
Clinical Pathologic Conference Case 1: A Woman with a Lump in Her Cheek
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Clinical Presentation: A 30-year-old woman presented with a painless lump in her right cheek. She reported that it had been present for 3-4 months and had noticed gradual enlargement. She was otherwise healthy and her medical history was non-contributory.

On examination, the lump measured 3 cm in diameter and had a slightly multinodular architecture (Figure 1). The overlying skin was slightly erythematous. Head and neck examination demonstrated no palpable cervical or submandibular lymph nodes; however, mild ipsilateral facial nerve weakness was noted (Figure 2). A fine needle aspiration biopsy (FNAB) revealed atypical squamous cells.

Differential Diagnosis: Given the location, a salivary gland neoplasm, specifically a pleomorphic adenoma, was initially considered. Pleomorphic adenomas are the most common of the salivary gland neoplasms, occur slightly more frequently in women than men, and tend to be multinodular or lobulated.1-3 They can have squamous features, and the atypical squamous cells noted on the FNAB and nerve weakness would be supportive of a carcinoma ex-pleomorphic adenoma. However, this particular location was also thought to be somewhat too far anterior for any type of salivary gland neoplasm.

Cutaneous neoplasms, although rare in the head and neck, should also be considered. Dermatofibrosarcoma protuberans is a rare cutaneous neoplasm, of which about 15% of cases occur in the head and neck region.3,4 It is also known to occur at nearly any age, have a multinodular architecture, and have slight erythema of the overlying skin.3-6 However, the majority of tumors exhibit slow but persistent growth over several years, in contrast to the history of this lesion.5,6

Soft tissues lesions such as nodular fasciitis and solitary fibrous tumor, although not common, are well known to occur at head and neck sites. Nodular fasciitis is a benign pseudotumor that can occur anywhere in the body, but will occur approximately 20% of the time in the head and neck region.7,8 It is also more commonly located in the head and neck region in young adults.5 Because of its rapid growth rate, it is often mistaken for a malignant process.7 Additionally, atypical epithelial or squamous features on FNAB have been reported in nodular fasciitis.7 Unlike this case, the majority of reported cases of head and neck nodular fasciitis occur on the scalp and not the cheek or buccal mucosa.8

Solitary fibrous tumor is a benign neoplasm that, in a recent review of 142 head and neck examples, was shown to occur most often in the buccal mucosa.9 It is primarily a tumor of adults, affects both sexes equally, and presents as a painless enlarging mass.5 Interestingly, in a case series of 21 oral cavity solitary fibrous tumors, a striking predilection (81%) for the right side was reported.10

Ultimately, based on the clinical presentation, especially the FNAB results and facial nerve weakness, a malignant process was favored. Synovial sarcoma is a malignant neoplasm typically occurring in young adults, although uncommon in the head and neck region, with fewer than 100 reported cases.11-13 Additionally, some papers have noted that head and neck synovial sarcomas have a predilection for the parotid gland region.11,12 The majority of cases are also noted to have a lobular architecture on radiologic examination.13 The biphasic variant of synovial sarcoma is composed of two distinct cell populations: epithelial cells and fibroblast-like spindle cells.5,13 However, most cases present with pain and a longer duration than noted in this case.5

Diagnosis and Management: An excisional biopsy was performed but the tissue fragmented during surgery and the lesion was removed piecemeal from the dermal and subcutaneous planes.

Histopathologic examination revealed a tumor that had the typical features of a pilomatricoma.

Fig. 1. Side view demonstrating a 3 cm mass located in the right cheek with a multinodular architecture and slight erythema of the overlying skin.

Fig. 2. Anterior view demonstrating slight weakness of the facial nerve involving the right upper lip.
There was evidence of a lobular contour with part myxoid and part dense fibrous tissue forming the periphery. It had uniform zones of basaloid (matrix) cells gradually merging with central masses of ‘ghost’ or ‘shadow’ cells (Figure 3). The basaloid cells had a high nucleus-to-cytoplasm ratio, resembled a syncytium, and contained frequent mitoses that appeared normal (Figure 4). Although the specimen was fragmented, it was possible to identify the encapsulated periphery in places (Figure 4); there were also areas of scarring with focal, keratin-induced foreign body reactions (Figure 5) with a variable degree of chronic inflammation. Overall, the tumor showed areas of both trichilemmal and infundibular differentiation.

An unusual feature of this tumor was the presence of foci of necrosis (Figure 6). This was consistently evident in the cellular areas and differed from the classical ‘necrosis’ seen in the ghost cell component in pilomatricomas.

Because of the piecemeal nature of the removal, the excision was judged incomplete and further excision recommended.

The surgeon was confident, however, that the tumor had indeed been removed and that nothing further could be achieved by additional surgery. Follow-up at 6 months revealed no evidence of recurrence, but the previously observed facial nerve weakness was unchanged.

Discussion: Pilomatricoma (pilomatrixoma) is a skin appendage tumor derived from the matrix cells of the hair follicle and is relatively common in the head and neck region; with the cheek, neck, and eyebrows being the most frequent sites, especially the parotid region. It has a wide age range, with the highest incidence in the first two decades and with no gender predilection. In retrospect, the ‘tent-like’ clinical presentation in the current case was classic (Figure 2), but palpation — rather than dependence upon photographs — would have established that this firm mass lay in a cutaneous or subcutaneous plane, mobile in relation to the deeper tissues.

Pilomatricomas evolve with time and have been classified into four histopathologic stages: early, fully developed, early regressive, and late regressive. According to this classification, the current case would represent a fully developed stage, dominated by the presence of ghost cells accompanied by proliferating matrix cells. For over a decade, it has been known that...
pilomatricomas contain mutations in the CTNNB1 gene that encodes for β-catenin,19 since found to occur in a number of different adenial tumors.19

Against a background of otherwise typical histologic features of pilomatrixoma, the presence of necrosis is rare and, in conjunction with the clinical finding of facial nerve weakness, raised the possibility of malignancy or a separate entity, proliferating pilomatrixoma.20 Specialist dermatopathologic opinion was sought and, although concern was expressed, there was reluctance to classify this tumor as malignant or even as a proliferating pilomatrixoma. Malignant variants of pilomatricoma (pilomatrix carcinoma) are rare and occur generally in the elderly. In view of the probability of incomplete removal, the recommendation was for further excision but, as indicated, it was decided to follow the patient instead. At the initial and at 6-month follow-up there was no evidence of residual tumor, an outcome that would support the interpretation of the lesion as benign. Reported recurrence rates of pilomatricomas are low, of the order of 1%–2%, and a conservative approach to their removal is generally advocated. The matter of the mild facial nerve weakness is unresolved; this was unchanged at review and the clinicians now understand that this asymmetry has been long-standing.

Skin tumors are among the less frequent causes of facial swelling, but this case illustrates the need for awareness of the spectrum of skin tumors by the oral diagnostician, particularly those with a propensity for the head and neck.

References

CLINICAL PATHOLOGIC CONFERENCE CASE 2: A DIFFUSE SWELLING OF THE NECK

Clinical Presentation: A 76-year-old man had a history of neck swelling that was noticed shortly after a mandibular posterior tooth was extracted 9 months prior to his referral to the Ohio State University College of Dentistry. Evaluation and management during that time by 3 different otolaryngologists had failed to resolve his problem. Medical history was significant for hypertension, treated with an angiotensin converting enzyme (ACE) inhibitor for many years. On examination, there was a diffusely firm and non-tender nodule involving the labial and buccal mucosa (Figure 2), and the mobility of the patient’s tongue was also reduced (Figure 3).

