meningioma typically reacts positively with vimentin, exhibits focal weak positive staining with epithelial membrane antigen (EMA), and may occasionally react with anti S-100 protein immunohistochemical stains.

Paragangliomas (PGs) of the head and neck are rare tumors, comprising approximately 3% of all paragangliomas.3 Primary cerebellopontine angle paragangliomas are rare, with the majority of tumors encountered in this region representing glomus jugulare or glomus tympanicum tumors with secondary extension to this region.7 These tumors also should be considered in the differential diagnosis of ELST, especially when involving the posterior portion of the temporal bone. PG may be distinguished by the precontrast T1-weighted pepper pattern, reflecting the high-flow voids observed within the tumor accompanied by the permeative destructive bony changes seen. The typical hyperintense salt-like foci, reflecting the low-flow nature of the lesion seen with ELST, is rarely or never observed in paragangliomas, which typically exhibit a salt-and-pepper pattern on imaging.8,10 Lipomas of the cerebellopontine angle are rare and represent fewer than 1% of tumors in that region; they may cause hearing loss, vertigo, dizziness, unsteadiness, and tinnitus.11 They are believed to be derived from the persistence and abnormal lipo-matous differentiation of meninx primitive; an essential mesenchymal tissue, which covers the brain and gives rise to the dura and other important tissues in that region. Histologically, these lesions have mature adipose tissue with well-vascularized background, and they therefore appear with low density on CT scans and are characteristically without contrast uptake. Furthermore, they appear hyperintense (to brain tissue) on T1 images and hypointense on T2 imaging.12 Metastatic tumors should also be included in the list of pathologies involving the cerebellopontine angle. Several malignancies may potentially metastasize to the cerebellopontine angle, such as breast, lung, prostate, skin, cervix, liver, brain, gastrointestinal, and oral cavity tumors.13 The presence of primary disease elsewhere, especially papillary renal cell carcinoma and papillary thyroid carcinoma, should definitely raise that possibility, especially because both tumor types exhibit a comparable papillary pattern on histomorphologic examination. A thorough clinical and pathologic examination supplemented by a tedious microscopic examination, which may or may not require additional immunohistochemical or molecular work-up, would help in differentiating ELST from metastatic tumors.

Middle ear adenoma (MA) may also exhibit clinical and histomorphologic overlap with ELST; however, the coexpression of epithelial and neuroendocrine markers in an adenomatous tumor of the inner ear that is typically confined to this region and does not exhibit bone involvement can readily distinguish ELST from MA. Similarly, a thorough clinical and radiographic as well as histologic work-up can help in separating ELST from other pathologies such as chordoid carcinoma, epidermoid cyst, and choroid plexus papilloma, among several others.

Diagnosis and Management: The patient underwent a resection of the neoplasm at the base of the posterior cranial fossa and jugular foramen extradurally, via a transcochlear approach to the posterior cranial fossa, including the jugular foramen. Total excision of the tumor also necessitated labyrinthectomy and complete mastoidectomy with decompression of the facial nerve without mobilization. He also received free abdominal fat and temporoparietal facial grafts. Histomorphologic examination found a cystic tumor with a papillary, cystic, or glandular architecture that exhibited rich vascularity and exhibited an ill-defined, locally infiltrative growth pattern with destruction of petrous bone. On higher magnification, the papillary and glandular structures were found to be lined by a single layer of flattened cuboidal-to-short columnar cells, and the stroma supporting the papillary fronds was richly vascularized and chronically inflamed and supported marked hemorrhage and hemosiderin pigment deposition. The epithelial cells had uniform nuclei that were usually situated either in the cell center or toward the luminal aspect. The cells had pale eosinophilic to clear cytoplasm and well-defined to vaguely defined borders; assuming plant-like morphology (Figures 3-4 and 3-5). There was minimal cellular pleomorphism, and only rare mitotic activity was seen. Many of the cystic glandular spaces were filled with colloid-like material that was remarkably similar to thyroid tissue but stained positively with periodic acid–Schiff special stains and negatively with TTF-1 (thyroid transcription factor) immunohistochemical staining (Figures 3-5 and 3-6). The tumor also reacted positively...
The inner ear is encased within the bony labyrinth of the temporal bone, which comprises 2 functional parts, the cochlea and vestibular system; together they are responsible for hearing and balance/equilibrium, respectively.15,16 The vestibular system comprises the utricle, the 3 semicircular canals, and the saccule. The endolymphatic duct arises from the posterior wall of the saccule and ends up in a blind pouch: the endolymphatic sac. Studies have suggested that the endolymphatic duct and sac possess absorptive, secretory phagocytic and immune properties and functions.17-18

