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CLINICAL PATHOLOGIC CONFERENCE CASE 1: A MULTILOCULAR RADIOCLUCENCY IN THE POSTERIOR MANDIBLE

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Clinical Presentation: A 22-year-old white female presented to the general dentist with swelling in the right mandible and submandibular area. Clinical examination confirmed expansion of the right mandible. Panoramic radiographic examination revealed a large, well-circumscribed multilocular radiolucency distal to the canine within the body of the mandible (Figure 1). An incision and drainage procedure was performed but was unsuccessful. Aspiration of the lesion also failed to yield output.

Differential Diagnosis: Differential diagnosis of a well-circumscribed, corticated, multilocular radiolucency within the molar region of the mandible should include several categories of pathology, including odontogenic cysts and tumors, non-odontogenic tumors, and other non-neoplastic conditions.

A large number of intrabony jaw lesions originate from odontogenic tissues; therefore, odontogenic cysts and tumors should be considered first in a differential diagnosis. Of the odontogenic cysts, odontogenic keratocyst (OKC) would be the most likely in the present case. OKCs affect the mandible approximately 70% of the time and demonstrate a tendency to involve the posterior body of the mandible and the ascending ramus. The majority of OKCs are identified in patients between ages 10 and 40 years. The radiographic presentation of OKCs consists of a well-defined radiolucency, with a smooth and often corticated margin. Larger lesions may present as a multilocular process. In this case, we are not considering the dentigerous cyst, a common odontogenic cyst, because of the absence of an unerupted tooth in the area, and the less common glandular odontogenic cyst because of patient demographic characteristics and biologic behavior.

Odontogenic tumors may also present as well-circumscribed, corticated radiolucencies, so a variety of odontogenic neoplasms should be considered in the present case. Given the patient demographic characteristics, ameloblastoma, odontogenic myxoma, and central odontogenic fibroma are considered. Ameloblastoma is the most common clinically significant odontogenic tumor. About 80% of ameloblastomas are found within the mandible, with the molar-ascending ramus area being the most common site. The average age at diagnosis is the middle to late 30s, although a wide age range is common, and a second peak is seen in the seventh decade of life. Odontogenic myxoma demonstrates a strong mandibular predilection, with the premolar–molar area most commonly affected, although the lesion in the present case did not demonstrate the typical “soap bubble” radiographic appearance seen in myxomas. Central odontogenic fibroma should also be considered in the present case. These unusual lesions present in a wide age range, although most patients present between the ages of 11 and 39 years. Central odontogenic fibromas exhibit a slight mandibular predilection, often posterior to the first molar, and most notably demonstrate a strong female predilection. They may cause significant bony expansion and may present as totally radiolucent or with faint internal septa.

As the lesion did not appear to be associated with a tooth, nonodontogenic neoplasms and tumors had to be considered in the differential diagnosis in the present case. Vascular lesions such as hemangioma were unlikely, based on negative aspiration. A central giant cell lesion (central giant cell granuloma) had to be considered, as these non-neoplastic lesions are commonly seen before the age of 30 and with a distinct female predilection. The mandible is affected the majority of the time, although the lesions are typically found anterior to the canines and without a corticated border. Central giant cell lesions have a tendency to cause expansion and may result in tooth resorption. Finally, simple bone cyst (idiopathic bone cavity) had to be considered, as these lesions are typically seen between the ages of 10 and 20 years and are rarely seen in patients above the age of 30. Simple bone cysts are almost exclusively seen in the mandible and may present with slight expansion. Negative aspiration is commonly seen, and surgical exploration is required for diagnosis.

Diagnosis and Management: Approximately 2 weeks following the attempted, but unsuccessful, incision and drainage procedure, an excisional biopsy of the lesion was performed. Aspiration of the lucent area was attempted before surgical entry but proved to be negative. At surgery, the lucent defect was found to contain a solid tissue mass without any evidence of a cystic component. Curettage yielded enough tissue to fill three cassettes.

Histologic examination of the biopsy material revealed a large majority of the tissue specimen to be composed of a relatively dense background stroma of fibrous connective tissue, within which there was an increased quantity of what appeared to be mildly proliferative odontogenic epithelium (Figure 2A). The odontogenic epithelium grew in thin but elongated strands, cords, and small islands, and the epithelium was fairly uniformly spread through the background fibrous tissue (Figure 2B). In some areas, the background fibrous tissue appeared mildly hypocellular and hyalinized. However, other fragments of tissue in the specimen showed a distinctly different histopathologic appearance. These tissue fragments showed a highly cellular proliferation of fibrohistiocytic–appearing cells surrounding an area of central hemorrhage (Figure 2C). Foreign body–type giant cells were scattered through the background fibrohistiocytic stroma in a roughly circular distribution around the areas of hemorrhage (Figure 2D). In most areas, the odontogenic fibroma component of the lesion remained separate from, but abutted against, the giant cell component (Figure 3A). Focally, however, the two patterns were intermingled, and giant cells were occasionally found directly adjacent to the odontogenic epithelium (Figure 3B).