Differential Diagnosis: Based on the patient’s history of neck swelling that was noticed shortly after a tooth extraction, along with the fact that the patient was on an ACE inhibitor for many years, angioedema was considered in the differential diagnosis. It is well-documented that angioedema attacks may occur as an unusual form of drug reaction in patients using ACE inhibitors.1,2 Interestingly, angioedema episodes precipitated by ACE inhibition-induced angioedema is estimated to be 0.1% to 0.2%. The action of ACE is mainly the generation of angiotensin II and degradation of bradykinin, a potent vasodilator that increases vascular permeability. Although not completely understood, the mechanism of ACE inhibitor-induced angioedema appears to be associated with increased local levels of bradykinin.3 Angioedema is characterized by the sudden onset of...
one or more soft, non-tender tissue swellings measuring up to several centimeters in diameter. The symptoms are typically short-lived and resolve without sequelae during the course of 24 to 72 hours.7

Amyloidosis may cause enlargement of the tongue, as well as oral submucosal nodules, similar to those seen in our patient.8,9 Amyloidosis represents a spectrum of diseases characterized by the extracellular deposition of fibrillar proteins, termed amyloid, in the tissues of the body. The majority of cases of amyloidosis in the head and neck represent localized amyloid composed of immunoglobulin light (L) chain molecules (AL type). Notwithstanding, 90% of patients with systemic amyloidosis will develop deposits in the head, neck, or respiratory tract. Amyloidosis can affect any site of the head and neck, but most often involves the larynx and tongue; other locations that can be involved by this condition include the oral cavity, oropharynx, trachea, orbit, nose, tonsils, and salivary glands. In contrast with laryngeal amyloidosis, which is rarely associated with systemic amyloidosis, amyloid deposits in the tongue suggest a systemic AL amyloidosis associated with plasma cell dyscrasia or multiple myeloma. Oral amyloidosis is usually characterized by a diffuse or nodular enlargement of the tongue, which may feel firm or rubbery to palpation and often demonstrates scalloping of the lateral borders because of indentation from the teeth.9,10 Diminished tongue mobility/elasticity and nodular growths involving other sites of the oral mucosa have also been reported. Sometimes the oral amyloid nodules demonstrate areas of ulceration and submucosal hemorrhage.8,9

Granulomatous diseases can sometimes cause neck swelling and/or oral mucosal nodules. Sarcoidosis is a systemic, multifocal granulomatous disease of unknown etiology.11,12 Although this disorder can involve any organ, it affects primarily the respiratory tract, skin, and eyes.12 Involvement of the oral cavity is uncommon and normally appears as localized swelling or nodules involving most commonly the buccal mucosa, gingiva, and lips. Sarcoidosis can also affect the major salivary glands, causing bilateral painless swelling and frequently resulting in xerostomia.11

Tuberculosis is a chronic infectious granulomatous disease that can involve almost any system in the body. Even though pulmonary tuberculosis is the most common form of the disease, this condition can occur in other locations such as lymph nodes, central nervous system, skin, kidneys, liver, and the gastrointestinal tract. In the head and neck, the most common manifestation of tuberculosis is cervical lymphadenitis, frequently involving the posterior triangle region.13,14 Oral tuberculosis is uncommon and may manifest as either the primary or secondary form of the disease. Most oral cases appear as an indurated and painless ulcer, usually located on the tongue, gingiva, lips, or buccal mucosa.15,16 Lesions presenting as swellings and nodules (tubercles) have also been reported.15,17

In the granulomatous disease category, we included regional ileitis (Crohn’s disease) and deep fungal infections in our differential diagnosis. Although Crohn’s disease does not perfectly explain this patient’s clinical findings, we decided to include it in the differential diagnosis because of the wide range of oral lesions that have been reported in patients with this condition. Crohn’s disease is an inflammatory gastrointestinal disorder characterized by granulomatous inflammation, which may affect any site along the gastrointestinal tract, including the oral cavity. The prevalence of Crohn’s disease appears to follow a bimodal age distribution, with the disease becoming evident in early adulthood as well as 50 to 70 years of age. The frequency of oral lesions seen in patients with Crohn’s disease has been reported to range from 0.5 to 80%, depending on the definition of oral involvement. The oral findings may precede the onset of intestinal symptoms in some patients.18 A wide variety of oral lesions have been reported in patients with Crohn’s disease, including aphthous-like ulcers, mucosal tags, lip swelling, cobblestone appearance of the oral mucosa, hyperplastic folds of...
buccal vestibule, deep granulomatous-appearing ulcers, and linear ulcers of the buccal vestibule.18-21

Deep fungal infection may cause lesions in the oral cavity, and such lesions can sometimes be seen in patients with aspergillosis, cryptococcosis, histoplasmosis, or mucormycosis. These fungal infections primarily affect sites other than the oral cavity, and oral lesions are rare. Furthermore, deep fungal infections are more commonly seen in immunocompromised patients. Deep fungal infections involving the oral region have been described as diffuse swellings, black or yellow necrotic lesions, nodules, granulomas, crater-like non-healing ulcers, or granular erythematous plaques.22,23 It is plausible that a fungal infection involving the oral tissues could cause cervical lymphadenopathy resulting in a neck swelling.

Neoplastic processes such as non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) were also contemplated in our differential diagnosis. NHL occurs primarily in adults and can present as a nodal or extranodal disease.22,24 When NHL presents as a nodal disease, there is usually a nontender mass that has been slowly enlarging for months in a regional anatomic lymph node site. One or two freely movable nodules are noticed initially. As the disease progresses, the enlarged nodes become more numerous, and as the tumor infiltrates outside the capsule of the lymph node, the nodules become fixed to adjacent structures or matted together. In the oral cavity, NHL usually appears as extranodal disease and the oral lesions can be either a component of more widely disseminated disease or they might originate in the oral tissues.22,25 Oral soft tissue lesions typically present as a nontender, diffuse swelling, with a boggy consistency and an erythematous or purplish color. Superficial ulceration of the tumor mass may be seen.22,24-26 These lesions are most commonly seen in the buccal vestibule, posterior hard palate, or gingiva.22 On occasion, affected patients may present with “B” symptoms such as fever and weight loss.25

In contrast with NHL, HL nearly always begins in the lymph nodes and the most common sites of initial presentation are the cervical and supraclavicular lymph nodes. There is a male predilection and the patient’s age at diagnosis shows a bimodal pattern, with one peak observed between 15 and 35 years of age and another peak seen after the age of 50. This disease typically presents as an enlarging, nontender mass or masses in one lymph node region. Similar to NHL, in the early stages the involved lymph nodes are movable, but as the disease progresses, the nodes become more matted and fixed. Some patients might have systemic signs and symptoms of the disease such as weight loss, fever, night sweats, and generalized pruritus.22 Oral involvement by HL is rare, but it has been reported in the literature.27 The oral lesions may represent the primary site of involvement or associated cervical lymphadenopathy or more widespread disease may be noted simultaneously.28

**Diagnosis and Management:** This gentleman was initially seen by a local otolaryngologist for painless swelling of his neck a few weeks after having a dental extraction performed. The swelling was assumed to be a complication of the dental procedure, but no resolution was noted after a course of antibiotics. The patient was then referred to a second otolaryngologist, who believed that the swelling could represent angioedema related to the patient’s antihypertensive drug, an ACE inhibitor. However, no change in the swelling was seen after discontinuing the drug. The patient was referred to a third otolaryngologist who practiced head and neck oncology at a major medical center. This clinician believed that the submandibular salivary glands were enlarged and performed 6 fine needle aspiration biopsies, 3 per gland, with a pathologic diagnosis of “no tumor identified.” The patient was discharged with a diagnosis of “salivary gland tumor of uncertain biologic potential.” Approximately 6 weeks later, the patient’s dentist suggested that he be evaluated by an oral and maxillofacial pathologist because of concern by the patient’s wife that he was getting weaker by the day.

Examination showed diffuse swelling of the tongue and neck, resulting in displacement of the submandibular salivary glands inferiorly and laterally. The glands were felt to be normal in size. Multiple nodules, which were variably demarcated and confluent, were apparent in the maxillary and mandibular labial mucosa, as well as in the buccal mucosa bilaterally. The nodules were rubbery firm and non-tender. The tongue could not be protruded very far, and an ulceration was noted on the ventral tip of the tongue. The patient was referred to an oral and maxillofacial surgeon for biopsy of the tongue lesion and the labial mucosal nodules. Because of what the surgeon believed was excessive bleeding related to the tongue lesion, biopsy of the labial mucosal nodules was deferred.