Adenomatous tumors of the temporal bone and middle ear in particular are rare and share many overlapping clinical and often radiographic features and exhibit pleomorphic morphology, which contributes to the difficulty of classification by both clinicians and pathologists. In 1976, Hyams and Michaels19 and Derlacki and Barney,20 working independently, spearheaded the defining of middle ear adenoma (MEA), recognizing its derivation from modified ear mucosa and its indolent, nonaggressive, nonresorptive biologic behavior, while Murphy et al.21 recognized the bimodal epithelial-neuroendocrine features of these tumors. Later on, Gaffey et al.22 described an aggressive, middle ear/temporal bone tumor that occurred in association with von Hippel–Lindau (VHL) syndrome, and they adopted the terminology “aggressive papillary tumor,” capable of bone resorption and locally aggressive biologic behavior, distinguishing it from MEA; currently equivalent to ELST. ELST is a rare, low-grade papillary adenocarcinoma that arises from ectodermally derived epithelial tissues of endolymphatic duct or sac or neuro-ectodermal tissues adjacent to an intermediate portion of the petrous bone, within the vestibular canal,23,24 which accounts for the propensity of these tumors to involve and erode the temporal bone and cerebellopontine angle.23,25

ELST was first recognized by Hassard et al.26 in 1984 and further characterized as a separate entity by Heffner in 1989,24 who reported 20 similar cases of low-grade papillary adenocarcinoma from the files of the Armed Forces Institute of Pathology, including the one reported by Hassard et al.26 Patients typically present with unilateral hearing loss (which may be sudden), vertigo, and tinnitus, and a minority of patients also report facial nerve paralysis and cerebellar disorders. The clinical features may often simulate those seen in Meniere disease, which include (among others) the presence of aura, headaches, increased ear pressure, dizziness, tinnitus, and hearing loss. ELSTs may be
encountered as sporadic cases, in which tumors are typically unilateral, whereas bilateral tumors are more commonly encountered as part of VHL, where ELSTs are considered to be an integral and essential part of the diseases. VHL is an uncommon autosomal dominant condition, characterized by the presence of several neoplasms including cerebellar, spinal, and retinal hemangioblastomas, pheochromocytomas, and renal cell carcinoma, and approximately 11% to 15% of patients with VHL also develop ELSTs. VHL disease is characterized by the presence of an abnormality of the VHL gene (von Hippel–Lindau tumor suppressor, E3 ubiquitin protein ligase, which is located on the short arm of chromosome 3), which occurs in association with the other copy of the VHL gene. This genetic alteration is observed in all tumor types occurring in association with VHL, including ELST; significantly, even the sporadic, non-VHL-associated ELSTs have the aforementioned VHL gene mutation.

The tumor occurs in a wide age range, which extends from childhood to the elderly. Female prevalence and younger age of occurrence are well documented in tumors seen in the context of VHL disease compared with sporadic tumors. Endolymphatic sac tumors have a low-grade papillary architecture with prominent stromal vascularity that is typically devoid of high mitotic activity and necrosis. However, it has propensity for local infiltration and focal bone destruction. The tumor may show a follicular pattern with cystic or glandular spaces (which contain colloid-like material) or a combination of papillary and solid architecture, where cells lining the cystic spaces display plantlike to clear cell features, as observed in the present case. ELST is best and most effectively managed by total excision with or without radiation therapy. Radiation is mostly implemented in large tumors that are unsectactable and difficult to manage, primarily owing to anatomic limitation. Resection is well documented, particularly with incomplete removal, and preoperative embolization may play a role in limiting tumor recurrence, especially in large tumors. In general, prognosis is excellent with complete excision, but distant metastasis has been rarely reported.