The diagnosis was hybrid central odontogenic fibroma/central giant cell lesion.

Discussion: The occurrence of central odontogenic fibroma containing areas of central giant cell granuloma–like...
proliferation was first reported by Allen et al., in 1992, as "central odontogenic fibroma, WHO type, with an unusual associated giant cell reaction." Three cases were presented in that initial report. Since 1992, only six additional reports of this combination have appeared in the literature, with another report of 19 cases added later. The trend within these seven publications is to label the lesion as a hybrid central odontogenic fibroma/giant cell granuloma. Although a summary of these seven cases was provided, specific demographic and clinical data on the individual cases were not included.

The hybrid central odontogenic fibroma/giant cell lesion occurs over a wide age range with cases reported to occur from the first to the eighth decade of life. The majority of cases cluster in the second and third decades of life. Females are affected most often, in at least a 2:1 female-to-male ratio. The race of the patient is documented in only six cases, but in all these six cases, the patient was Caucasian. The mandible is the preferred site of occurrence, with only two cases documented in the maxilla. The premolar–molar region is most commonly involved, with only one lesion identified as being exclusively anterior in its position. The case described by de Lima et al. is somewhat unique, with these authors reporting an extremely large lesion that extended from the left first molar region across the midline to the right first molar. However, the photomicrographs included in this case report do not clearly delineate a central odontogenic fibroma component of the lesion, leaving the accuracy of the diagnosis in question. Treatment typically entails excision or thorough curettage, usually with a good outcome. The literature documents recurrence in only 3 of the 19 cases in which follow-up was documented with a recurrence rate of 15.7%. However, the article by Hassan et al. describes three additional recurrences among their seven cases. Including these cases in the total yields a recurrence rate of 23.1% (6 of 26). Five of the six recurrences are reported to have contained both central odontogenic fibroma and giant cell granuloma components. One recurrence reported by Hassan et al. contained only the giant cell granuloma component.

The etiology of the hybrid central odontogenic fibroma/giant cell lesion has yet to be confirmed. One theory is that the lesion represents a “collision tumor” with a separate central odontogenic fibroma arising in juxtaposition to a central giant cell granuloma. This theory has largely been discarded as highly unlikely given the rarity of the two lesions individually. In addition, occasional recurrences of the hybrid lesion have been reported to contain both elements of the hybrid lesion, with the suggestion that there is an interrelationship between the two processes. Several authors believe that the hybrid lesion initially develops as a central odontogenic fibroma, which subsequently results in a giant cell lesion in response to some traumatic or irritating stimulus. In several of the reported cases, a potential source of trauma to the area of the tumorous proliferation was present in the history. Cases in which the odontogenic fibroma component is the predominant tissue present in the specimen with only a very small proportion being the giant cell lesion are also cited as evidence of origin as a central odontogenic fibroma. The case being presented here would appear to strongly support this concept. The history of a prior, nonproductive attempt at incision and drainage, combined with the histologic finding of an area of central hemorrhage surrounded by a circular array of giant cells, suggests that the incision and drainage procedure may have initiated bleeding in the odontogenic fibroma, with the giant cell area representing a reactive response to the injury. Other authors believed that the hybrid lesion most likely begins as a central giant cell granuloma. They cited evidence that the giant cells in giant cell granulomas secrete growth factors that can stimulate epithelial proliferation, initiating the odontogenic fibroma-like proliferation as a secondary effect of the giant cell granuloma. One author also cited examples of hybrid lesions in which the giant cell granuloma component is the predominant tissue present in the specimen. A potential argument against this theory is the general lack of odontogenic epithelial proliferation in the vast majority of cases of central giant cell granuloma. Since giant cell granuloma routinely occurs in the areas of the jaws where odontogenic epithelium is expected to be present, the question is: Why isn’t an associated epithelial proliferation a more consistent finding in giant cell granuloma if this is, in fact, the pathogenic mechanism of development of the hybrid lesion?
Fig. 2. **A**, Central odontogenic fibroma component. Dense fibrous stroma with numerous mildly proliferative strands, cords, and islands of odontogenic epithelium. **B**, Central odontogenic fibroma component. Thin elongated strands, cords, and small islands of odontogenic epithelium fairly uniformly spread through the background fibrous tissue. **C**, Giant cell lesion component. Highly cellular proliferation of fibrohistiocytic appearing cells surrounding an area of central hemorrhage. **D**, Giant cell lesion component. Foreign body type giant cells were scattered through the background fibrohistiocytic stroma in a roughly circular distribution around the areas of hemorrhage.

Fig. 3. **A**, In most areas, the odontogenic fibroma component of the lesion (right) remained separate from but abutted against the giant cell component (left). **B**, Focally the two patterns were intermingled, and giant cells were occasionally found directly adjacent to the odontogenic epithelium.