Histopathologic examination of the tongue lesion showed ulcerated surface epithelium in association with underlying fibrous connective tissue and skeletal muscle, both of which were diffusely infiltrated by an amorphous hypocellular eosinophilic material suggestive of amyloid (Figures 4 and 5). This material was quite positive upon staining with the Congo red method (Figure 6), and apple-green birefringence was seen upon viewing with polarized light (Figure 7), confirming that the material was amyloid, although further immunohistochemical characterization of the amyloid was not performed. The patient was subsequently referred to the Division of Hematology and Oncology for evaluation to rule out multiple myeloma. The patient’s routine peripheral blood studies (red cell parameters, white cell parameters, and platelets) were within normal range. Evaluation of serum immunoglobulins and light chain products showed markedly increased levels of kappa light chain (3,650 mg/L; normal range: 3.3-19.3) and slightly depressed lambda light chains (5.68 mg/L; normal range: 6.71-26.3), with a kappa/lambda ratio of 642 (normal range: 0.26-1.65). In addition, suppression of immunoglobulins IgG,
IgA, and IgM below their normal levels was identified, and the patient’s 24-hour urine protein was 860 mg/day, with polyclonal kappa and lambda light chains.

A skeletal survey identified diffuse osteopenia in addition to equivocal lesions affecting the cervical spine, right humerus, both femurs, as well as both tibias and fibulas. Bone marrow biopsy showed 30% cellularity with 20-30% plasma cells that were positive for kappa light chain. Staining of the bone marrow for amyloid was negative. He had no other organ involvement with amyloid.

Based on these findings, a diagnosis of multiple myeloma, stage I (International Scoring System)/stage III (Durie/Salmon System — due to bone lesions) with localized primary amyloid of the tongue was made.

Treatment was initiated with multi-agent chemotherapy that consisted of 4 cycles of VRd (Velcade — bortezomib, a proteasome inhibitor; Revlimid — lenalidomide, a thalidomide analogue; and dexamethasone) with a very good partial response (VGPR). The patient decided not to undergo autologous stem cell transplant (ASCT) because of his age (even though age by itself is not an exclusion criteria for ASCT). He then continued with 4 cycles of lenalidomide and dexamethasone (the bortezomib was stopped because of fatigue and exertional shortness of breath), followed by maintenance lenalidomide.

Currently, the patient is 3 years out from diagnosis and continues to be in VGPR on maintenance regimen of lenalidomide, 5 mg daily on days 1-21, every 28 days. His serum kappa light chain levels dropped from 3,650 mg/L to 68 mg/L at his last examination, with a kappa/lambda ratio of 2.37. He feels well and is performing normal everyday activities, although minimal change in his tongue enlargement has been seen.

Discussion: This case represents an unusual presentation of symptomatic multiple myeloma. Generally, patients present with anemia, bone pain, or renal insufficiency as the most common signs and symptoms. While 10% of systemic primary amyloidosis patients will have coexisting multiple myeloma, newly diagnosed multiple myeloma patients generally do not have coexisting systemic primary amyloidosis, but may have localized amyloid (although unusual) as in this case.

The treatment for multiple myeloma consists of an induction regimen that includes a novel agent (lenalidomide, bortezomib, thalidomide) in combination with a corticosteroid (usually dexamethasone). Two- or 3-drug regimens can be used, followed by ASCT after 2-6 cycles in transplant-eligible patients. In transplant-ineligible patients (poor performance status, poor cardiac, and pulmonary function), a 2- to 3-drug regimen may be used as above (or containing melphalan) in a 3-drug regimen for 8-12 cycles. Maintenance treatment post-ASCT or post-induction treatment (in non-transplant patients) have improved progression-free and overall survival. With the incorporation of the novel agents and ASCT, the overall response rate has improved from 50-60% to now 80-100%, and the 5-year overall survival has increased from 30-40% to as high as 80%.

References
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Clinical Pathologic Conference Case 3: Painful, Mobile Mandibular Molar RH Younis, R Gold, RF Reich, College of Dental Surgery, University of Maryland, Baltimore; Private Practice, Randolph, NJ; New York Presbyterian Hospital

Clinical Presentation: A 73-year-old man presented to his general dentist with a chief complaint of 1-week history of a loose tooth and pain of the left mandible. The patient had a medical history significant for chronic obstructive pulmonary disease (COPD) and chronic cough, but was not on any medications except for naproxen on occasion for pain. The patient reportedly smoked half a pack of cigarettes a day for many years. Extraoral examination showed swelling of the left side of the face over the body of the mandible. Red crusty to papular cutaneous lesions were scattered on the skin of the forehead, ear, chin, and neck (Figure 1). A periapical radiograph showed a large restoration and evidence of destruction of the crown of the left second mandibular molar. Involvement of the furcation maxillofacial region: a clinical study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;99:303-310.

Fig. 1. Extra-oral examination shows swelling of the left face overlying the body of the mandible extending to the angle and ascending ramus. Red crusty to papular cutaneous lesions spread over the skin of the forehead, ear, chin, and neck.
area and significant resorption of the distal root was noted. A mottled-to-patchy radiolucency of the tooth-bearing area, with areas of radiopacity at the crestal bone and overshadowing the mesial root of the left second mandibular molar, was evident (Figure 2). The patient was prescribed an antibiotic and referred to an oral surgeon. Tooth number 18 was extracted by the oral surgeon and the surrounding tissue was harvested and submitted for pathologic examination. At 1 week follow-up, the patient

Fig. 2. A, Periapical radiograph of the left second mandibular molar shows a large restoration and evidence of involvement of the furcation area, significant resorption of the distal root and bone. Radio-opacity of the crestal bone extends to overshadow the mesial root. B, Enhanced contrast view shows mottled to patchy radiolucency throughout the tooth-bearing area that is accentuated at the distal area.

Fig. 3. One week after extraction. Non-healing extraction socket shows inflamed surrounding gingival tissue, necrotic and granulation-like tissue extruding from the socket.

Fig. 4. Low-power view of diffuse round blue cell infiltrate with a large zone of necrosis (hematoxylin and eosin; magnification ×20).

Fig. 5. Diffuse infiltration of muscle by atypical myeloid cells (hematoxylin and eosin; magnification ×100).

Fig. 6. Tumor cells exhibiting convoluted nuclei, prominent nucleoli, and atypical mitotic figures (hematoxylin and eosin; magnification ×400).
returned with necrotic and white granulation-like tissue growing out of the extraction socket (Figure 3).

Differential Diagnosis: The clinical differential diagnosis of this case includes dental infection that spread to the supporting tissue, osteomyelitis, delayed healing, medication-induced osteonecrosis of the jaw, and malignancy. The initial clinical presentation of the large restoration, root resorption, furcation involvement, and patchy radiolucency of the tooth-bearing area is consistent with that of a common dental infection that has spread to the surrounding bone, causing periapical abscess and subsequent osteomyelitis, most likely of the suppurative type based on the patchy radiolucent pattern (“moth eaten”). Yet the mixed areas of radiopacity, especially at the crestal area and along the mesial root, although potentially part of a reactive process secondary to mastication on the edentulous ridge next to a long-standing tooth, could still represent diffuse sclerosing osteomyelitis (DSO), which is characterized by sclerosis of the crestal bone presenting as a mixed radiopaque radiolucent pattern. DSO usually shows resistance to antibiotic therapy and delay in the healing process and bone remodeling because of the sclerotic vascular bone. The skin lesions in conjunction with the bone lesion are suggestive of SAPHO (synovitis-acne-pustulosis-hyperostosis osteomyelitis) as a primary type of osteomyelitis. In SAPHO, multiple bone lesion involvement is a clue. The skin lesions can be one of a wide variety of dermatologic conditions varying from pustules or psoriasis, to acne, or hidradenitis. Second, the differential diagnosis of the non-healing socket 1 week after extraction can be suggestive of a delayed healing process, as a presentation of DSO or as one of the common COPD comorbidities: vitamin C and D deficiency, especially if combined with smoking, with subsequent abnormalities in vasculature, bone remodeling, and delayed healing. The use of anesthesia with vasoconstrictor during extraction can also contribute to more delay in the healing process. The radiolucency and non-healing socket can also be suggestive of medication-induced osteonecrosis of the jaw, because COPD patients commonly use bisphosphonates or denosumab to treat osteoporosis that develops as a COPD-associated comorbidity. Finally, the clinical presentation of a loose tooth followed by a non-healing socket and extrusion of tissue out of the socket can be the first sign of a central primary malignancy or metastasis from an unknown primary malignant neoplasm. Prostate cancer can be suggested based on the radiographic presentation of patchy radiolucency mixed with radiopacity, especially because prostate cancer can present with areas of calcification. Another consideration is lung cancer, where the combination of smoking and COPD may increase the risk of lung cancer 4.5 times. In addition, lung cancer is one of the most common tumors to metastasize to the jaw.