References


**CLINICOPATHOLOGIC CONFERENCE CASE 4: PAINFUL NONHEALING ORAL ULCERATIONS**

**KK McNamara, P Pugalagiri, Ohio State University, College of Dentistry, Columbus, OH, USA; Private Practice, Plano, TX, USA**

**Clinical Presentation:** A 58-year-old white woman presented with a painful nonhealing ulcer of the right ventrolateral tongue. She reported that the lesion had been present for 8 weeks and that painful ulcerations of the uvula and right buccal mucosa arose within the past 2 weeks. Her medical history was significant for hypothyroidism and autoimmune hepatitis. She had had a liver transplant 4 months earlier and was taking levothyroxine (Synthroid), tacrolimus (Prograf), mycophenolate mofetil (CellCept), and a daily multivitamin.

The patient was initially evaluated by a local otolaryngologist, and recent blood studies were unremarkable. After 2 hospitalizations for dehydration and malnutrition, an oral and maxillofacial surgeon was consulted, who decided to perform an incisional biopsy of the right tongue lesion. A diagnosis of “nonspecific ulcer” was rendered, and the patient was referred for evaluation by an oral and maxillofacial pathologist.

Oral examination found a 1.5-cm-diameter shallow ulceration of the right ventrolateral surface of the tongue, exhibiting mild peripheral erythema and an irregular superior margin consistent with recent biopsy site (Figure 4-1, A). A 0.5-cm diameter shallow ulceration surrounded by a hint of white striae-like changes was noted on the right posterior buccal mucosa (see Figure 4-1, B), and a 0.8-cm diameter ulceration was seen on the uvula, without evidence of any peripheral mucosal alterations (see Figure 4-1, C).

**Differential Diagnosis:** Considerations in the differential diagnosis included infectious diseases, drug-induced ulcerations, and immune-mediated disorders, such as aphthous ulcerations.
Given the patient’s posttransplant immunosuppressive therapy, an infectious etiology was initially considered. Viral diseases caused by herpes simplex virus, varicella zoster virus, and cytomegalovirus can present with multiple, chronic oral mucosal ulcerations in an immunocompromised patient. Theses ulcers are often larger and more irregular than those seen in immunocompetent individuals and will persist and spread until the infection is treated or the immune function returns.

Fungal disease, such as histoplasmosis, and bacterial disease, such as tuberculosis and syphilis, were also considered in the differential diagnosis. Although most oral lesions of histoplasmosis present as a solitary, variably painful ulceration, occasionally multiple oral ulcers may be seen. Tuberculosis, caused by *Mycobacterium tuberculosis*, can also occasionally present as multiple oral ulcers with irregular borders and thus appear clinically similar to the current case. Additionally, syphilis, a venereal disease caused by *Treponema pallidum*, in its secondary or disseminated stage may occur as multiple, shallow oral mucosal ulcerations.

The patient was on an immunosuppressive regimen of mycophenolate mofetil (CellCept) and tacrolimus (Prograf), both of which have been associated with oral ulcerations in transplant patients. Although relatively uncommon, 7 cases of oral ulcers associated with the use of mycophenolate mofetil and 1 case of oral ulcerations associated with tacrolimus have been previously reported. Whereas ulcers due to mycophenolate mofetil may be caused by either drug toxicity or leukopenia, ulcers caused by tacrolimus are due to direct drug toxicity. Although recent blood studies ruled out the possibility of leukopenia in this patient, the rather nonspecific histopathologic features could be consistent with a drug reaction.

The lichenoid appearance of the buccal mucosal lesion (white striae-like changes surrounding an ulcer bed) provided further support for the possibility of a drug-induced process, specifically a lichenoid drug reaction. However, graft-vs-host disease (GVHD) was also a consideration, as it can present with oral ulcerations in association with reticular white striae involving the oral mucosa. Although GVHD occurs most commonly after bone marrow transplantation, any procedure that introduces viable allogeneic lymphocytes is capable of inducing GVHD. More than 40 cases of GVHD in liver transplant patients have been reported since the first case report in 1988.

Ultimately, a diagnosis of aphthous ulcerations was favored. Large, superficial and atypical ulcerations that clinically resemble major aphthous ulcerations have frequently been reported in immunocompromised patients. A strong association has been seen in patients infected with human immunodeficiency virus; but this process has also been well documented in association with immunosuppressive therapy, particularly with sirolimus and less frequently with tacrolimus. The nonspecific histopathologic findings supported this working diagnosis.

**Diagnosis and Management:** Review of the previous histologic sections confirmed the diagnosis of nonspecific ulcer. Ulcerated surface oral epithelium was seen in association with granulation tissue (Figure 4-2, A). The granulation tissue supported a predominantly chronic inflammatory cell infiltrate, including scattered eosinophils and occasional mononuclear cells exhibiting relatively large nuclei (B) (hematoxylin-eosin, original magnification ×40). The epithelial pattern of maturation was unremarkable, and no evidence of viral cytopathic effect was observed.

Based on the nonspecific histopathologic findings, in conjunction with the clinical setting, a working diagnosis of major aphthous ulcerations was rendered. An oral fungal culture was performed, which proved to be strongly positive for *Candida albicans*, and the patient began a course of clotrimazole (Mycelex) oral troches. After the antifungal regimen, she was instructed to commence use of prednisolone (Prelone) syrup (15 mg/5 mL), with 2 teaspoons used as a mouthrinse and swallowed once daily for 6 days, then 1 teaspoon used as a mouthrinse and expectorated twice daily until the mucosa felt comfortable.

The patient returned for reevaluation after 1 week of corticosteroid use; there was minimal response to treatment. She was asked to continue the corticosteroid regimen and return for follow-up the following week. At 2.5 weeks of corticosteroid use, she presented with low-grade fever and malaise and minimal to no improvement in the oral lesions. She also reported a 5-day history of cutaneous lesions on her back (Figure 4-3, A). The vesicles appeared somewhat translucent with an erythematous base (see Figure 4-3, B). Based on these findings, a viral etiology
was suspected, and the patient was instructed to discontinue corticosteroid use, with immediate referral for dermatologic evaluation.

A cutaneous shave biopsy of the right upper back was performed, which found an intraepithelial vesicle with acantholytic changes and virally altered epithelial cells (Figure 4-4, A). Ballooning degeneration of epithelial cell nuclei and multinucleation were occasionally observed (see Figure 4-4, B). Immunohistochemical probe analysis for antibodies directed against varicella zoster virus was positive in the majority of the altered keratinocytes (see Figure 4-4, C), consistent with infection by varicella zoster virus. Probes for herpes simplex virus types 1 and 2 were negative.

The histopathologic and immunohistochemical findings, in conjunction with the clinical setting, supported a diagnosis of disseminated herpes zoster. The patient was immediately admitted to the hospital, and intravenous acyclovir (Zovirax) was administered, resulting in swift resolution of the cutaneous and oral mucosal lesions. At the 2-month follow-up, the patient was without recurrence.

Discussion: Primary infection with varicella zoster virus (VZV), yielding chickenpox, usually presents in children. After initial infection, VZV establishes latency in dorsal-root ganglia and can undergo future reactivation as herpes zoster (HZ), that is, shingles. Up to 20% of individuals develop HZ during their lifetime, and the prevalence is rising in the elderly and in individuals with impaired immune function or underlying malignancy. Because of the need for lifetime immunosuppression, solid organ transplant recipients are at increased risk for developing HZ, with an incidence 10-fold to 100-fold greater than the general population. The overall incidence of zoster after solid organ transplant is 8.6%, and it is 5.7% when limited to liver transplant recipients.