Fig. 7. Immunohistochemical stains highlighting tumor positivity for Ki-67, muramidase, CD33, and MPO, demonstrating the high proliferation index and myeloid nature of the tumor cells (magnification ×100).

Fig. 8. Skin biopsy showing psoriasiform epidermal hyperplasia. A superficial and angiocentric infiltrate of leukemic myeloblasts is seen (hematoxylin and eosin; magnification ×40).
Recommended to predict prognosis but was not performed. A normal karyotype. FLT3 and NPM1 mutation analysis was performed, which demonstrated a psoriasiform diathesis with granulocytic sarcoma was rendered. A diagnosis of granulocytic sarcoma was rendered.

Subsequent to the diagnosis of granulocytic sarcoma, the patient was referred to Head and Neck Surgery and Hematology/Oncology for further evaluation. A bone marrow biopsy performed during his pre-treatment work-up showed that the bone marrow was involved by acute myeloid leukemia (AML) with a normal karyotype. FLT3 and NPM1 mutation analysis was recommended to predict prognosis but was not performed. Complete blood count with differential showed leukocytosis, severe anemia, and thrombocytopenia. Blasts were reported in the peripheral blood. On thorough examination, plaque-like abdominal lesions, similar to the areas noted on the patient’s face, were identified. Skin biopsy of one of these plaque-like lesions was performed, which demonstrated a psoriasiform diathesis with concomitant dermal leukemic infiltrate (Figures 8 and 9). The patient expired before commencing treatment, 2 months after initial presentation.

Discussion: Granulocytic sarcoma is defined as a tumor mass composed of immature myeloid cells involving an extramedullary site or bone, the most common sites being subperiosteal bone structures of the skull, paranasal sinus, sternum, ribs, vertebrae, pelvis, lymph nodes, and skin. Lesions of the head and neck have been reported. Granulocytic sarcoma has also been referred to as extramedullary myeloid tumor, myeloid sarcoma, and chloroma, because of the green color it often displays from the presence of abundant myeloperoxidase. It may precede, occur concurrently with, or arise subsequent to a diagnosis of AML. In a person with previously diagnosed AML, its presence may indicate relapse or transformation to a blast phase (blast crisis).

The pathogenesis for presenting with a solid tumor mass rather than a leukemic infiltrate is not known. It is also not clear why a person would develop a granulocytic sarcoma in the setting of AML. Patients with myeloproliferative or myelodysplastic diseases are also at risk for developing granulocytic sarcomas. However, granulocytic sarcomas are uncommon and only occur in 1% to 3% of patients with AML or myelodysplastic syndrome/chronic myeloproliferative disease. While granulocytic sarcomas are rare, certain subtypes of AML are predisposed to developing granulocytic sarcomas, including those with either (8;21) translocation or inv (16) (p13q22) as well as acute monoblastic/monocytic leukemia. Risk factors for AML, such as exposure to ionizing radiation, certain chemotherapeutics, exposure to benzene products and pesticides, and smoking also predispose people to the development of granulocytic sarcomas. The age range for these tumors is broad, spanning from childhood to adulthood. However, they are more commonly seen in adults. Both males and females are affected equally.

Some studies suggest that both older age and male gender impart a worse prognosis. Granulocytic sarcomas are treated with the same chemotherapeutic regimens as AML. Therapy for AML may be curative, but prognosis is poor for patients with evidence of leukemia involving their blood and bone marrow. Because granulocytic sarcomas can histologically resemble lymphoma, immunohistochemical studies are invaluable in establishing the appropriate diagnosis. This is of utmost importance when the presence of the tumor precedes bone marrow involvement or when overt leukemic symptoms are absent. This will allow for the appropriate chemotherapeutic regimen to be instituted in a timely manner.

Unfortunately, the extent of disease of our patient was not known at initial presentation, and he expired before receiving treatment. The presence of leukocytosis, severe anemia, thrombocytopenia, and blasts noted on peripheral smear during his work-up, as well as male gender and age, are all bad prognostic indicators and potentially played a role in the rapid progression of his disease.

The unusual presentation of this case and the short time span from presentation to the death of our patient emphasizes the importance of performing biopsies on any periapical curdled material as a routine measure to exclude any significant pathologic conditions.

References

**CLINICAL PATHOLOGIC CONFERENCE CASE 4: AN INCIDENTAL MAXILLARY SINUS FINDING JM Bastaki, DR Schafer, Sabah Hospital and Kuwait Cancer Control Center, Ministry of Health, Kuwait; Marine Corps Recruit Depot, Parris Island, South Carolina, USA**

**Case Presentation:** A 19-year-old African-American man reported to an outpatient dental clinic for an initial dental examination. Review of the medical history was without significant findings, including no history of sinus diseases. Radiographic evaluation identified a complete adult dentition in excellent restorative condition without any detectable carious lesions. However, a pneumatized left maxillary sinus with associated divergence of teeth #13 and #14 was identified on a panoramic radiograph (Figure 1). Periapical radiographs failed to elucidate an etiology for the sinus anomaly, so further evaluation by computed tomography (CT) study was undertaken. CT findings noted a non-aggressive lytic lesion present in the left maxillary sinus measuring 4.2 cm × 2.2 cm × 4.3 cm. Expansion and thinning of the anterior maxillary sinus wall and the posteromedial maxillary sinus wall was noted (Figure 2). Additionally, the lesion was noted to expand inferiorly, interdigitating between the roots of the maxillary second bicuspids and first molars. The remainder of the paranasal sinuses and soft tissues were within normal limits. The radiology impression was that of a nonaggressive lytic lesion with expansion, most consistent with a mucocele.

**Differential Diagnosis:** A working differential diagnosis was established and included sinus mucocele, antral pseudocyst, sinonasal tumor, and odontogenic cyst or tumor.

A true sinus mucocele may affect the frontal, ethmoid, sphenoid, or maxillary sinus; with the maxillary sinus accounting for <10% of cases.1-3 The lesion is the result of accumulation of mucin encased by respiratory epithelium, and can take as long as 10 to 15 years to produce symptoms. The etiology is often traced to prior trauma or maxillofacial surgery, resulting in a blocked ostium. The lesions will often be expansile, and can erode bone. When the maxillary sinus is involved, treatment consists of...
a Caldwell-Luc surgical approach, with or without complete cyst epithelium removal, with the main objective being to re-establishing sinus drainage.  

Antral pseudocysts are common maxillary sinus findings, occurring in 1.5% to 14% of the population. Pseudocyst formation is caused by the accumulation of inflammatory infiltrate and edema beneath the sinus mucosa. An inflammatory process of odontogenic origin is the most frequent causative agent, with secondary symptomatology to include sinus infection or allergic-type sinusitis. More frequently, the lesions are asymptomatic. The classic finding is that of an incidentally noted dome-shaped relative opacity appearing to emanate from the sinus floor. Generally, no treatment is required. Bacterial and fungal infections can arise within any of the craniofacial sinuses. While immunosuppressed individuals may be at higher risk of developing infectious sinusitis, immunocompetent patients are not invulnerable. Facial pain, discharge, and headache are the most commonly reported symptoms. Following a thorough evaluation to rule out other causes, treatment is usually pharmacologic with or without surgical intervention.

A broad range of epithelial-based, as well as mesenchymal neoplasms can occur within the sinonasal tract. Sinonasal papilloma, squamous cell carcinoma, and adenocarcinoma can present as primary tumors and affect the nasal cavity and or maxillary and ethmoid sinuses. Additionally, salivary-type neoplasms can arise in the sinonasal tract. Complaints of congestion, headache, blurred vision, or numbness of the face and teeth may ultimately lead to the diagnosis. Treatment is usually surgical, with tumor location, size, and aggressiveness dictating the specific protocol.

Diagnosis and Management: After consideration of all the pathologic possibilities, surgical exploration (Figure 3) was undertaken and tissue submitted for histologic examination. A diagnosis of KOT was rendered (Figures 4-6). Because the initial treatment consisted solely of enucleation and biopsy, it was determined that additional therapy was
warranted. A second Caldwell-Luc procedure with peripheral ostectomy was performed. The patient was referred for genetic testing to rule out nevoid basal cell carcinoma syndrome.

**Discussion:** KOT is a benign odontogenic tumor with distinct histologic features and clinical behavior. In the 2005 edition of the World Health Organization classification of head and neck tumors, odontogenic keratocysts were renamed and reclassified as benign tumors reflecting evidence that genetic alteration drives the pathogenesis in many cases.9 KOTs are more frequently discovered in the mandible (70% to 85% of cases). Of the maxillary lesions, only 1% are noted to have sinus involvement. While a query of PubMed returned 358 responses for “KOT + sinus,” review of these articles determined that most were ultimately diagnosed as denticigerous cysts. Fewer than 20 were KOTs, many of which occurred in patients previously diagnosed with nevoid basal cell carcinoma syndrome. Whether or not this is coincidental is unclear.

Interestingly, in a few case reports, the characteristic epithelial lining of the KOT was noted to fuse with the respiratory epithelium of the sinus membrane.12-14 That being said, when respiratory epithelium is found in the lining of a maxillary KOT, clinical correlation to rule out possible sinus involvement may be of value.

Treatment of KOT includes total removal of the cyst lining by enucleation and curettage.5,8,9,15,16 Because of the high recurrence rate, approximately 30% and up to around 60% in some studies,5,8,9 some surgeons prefer to perform a peripheral ostectomy.15 In cases of very large lesions, marsupialization can be performed to decompress the lesion, reducing its size with associated with a lower recurrence rate.15

**References**


**CLINICAL PATHOLOGIC CONFERENCE CASE 5: UNUSUAL SEVERE GLOSSITIS**

**Bhattacharyya, JM**

**Kramer, University of Florida College of Dentistry; The Feinstein Institute for Medical Research; Long Island Jewish Medical Center; Hofstra North Shore-LIJ School of Medicine**

**Clinical Presentation:** A 69-year-old white woman reported a lengthy history of painful glossitis that, according to the patient, started almost 10 years ago coincident with rupture of colonic diverticula treated with a colostomy. Subsequently, she developed an irritation of the right lateral tongue followed by involvement of the left lateral tongue. Approximately a year later, the irritation progressed to involve the entire dorsum of the tongue. The tongue was intensely painful and interfered with normal eating, drinking, and speech. The patient’s medical history included recurrent urinary tract infections, ruptured breast implant, and arthritis, which were treated with long-term antibiotic therapy. She reported sialorrhea, slurred speech, and diarrhea of unknown duration. She was a former smoker (1 pack per day for 30 years) who had discontinued smoking a year ago. Upon further questioning, the patient disclosed consuming multiple alcoholic drinks (at least 6 beers) on a daily basis.

On examination, the tongue appeared slightly enlarged and beefy red with significant areas of atrophy, exaggerated papillation, hyperplasia, and ulceration. Areas of ulceration were also noted on the ventral surface, left buccal mucosa, and posterior soft palate (Figure 1). No lymphadenopathy was evident. The tongue was extremely tender to touch and movement.

**Differential Diagnosis:** Several considerations, including nutritional deficiencies, infectious processes, chemical or thermal injury, allergic reactions, as well as autoimmune diseases, were considered in this scenario of a patient with severe glossitis with areas of ulceration.

The most common nutritional deficiencies associated with mild to moderate symptomatic glossitis include anemia (iron deficiency and deficiencies of the B vitamin family). Because of the patient’s history of long-term alcohol use and difficulty in eating, the possibility of nutritional deficiencies was a primary consideration. Iron deficiency anemia is the most common form of anemia worldwide.3 The usual symptoms associated with iron deficiency anemia include papillary atrophy, glossodynia, and xerostomia. The features associated with folic acid and B-vitamin deficiencies are very similar.2 However, the presence of ulceration is very unusual.3 The dorsum of the tongue may exhibit degeneration of filiform and fungiform papillae and epithelial atrophy, leading to significant pain or discomfort during eating. Patients with iron or vitamin deficiency may often have an associated
candidal infection that could further contribute to burning. In addition to glossitis, patients with nutritional deficiencies may also present with angular cheilitis, recurrent aphthous-like oral ulcerations, and diffuse erythema of the oral mucosa.

Lack of vitamin B12 (cobalamin) results in pernicious anemia, the most common B vitamin deficiency in the Western world. This deficiency may be caused by malabsorption or from inadequate intake. Vitamin B12 deficiency may have profound clinical effects, including hematologic, neurologic, psychiatric, and cardiovascular manifestations. The tongue is most severely affected. Oral signs of vitamin B12 deficiency are glossitis with papillary atrophy resulting in a bald, smooth appearing tongue. Patients are more susceptible to candidiasis, and angular cheilitis may be observed. Aphthous ulcers may be seen, along with diffuse erythematous mucositis. Frequently, patients report a burning sensation that may be the first indication of a vitamin deficiency. Treatment involves either oral or intramuscular injections of vitamin B12.

Pellagra results from vitamin B3 (niacin) deficiency, and is much more common in developing nations. Pellagra results in dementia, dermatitis, diarrhea, and eventual death. In the West, pellagra is rare, but may be seen in association with alcoholism and anorexia nervosa. Patients with niacin deficiency may exhibit striking oral manifestations, including severe glossitis, gingivitis, and stomatitis. Within the oral cavity, the tongue is typically most severely affected, and may appear bald as a result of lingual desquamation. The tip of the tongue and margin are affected initially, and eventually the entire tongue appears dry, beefy red, and swollen. Moreover, the tongue may exhibit pseudomembranous furrows, erosions, or ulcers. In the later stages of disease, papilla atrophy is evident and necrosis follows. As a result, patients report marked sensitivity.

Vitamin B6 deficiency (pyridoxal, pyridoxamine, pyridoxine) may result in pellagoid syndrome. The active form of this vitamin is an essential intermediate in the synthesis of niacin from tryptophan. Thus, deficiency in vitamin B6 manifests much like pellagra, and is termed "pellagroid syndrome." While vitamin B6 deficiency is rare in the developed world, there are isolated reports of the condition in alcoholics. Of note, certain medications deplete vitamin B6, most notably isoniazid. While the clinical presentation of this case mimics a B vitamin deficiency, and the patient’s report of significant alcohol use may support this, a vitamin deficiency of this severity is unlikely to remain undetected in an individual with access to medical care.

The possibility of infectious processes, including human herpes simplex virus, streptococcal, syphilis, and candidal infections, have been reported in association with cases of severe glossitis and oral ulcerations. In addition, usually localized infections of these agents other than candida would be highly unusual without concomitant systemic signs and symptoms. Moreover, she had been empirically treated in the past with antifungals by her physician with no resolution of her condition.

A sustained adverse reaction to a drug, toothpaste, or mouthwash can rarely present with ulcerations and symptomatic oral lesions, but these would respond to discontinuation of any product the patient might be using. The patient was on antibiotics for treatment of recurrent urinary tract infections that she had been intermittently prescribed for many years, before onset of these lesions. She was using omeprazole for treatment of hyperacidity for a long duration as well.

Radiation to the head and neck often produces severe oral mucositis, which may resemble the lesions seen here. Also, chemotherapy for treatment of leukemia can result in significant oral lesions. Physical damage to oral tissues within a wide range has been reported in virtually 100% of patients undergoing radiation to the head and neck region. However, there were no indications of any such treatment in this patient.