The clinical features of HZ typically include intense pain, followed by an eruption of clusters of vesicles that quickly web 4C

Fig. 4-4. Microscopic examination found an intraepithelial vesicle with acantholytic changes (A) (hematoxylin-eosin, original magnification ×10) and virally altered epithelial cells exhibiting ballooning degeneration of epithelial cell nuclei and multinucleation (B) (hematoxylin-eosin, original magnification ×40). Immunohistochemical probe analysis for antibodies directed against varicella zoster virus was positive in the majority of the altered keratinocytes (C) (original magnification ×10).
rupture and result in small ulcerations and crusted lesions. The mucocutaneous lesions occur along an area innervated by a single sensory nerve (dermatome). By definition, HZ is considered “disseminated” when the viral exanthema affects 3 or more dermatomes2-4 and in an immunocompromised host, disseminated disease is of increased incidence.24-26 In this clinical setting, lesions are also frequently larger and more irregular, and they will persist and spread until the infection is treated or the immune function returns. In contrast, the clinical course of disease in immunocompetent individuals typically results in complete resolution of lesions within 2 to 3 weeks. Persistent pain, referred to as postherpetic neuralgia, occurs in up to 15% of affected patients and is a complication seen with greater frequency in elderly or immunosuppressed patients.23-25 In addition, visceral involvement and disseminated intravascular coagulation may occur with disseminated zoster, making it a potentially fatal illness, with a mortality rate as high as 30%.26 In solid organ transplant recipients, the median time to onset of HZ is 9 months posttransplant, and the independent risk factors include female gender and mycophenolate mofetil therapy,25,26 which are consistent with the current case.

A strong presumptive diagnosis of HZ can often be made based on the clinical presentation alone. However, laboratory procedures may be desirable for confirmation and may be a necessity for atypical cases. In the present case, the diagnoses of herpes zoster were supported by histopathologic and immunohistochemical findings of the cutaneous biopsy. The lack of characteristic histologic features of viral cytopathic effect in the initial oral mucosal biopsy is somewhat perplexing but most likely represents sampling error. Although it is possible that this patient had 2 unrelated conditions, complete resolution of the long-standing oral mucosal ulcerations after intravenous administration of acyclovir supported the diagnosis of disseminated HZ.

This case represents an unusual presentation of HZ in a liver transplant recipient. The annual number of solid organ transplants that are performed in the United States has dramatically increased over the past few decades,27 and although improvements in immunosuppression have increased survival, complications of an infectious etiology are prevalent and should be a diagnostic consideration for any nonhealing oral ulceration.

References


**CLINICOPATHOLOGIC CONFERENCE CASE 5: PATIENT PRESENTING WITH FACIAL ABSCESS AND AGGRESSIVE OSTEOLYSIS WITH PROMINENT PERIOSTEAL REACTION OF THE MANDIBLE**

_H. Chehal, JW Rohrer, JA Kini, MJ Palazzolo, Creighton University, School of Dentistry, Omaha, NE, USA; San Antonio Military Medical Center, Fort Sam Houston, TX, USA_

**Clinical Presentation:** A 78-year-old man, a nonsmoker and nondrinker, presented with right-sided facial swelling of the cheek and neck for 2 months. He reported periodic drainage into his oral cavity. Eventually, the facial swelling involved the area from his ear to the area under his chin and made talking and retaining saliva difficult. Additionally, his right eye was becoming difficult to open, owing to the edema. He reported 20 lb of recent weight loss over the last month that he attributed to stress from a financial situation. Clinical evaluation found CN VII near complete paralysis, House-Brackmann grade 6, and a firm mass in the area of the parotid. He was admitted to the medicine service with a large parotid gland/jaw abscess for intravenous antibiotics and further work-up. The patient was started on broad-spectrum antibiotics, underwent incision and drainage, and had an additional diagnosis of bacterial endocarditis. Magnetic resonance imaging of the face found a 2.5 × 3.0 × 2.8-cm enhancing parotid mass with associated calcifications and central necrosis (Figure 5-1, B). In addition, aggressive osteolysis, with a prominent periosteal reaction of the adjacent mandible (standardized uptake value, 12.7) was noted (see Figure 5-1, A, B).

**Differential Diagnosis:** Jaw lesions that frequently exhibit a periosteal reaction include osteomyelitis, trauma, and bisphosphonate-related osteonecrosis. Less commonly, such reactions may be seen in association with osteosarcoma, chondrosarcoma, and metastatic lesions to the jaws. Other rarer but important lesions presenting with periosteal reactions include Ewing sarcoma, lymphoma, and leukemia. Periosteal reactions can be of varying radiographic presentations, including solid, single-layered, multilaminated, spiculated, disorganized, and Codman triangle. Spiculated periosteal reaction, considered to be aggressive, can be of hair-on-end or sunray type. Hair-on-end periosteal reaction may be seen most often in Ewing sarcoma, osteosarcoma, or metastatic lesions, whereas a sunray reaction may be seen commonly in osteosarcoma, hemangiomia, or osteoblastic metastasis (prostatic, bronchial, and breast). Osteomyelitis, an inflammatory process of bone, may also show a nonspecific periosteal reaction with cortical plate disruption.

**Diagnosis and Management:** Further imaging, after the initial control of the infection, found extensive disease in the area of the parotid gland, extending to the parapharyngeal space, wrapping around the carotid vessels and extending to the base of the skull. This made the tumor surgically unresectable. Fine-needle aspiration of the parotid gland found abundant groups of malignant cells with large, pleomorphic nuclei and no obvious stromal component. Some of these groups formed glandular structures (Figure 5-2). Immunohistochemical stains were positive for a keratin cocktail (Lu-5). However, the tumor cells were...
negative for CK5/CK6. Prostate-specific antigen, Cdx-2, smooth muscle actin, S-100, and monoclonal carcinoembryonic antigen.

These findings were consistent with adenocarcinoma with high-grade features. A positron emission tomography–computed tomography scan found diffuse cervical lymphadenopathy. There was a 6.0 × 5.6 × 4.0-cm fluorodeoxyglucose (FDG)-avid mass (maximum standardized uptake value [SUV], 21.2) in the right parotid with corresponding 2.0-cm FDG-negative component, representing the central necrosis (see Figure 5-1, B). The remaining enlarged parotid gland had significant FDG avidity (SUV, 10.2). An incisional biopsy of the right mandible found adenocarcinoma involving bone. In the absence of a distant tumor, the patient was staged at T4 N2B M0 and combined chemo-therapy and radiation therapy were recommended, according to the multidisciplinary tumor board. After 12 months of follow-up, re-imaging of the patient found that the tumor in the area of the parotid had increased in size with marked soft tissue thickening and enhancement of the right face extending inferiorly into the neck, concerning for dural lymphatic invasion. In addition, at 12 months of follow-up, no evidence of another distant tumor was found. Other images from this case are shown in Figures 5-3 to 5-5.

Discussion: Salivary gland tumors account for about 5% of all neoplasms of the head and neck. Most occur in the parotid gland.1 Only about 15% to 32% of parotid gland tumors are malignant.2 The average annual incidence rate of salivary gland malignancies in the United States is reported at 1.41 cases per 100,000 males and 1.00 cases per 100,000 females.3 According to various studies, the peak incidence of salivary gland tumors occurs in the sixth and seventh decades of life.2,4 The factors responsible for carcinogenesis in the major salivary glands remain unclear; however, one of the well-established risk factors is exposure to ionizing radiation, as supported by studies on atomic bomb survivors.5-7 Therapeutic radiation and radioactive iodine have also been linked to salivary gland carcinogenesis.8,9,10 The 5-year relative survival rate for salivary gland cancer depends on the stage. From stage I to IV, the rates are 96%, 77%, 73%, and 37%, respectively.12 Although parotid malignancies are relatively rare, they still constitute a serious disease burden because of their poor prognosis, particularly in patients with high-grade malignancies with advanced disease.

Disclaimer: The opinions and assertions expressed herein are those of the authors and are not to be construed as official or as reflecting the views of the Department of the Air Force or the Department of Defense.

References
12. American Cancer Society, from the National Cancer Database, based on people who were diagnosed with cancer of the major salivary glands between 1998 and 1999.