Autoimmune diseases such as erosive lichen planus, pemphigus vulgaris, or benign mucous membrane pemphigoid commonly manifest as severe erosive lesions of the oral tissues. These conditions may involve any region of the oral cavity and present with a wide variety of signs and symptoms. A host of other conditions may similarly manifest with non-specific mucositis and ulcerations, including sarcoidosis, chronic ulcerative stomatitis, lichenoides pemphigoides, pemphigus vulgaris, and paraneoplastic pemphigus.

Fig. 1. The patient’s tongue appeared slightly enlarged and intensely erythematous with large areas of atrophy, hyperplastic papillae, and extensive ragged ulcers. Large eroded and ulcerated areas were also noted on the ventral surface, left buccal mucosa, and posterior soft palate. Many of the ulcerated surfaces were covered by a necrotic membrane.
Originally described in 1990, chronic ulcerative stomatitis (CUS) is an autoimmune disease that affects mucosal surfaces primarily. Clinically, CUS may resemble erosive lichen planus or other vesiculoerosive processes, although patients with CUS may respond poorly to corticosteroid therapy. Both circulating and tissue bound IgG antibodies to keratinocyte nuclear antigen are present in CUS. This autoantigen is a 70 kD isoform of p63, termed “p63,” which appears crucial for epithelial development and regeneration. Both direct and indirect immunofluorescence should be performed to confirm a diagnosis of CUS.

Paraneoplastic pemphigus is typically seen in patients with underlying benign or malignant lymphoreticular neoplasms, such as thymoma or Hodgkin’s lymphoma. Oral lesions seen in paraneoplastic pemphigus are commonly very painful and may represent the only manifestation of disease. Diffuse, shallow ulcers usually begin in the oral cavity and may affect the vermilion border of the lips. This presentation resembles erythema multiforme or primary gingival herpetic gingivostomatitis. Lesions may extend to other parts of the body. Paraneoplastic pemphigus is diagnosed by serological screening for antibodies directed against numerous epithelial antigens including plakin proteins and desmoglein 1 and 3.

Although the patient’s clinical presentation mimics a vesiculoerosive process, the history suggests otherwise. If she had an underlying neoplasm, it is unlikely it would have gone undiagnosed for such a significant period of time. Moreover, vesiculoerosive processes, such as CUS, typically wax and wane, and this patient reports continual worsening of her disease. Very rarely, severe glossitis may be associated with a systemic condition such as celiac disease, Crohn’s disease, psoriasis, or ulcerative uremic stomatitis. However, these conditions should either be accompanied with systemic signs.

Carcinoid tumor is a rare neuroendocrine malignancy that may result in a pellagra-like clinical presentation. A subset of patients display elevated serotonin levels, resulting in carcinoid syndrome, which is characterized by flushing, diarrhea, and abdominal cramps. Both the serotonin and niacin pathways share a common precursor, tryptophan. Thus, active carcinoids may shunt tryptophan away from the synthesis of niacin towards serotonin, resulting in B vitamin deficiencies. Carcinoid tumors are usually indolent in nature. However, because a carcinoid tumor would have caused additional symptoms, it is unlikely that this neoplasm would have gone undetected for several years.

Diagnosis and Management: The patient was extensively tested for nutritional deficiencies including iron, folate, vitamin B12, niacin, pyridoxine, zinc, and thiamine, but no significant abnormalities could be identified. Multiple biopsies were performed and sampling of the dorsal and ventral tongue, buccal mucosa, and soft palate were done. All the samples revealed a range of significant premalignant and malignant epithelial alterations, ranging from severe epithelial dysplasia to carcinoma in situ to superficially invasive squamous cell carcinoma (SCC). Microscopic examination of the biopsy specimen revealed a neoplastic epithelial process arising from significantly dysplastic and ulcerated keratinized stratified squamous epithelium (Figure 2A). Small islands, clusters, and extensions of neoplastic epithelium were seen arising from dysplastic epithelium (gray arrow indicates dysplastic epithelium). The neoplastic islands demonstrated prominent basaloid architecture and peripheral palisading in some foci. (Hematoxylin and eosin stain; magnification × 40.)
reported severe burning and discomfort associated with the entire tongue.

This case illustrates the fact that oral SCC may have diverse presentations and may not present as the typical red/white/red-white/ulcerated lesion. Diffuse erythematous alterations with ulcerations of long-standing origin should be explored and, when indicated, tissue biopsy should be performed to establish and confirm clinical suspicions. SCC is the most common malignancy of the oral cavity and occurs commonly on the ventral and lateral borders of the tongue, followed by the floor of mouth and soft palate.27 Traditional risk factors for oral SCC in the US include significant alcohol and tobacco use.28 Rarely, iron deficiency anemia (Plummer Vinson syndrome), as well as syndromes such as Fanconi anemia, are linked to the development of oral cancer.29,30 While the concept of field cancerization is well accepted, it is unusual for an individual to develop multifocal, confluent SCC within the oral cavity.31 Because of the chronic, progressive nature of this individual’s disease in conjunction with her history of significant alcohol use, SCC should be considered in this case.

References

CLINICAL PATHOLOGIC CONFERENCE CASE 6: A PAINFUL MULTILOCULAR RADIOULCERENCY

D Sundararajan, J Bouquot, Boston University School of Dental Medicine; University of Texas School of Dentistry at Houston

Clinical Presentation: A 51-year-old woman sought evaluation of a mildly painful area of the posterior right maxilla of 5 year's duration. She had not visited a dentist earlier because of financial difficulties but was now employed and wanted to have her problem treated. She described her symptoms as being
In formulating the differential diagnosis, more information about her medical history would be helpful. Is there any history of chronic illness or malignancy? Does she take any medications? Does she have any personal or family history of diabetes, heart problems, stroke, or tumors? Does she have any history of tobacco, alcohol, or recreational drug use? Because no such information is available, however, it seems best to address the radiographic changes first.

A multilocular radiolucency in a middle-aged adult brings to mind a number of lesions that should be included in a differential diagnosis. The most common lesions with this presentation are odontogenic keratocyst, ameloblastoma, central giant cell granuloma, and odontogenic myxoma.

However, none of these fit the present case. Each should have produced a jaw swelling after 5 years’ duration, while there is no expansion in the present case. Additionally, none are typically characterized by pain. Only if we assume that the patient’s pain and her multilocular lesion are unrelated, or that there is a secondary, unidentified inflammation involved, can the above list remain acceptable. This seems unreasonable, but should remain a possibility until biopsy proves otherwise.

Other less common lesions to be considered include intraosseous mucoepidermoid carcinoma, metastatic carcinoma, primary intraosseous carcinoma, chondrosarcoma, lymphoma, multiple myeloma, focal osteoporotic marrow defect, osteomyelitis, intra-osseous benign neural lesions, Langerhans cell disease, osteosarcoma, and other odontogenic cysts and tumors. Of these, carcinoma, sarcoma, myeloma, and osteomyelitis are most likely to be painful, although it is hard to imagine them remaining undetected for 5 years, as they are all likely to produce severe destruction in a much shorter time frame. Other multilocular lesions, such as ameloblastic fibroma, central hemangioma, aneurysmal bone cyst, and cherubism are considered much less likely because they have a strong tendency to occur in younger patients.

To 99m-methylene diphosphonate (99mTc-MDP) radioisotope scintigraphy (Figure 2) shows an increased uptake in the right maxillary tuberosity. There are also other areas of the jaw, including the anterior maxilla and focal areas in the mandible that show a milder increase in isotope uptake. This multifocal phenomenon, combined with the bone pain, suggests that the differential diagnosis should include infections and inflammatory conditions, metastatic disease, hematologic disorders such as multiple myeloma and lymphoma, hormone related disorders such as hyperparathyroidism with its brown tumors, Langerhans cell disease, BRONJ (bisphosphonate related osteonecrosis of the jaws) and ischemic osteonecrosis.

Brown tumors of hyperparathyroidism occur commonly in older females. Although patients are usually asymptomatic, bone pain and tenderness may be present in some cases. Radiographically, these lesions can present as a well-demarcated multilocular radiolucency in the jaws. Multiple lesions can develop in the jaws. But the surface mucosa is less likely to remain normal in a long-standing lesion. Typically cortical expansion occurs and a gingival mass is produced when the lesion erodes through the bony cortex.

Langerhans cell disease affects both sexes and can occasionally present with dull pain and tenderness. But Langerhans cell disease typically occurs in younger patients. It is rare in older adults. When the lesion breaks out of bone, a gingival soft tissue swelling is produced. Radiographically, the lesion presents as a sharply punched out lucency or as an ill-defined lucency.

Intermittent and “livable,” but she was concerned that they were gradually increasing in intensity.

On examination, she rated her pain as 3-4 on a 10-point scale. The surface mucosa in this area appeared unremarkable and the right maxillary molars were vital by electric pulp testing. The right tuberosity was moderately tender to palpation and diagnostic anesthesia of the facial surface of the tuberosity eliminated her pain entirely. Periapical radiographs revealed a multilocular radiolucency with fine trabeculations in the painful area (Figure 1) at the right tuberosity. The right maxillary tuberosity was moderately tender to palpation and diagnostic anesthesia test suggests a maxillary source for the pain, rather than a more central neuropathy.

In formulating the differential diagnosis, more information about her medical history would be helpful. Is there any history of chronic illness or malignancy? Does she take any medications? Does she have any personal or family history of diabetes, heart problems, stroke, or tumors? Does she have any history of tobacco, alcohol, or recreational drug use? Because no such information is available, however, it seems best to address the radiographic changes first.

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There is bone destruction and loosening of the teeth; features not seen in our case.

Hematologic disorders, like multiple myeloma and lymphoma, affect both genders, usually middle-aged or older adults.1 Patients may experience symptoms of bone pain. However, as with other long-standing lesions of bone, these lesions also tend to produce cortical expansion and a soft tissue swelling develops when the lesion breaks out of bone. Radiographically, the lesions can present as a multilocular radiolucency but usually present as multiple ill-defined or punched out radiolucencies.

Malignant neoplasms and metastatic disease to bone can affect middle aged and older females.1 Although the jaw bones are uncommon sites for metastasis, metastasis to the mandible and, less commonly, to the maxilla can occur. Patients can complain of bone pain and tenderness but other symptoms usually associated with malignancy, such as swelling, loosening of teeth, and paresthesia, are absent in the present case. Metastatic lesions may present as a radiolucent area, but the surface mucosa is less likely to appear normal after 5 years in the case of a malignant lesion.

Ischemic osteonecrosis typically affects middle aged females.1,2 The third molar area is the most commonly involved site. The disease may or may not produce pain and the pain produced is variable. Patients may have mild or intense pain that may be present for many years. The overlying surface mucosa usually appears normal or may show mild erythema. Involved bone is typically tender to palpation. A positive diagnostic anesthesia test is helpful in the diagnosis of the disease. This disease can show a variety of radiographic presentations, occasionally including a multilocular radiolucency with scalloped margins. The disease can involve multiple bones and multiple sites of the same bone. Technetium bone scan is considered to be a very important diagnostic tool in the diagnosis of maxillofacial osteonecrosis.2,3 Lesions show increased uptake or hot spots, which typically represent bone affected by diseased marrow.

The primary dilemma in this case is the presence of pain in a multilocular lesion, a type of lesion seldom associated with long-standing pain. Likewise, few chronically painful conditions are associated with multilocular radiolucencies.

Based on the patient’s signs and symptoms, the tentative diagnosis in this case is ischemic osteonecrosis.

**Diagnosis and Management:** Additional clinical information obtained as the patient was evaluated was not directly helpful. For example, she indicated that her pain started “a few days” after extraction of her carious maxillary right third molar. She was diagnosed with and “successfully treated” for a “dry socket.” After the intense pain of that process abated, a “dull ache” remained and slowly increased over time. This suggested that trauma may have precipitated the pain, but continued pain is quite unusual after dry socket and in no way explained the maxillary multilocular radiolucency.

The patient also underwent several thorough medical examinations as part of her work-up. An internist found no systemic disorders of any kind. An otolaryngologist found no abnormalities of the nasal or paranasal sinuses. A neurological work-up, including brain MRI, found no cause for the pain and the patient was subsequently diagnosed with atypical facial neuralgia.

The latter diagnosis, of course, presumed no underlying cause for the pain and, if correct, suggested two superimposed, unrelated lesions: neuralgia in the region of a multilocular radiolucency.

At presentation, no other painful areas of the face or jaws were noted, but firm palpation identified focal regions of tenderness on the facial surface of the right mandibular cuspid area and under the nasal spine. These correlated well with hot spots on the Tc 99m-methylene diphosphonate (99mTc-MDP, technetium-99m MDP) scintigraphy scan (Figure 2). There was a Grade III spot in the cuspid area and a Grade II spot beneath the nose (using the 4-point Indiana Isotope Grading System).3 The mandibular right third/second molar hot spot (Grade II) was nontender, but the radiographic appearance was atypical. Long-lasting residual sockets were present in that edentulous region (Figure 3A). The original painful lesion in the right posterior maxilla had a strong (Grade III) hot spot.

The 99mTc-MDP scan uses a bisphosphonate isotope that generically attaches to bone crystals, i.e. hydroxypatite.4,6 A hot spot in this test, then, identifies only an area of abnormal bone turnover or destruction. It does not provide a diagnosis and does not show regions of increased leukocyte accumulation.

**Fig. 3. A,** Periapical radiograph from a previous dentist, taken 6 years earlier and showing multiple residual sockets in the molar region. **B,** QUS images of the entire right maxilla (numbers below images correspond to tooth numbers) superimposed over the radiograph and showing short, red columns, representing severe attenuation of sound through the alveolus in the third molar region and complete through transmission (tall green columns represent normal bone) in the anterior maxilla.
as later variants do. While this test is notorious for its high rate of false negatives, it has a very low rate (<3%) of false positives.3.6,7 The presence of a strong hot spot in the region of maxillary pain in the present case suggests that her neuralgia diagnosis was not justified because the site of pain involvement was not appropriately evaluated. A complete work-up is required before applying that diagnosis. It is quite significant in this regard that several publications have found hot spots in more than three quarters of painful quadrants in atypical facial neuralgia/pain.3,8,9

Quantitative ultrasound (QUS, through-transmission ultrasound) scanning of the patient’s jaws showed almost complete blockage of sound waves in the posterior right maxilla (Figure 3B). This was a Grade IV level of severity on the 4-point Bouqout grading scale (Table I), while the adjacent second molar region showed Grade III involvement.9,10 Two other sites of positive imaging were noted in her scan: 1) a Grade III area in the asymptomatic and radiographically unremarkable left maxillary tuberosity and; 2) a Grade II area in the asymptomatic right mandibular molar region with the residual sockets. QUS is cleared by the FDA for localizing desiccated, low-density, or cavitated (hollow) bone.9,11 It is used extensively to screen for osteoporosis and less extensively for localization of chronic ischemic bone disease (CIBD). A strongly positive QUS scan in the painful tuberosity of the present case provided additional evidence of an underlying cancellous bone problem, possibly ischemic in nature but perhaps only associated with low bone density.

To recap, despite the neuralgia label applied to the current patient, there were at least 5 features that point to an organic, probably osseous explanation for the pain in her right maxillary molar region: 1) a positive diagnostic anesthesia test; 2) a strong hot spot on a bone scan; 3) a strong QUS-positive image; 4) tenderness on palpation; and 5) a multilocular radiolucency in the area of pain. The latter, as has been mentioned, is the only feature not regularly associated with long-standing pain.1 Conversely, the diagnostic anesthesia test is so strongly associated with ischemic or inflammatory change in the underlying bone that such bone disease is virtually always found at biopsy of a positive site.7,12

To confuse our interpretation further, multiple other hot spots and QUS-positive sites were without pain. If those positive sites were somehow associated with the problem in the maxillary right molar region, only CIBD, producing bone damage variously diagnosed as ischemic osteonecrosis, bone marrow edema, and regional ischemic osteoporosis, depending on the histopathology, is known to produce multifocal 99mTc-MDP hot spots and QUS-positive images, with and without pain, and with variable, perhaps subtle radiographic changes.1,3,13-15 The presence of residual sockets and the history of dry socket in the current patient has also recently been linked to ischemia-related poor healing after extraction.18 It is tempting to assume CIBD in this case, but how do we explain the multilocular, nonexpansile radiolucency in a region without any of the clinical signs of inflammation, except pain?

At surgery, the cortex was found to be extremely thin, with an intraosseous cavitation or void immediately beneath it. Tissue fragments curedt from the lateral cavitation walls showed partially denuded, viable bony trabeculae, often with a thin layer of fibrous tissue covering the surfaces (Figures 4A and B). This was consistent with ischemic marrow atrophy but was not the only pathosis.16,17 The void represented only a small portion of the radiolucent lesion. Firm curettage of its superior aspect eventually yielded globular “soft, fatty” tissue with a few thin “bony bands.” Microscopic analysis showed that the “bands” were actually widely spaced, thin and inactive, viable bony trabeculae. One globule from the tuberosity proved to be relatively normal hematopoietic/fatty marrow with small regions of ischemic damage (Figures 4C and D). More anterior tissue was comprised only of fatty marrow, but approximately 20% of the tissue was represented by multifocal, sometimes large regions of ischemic change: wispy ischemic myelofibrosis streaming between residual adipocytes, small numbers of chronic inflammatory cells, occasional mast cells, dilated capillaries, and small areas with plasmastosis (i.e., high protein, thick oozes between fat cells) (Figure 5). The bone appeared viable.

The biopsy diagnosis was “locally osteoporotic marrow defect (FOMD) with bone marrow edema, ischemic osseous cavitation, and ischemic marrow atrophy.”15,17,19-21

After curettage, the patient’s right maxillary pain diminished progressively for 3 weeks, at which time she was completely pain free. The maxilla remained pain free for 7 years, after which she was lost to follow-up. Two years after maxillary surgery, she developed increasing pain of the right posterior mandible in the region of the previously noted hot spot. This pain disappeared temporarily with a small amount of local anesthesia and disappeared permanently immediately after curettage (biopsy diagnosis: intramedullary fibrous scar). The patient remained pain free to the end of follow-up.

### Table I. Grading categories for individual 3-D cube images (64 columns in each) of the Cavitat, a QUS imaging device designed for maxillofacial use

<table>
<thead>
<tr>
<th>QUS Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>“Green bone.” Cube shows no loss of column height and is 100% green; or mild loss of column height in less than 1/4 of columns (16 columns); and/or moderate to severe loss of column height in less than 4 non-adjacent columns.</td>
</tr>
<tr>
<td>I</td>
<td>Cube shows mild loss of column height in more than 1/4 of columns; and/or moderate loss of column height in 1/16 to 1/4 of the columns (5-16 columns); and/or severe loss of height in 1/16 to 1/8 of the columns (5-8 columns).</td>
</tr>
<tr>
<td>II</td>
<td>Cube shows moderate loss of column height in 1/4 to 1/2 of columns (17-32 columns); and/or severe loss of height in 1/8 to 1/4 of columns (8-16 columns).</td>
</tr>
<tr>
<td>III</td>
<td>Cube shows moderate loss of column height in more than 1/2 of columns (32 columns); and/or severe loss of column height in 1/4 to 1/2 of columns (17-32 columns).</td>
</tr>
<tr>
<td>IV</td>
<td>Cube shows severe loss of column height in more than 1/2 of columns (32 columns).</td>
</tr>
</tbody>
</table>

*High grade lesion = Grade III and IV scans; low-grade lesion = Grade I and II scans; “green bone” = normal or Grade 0 scan. **Definition of loss of column height: mild (crown is green, less than 1/3 loss of height); moderate (crown is yellow or brown, 1/3 to 2/3 loss of height); severe (crown is orange or red, more than 2/3 loss of height).
The mandibular right cuspid area with a hot spot remained tender, as did the maxillary midline, but the patient refused additional surgery because there was no spontaneous pain in those regions.

Discussion: Painful CIBD of alveolar bone, sometimes referred to as NICO (neuralgia-inducing cavitational osteonecrosis), is the one disease that best fits the pattern of the current patient’s symptoms and scanned images. Two ischemia-related
bone disorders occasionally present as multilocular lesions, and both occasionally present with pain or tenderness: traumatic (simple) bone cyst and FOMD. In persons older than 35 years of age, the designation of traumatic bone cyst for an intraosseous void is not typically applied. “Ischemic osseous cavitation” is the preferred term and such lesions appear to be part of the CIBD spectrum. Many cases may represent poor healing after extraction.

The cavitation was only a small part of the present lesion, but the rest of the diagnosis, FOMD, is also considered by some to have an ischemic etiology or pathophysiology. It is probably telling, in this regard, that focal areas of bone marrow edema, the quintessential ischemic marrow disease, were found in the lesion. Moreover, because approximately two thirds of bone marrow edema cases are painful, this may be the best explanation for the neuralgia-like pain. In this regard, it should be mentioned that, although FOMD is not thought to be inherently painful, one of the largest reported series identified cases from a facial pain clinic.

The FOMD diagnosis eventually applied to this case is a well-accepted, typically innocuous but poorly understood lesion. For decades it was called hematopoietic marrow defect, hematopoietic bone marrow defect, or hematopoietic marrow hyperplasia, until larger studies demonstrated that the majority of examples contained primarily or only fatty marrow. Initially thought to be a response to increased need for erythrocytes in anemic conditions, it is now known to have no strong systemic associations and no proven etiology, although approximately 40% of cases occur at the site of an old extraction, suggesting poor healing after surgery. The remaining 60% of cases, however, lack this explanation and point to an as-yet unidentified multifactorial etiology, perhaps involving medullary infarction or ischemia.

FOMD typically presents as a localized, poorly demarcated, non-expansile radioluency less than 1.5 cm. in diameter. It is a disease of adults, affecting persons aged 20-80 (mean age, 49 years). Three fourths of cases are found in females, and almost all are located in an edentulous region of the alveolus, often in the site of an old extraction. More than 80% occur in the retromolar or third molar regions, and very few lesions are found anterior to the first molar. While early, smaller series indicated a predilection for the mandible, more recent, larger studies show a relatively even distribution between the mandible and maxilla. Approximately 3% of cases involve multiple lesions, usually bilateral.

The biopsy in this case principally showed normal fatty or fatty/hematopoietic marrow, hence the FOMD designation. Additionally, however, multifocal regions of ischemic marrow change were found, typically as bone marrow edema. This phenomenon has earlier been suggested as the likely explanation for the pain, but we do not know how often ischemic disease occurs in FOMD. The largest series of FOMD cases found so many examples of ischemic marrow change (88%) that the authors suggested chronic marrow ischemia as one, perhaps the major, underlying pathoetiology and pathophysiology for FOMD. The only available CIBD classification system now includes FOMD as a subset of ischemic bone disease.

A final point should be made. Accepting CIBD as a feature of the present FOMD case also explains the multifocal features noted on the bone scan and ultrasound images, as well as the multiple areas of tenderness. Ischemic bone disease is, regardless of the bone involved, routinely multifocal and bilateral. This has long led researchers to presume osteonecrosis, for example, to be a systemic disease, or to be created by an underlying systemic disease. To date, only one systemic condition has been found to strongly correlate with osteonecrosis and other ischemic bone disorders: hypercoagulation. More than 71% of patients with CIBD of the hip have hypercoaguloma or thrombophilia, usually as hereditary conditions. Similar percentages have been found in patients with CIBD of the knees and jawbones. The observation of significantly more thrombi in CIBD of the jaws compared with tissue from peri-apical infections, 12.5% versus 3.0%, adds credence to this as an underlying problem. Additional processes, however, may be at work and further research must be done before we have a thorough understanding of the mechanisms involved in ischemic bone damage.

The present case illustrates very well the need for in-depth evaluation of patients with chronic facial or alveolar pain, including occasional tests, such as the 99mTc-MDP scan and QUS imaging, which are not frequently used by dentists. It also illustrates the fact that at least some well-demarcated, multilocular radioluencies, such as FOMD, can be painful, presumably as a result of chronic ischemic conditions. We suggest adding FOMD more frequently to the differential diagnosis of symptomatic radioluencies. The lack of consideration of this lesion, and an appropriate work-up, may result in misdiagnosis of the pain and improper treatment.

**References**