**Table I.** Demographic and clinical data from 23 cases

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References


CLINICAL PATHOLOGIC CONFERENCE CASE 2: PALATAL PERFORATION

A 41-year-old man presented with a 1-week history of a “hole in the roof of his mouth” with associated discomfort (Figure 1). He reported burning the roof of his mouth 4 weeks previously while eating a hot slice of pizza. Initially, there was a pin-sized hole on the palate that continued to enlarge over 1 week. He had since been unable to eat or drink anything comfortably, as whatever he ate or drank entered his nasal passage. At his initial visit, he presented with an “obtrurator” that he fashioned out of chewing gum that allowed him to sip on soup and Ensure. The patient’s medical history was significant for back problems and chronic sinus infections managed with over-the-counter medications. The patient reportedly smoked 1 pack of cigarettes a day for many years and did not consume alcohol. As a warehouse custodian, he reported working in a chalk-filled environment. He lived with his wife, 6-year-old son, 3 dogs, and 2 cats.

Oral examination revealed a uniformly round perforation, approximately 8 mm in diameter, in the left anterior hard palate region, just off the midline and posterior to the palatal rugae (Figure 1). The defect did not have a base, and oral—nasal
communication was evident. The surrounding mucosa demonstrated diffuse erythema, which extended posteriorly and across the palatal midline.

**Differential Diagnosis:** The acute presentation of a uniformly round perforation on the palate suggested several possibilities. Physical trauma was among the first considerations, especially in light of the patient’s own report of having burnt his palate. However, it was highly unlikely that a pizza burn would cause destruction of underlying hard tissue. The round defect also suggested a physical injury with a foreign object (pencil, tool, etc.), but there was no history of such trauma. Nasotracheal intubation during general anesthesia administration can result in palatal perforation, especially if the patient has diabetes or is immunocompromised. The patient reported being generally healthy, with no history of recent or past surgery.

Drug related chemical injury was considered highly likely given the clinical presentation and lack of other systemic or localized symptoms. Drugs such as cocaine when insufflated (snorted) can produce the type of defects presented due to localized vasculitis and ischemia. The patient did not report his previous history of cocaine abuse at this initial visit and admitted to it only after initial diagnostic radiographs were obtained.

A number of infectious diseases are known to cause palatal perforation in some cases. Tertiary syphilis can cause large areas of granulomatous inflammation and necrosis with perforation of the palatal bone resulting in an oronasal fistula. Other infections associated with palatal perforation, necrosis, and destruction include zygomycosis, aspergillosis, sinusonal blastomyocosis, histoplasmosis, coccidiodimycosis, tuberculosis, leprosy, rhinoscleroderma, toxoplasmosis, and leishmaniasis. At the initial visit, at least on the surface, there appeared to be no granulomatos inflammation with necrosis, ulceration, or both. Our patient was generally healthy, with no history of constitutional signs or symptoms. His routine physical and bloodwork results were reportedly within normal limits. Furthermore, no necrotic or ulcerative tissue was present, requiring biopsy and histopathologic examination.

Next, an immune-mediated etiology was considered. Diseases, such as systemic lupus erythematosus, granulomatous polyangitis (GPA, or Wegener disease), sarcoidosis, and other vasculitides, can potentially present with palatal perforation but usually present with evident necrosis and soft tissue destruction. Also, patients with these diseases present with generalized multisystem involvement with accompanying constitutional signs and symptoms. Our patient did not present with any of the above findings making these diagnoses unlikely.

Finally, a malignant neoplasm extending from the maxillary sinus or nasal cavity capable of causing the palatal perforation was considered. These malignancies may include natural killer—cell or T-cell lymphomas and other destructive midline malignancies, including olfactory neuroblastoma (estheticoneuroblastoma) or sinonasal undifferentiated carcinoma. Palatal malignant neoplasms that may also cause extensive tissue destruction include malignant salivary gland tumors (mucoepidermoid carcinoma, adenoid cystic carcinoma, and other malignancies of minor salivary gland origin), malignant nerve sheath tumors, and metastasis. These processes are generally associated with a fungating mass, with evident ulceration, as well as necrosis with or without constitutional signs or symptoms. Our patient was asymptomatic, and the presenting lesion was inconsistent with a neoplastic process.

Given the initial clinical presentation, a diagnosis of either physical trauma or drug-induced (cocaine) nasal floor perforation was considered.

**Diagnosis and Management:** The patient’s initial interview was conducted in the presence of his 6-year-old son. Additional clinical information revealed that there was no history of pain, paresthesia, exudative discharge, foul odor, or swelling. The patient was healthy and reportedly received a full physical with bloodwork 2 months ago, and the findings had been within normal limits. Extraoral examination was unremarkable, with no evidence of swelling or lymphadenopathy. Not surprisingly, following removal of the “obturator,” pronounced rhinolalia was noted upon enunciation. Oral examination revealed the perforation described above. The further oral examination revealed a moderately restored, partially edentulous dentition. There was no evidence of ulceration, discharge, or swelling; the area in question was not tendent to palpation.

A panoramic radiograph showed partially edentulous adult dentition with several restorations (Figure 2). The palatal perforation could not be properly evaluated. Occlusal radiographic examination confirmed the presence of a large oral—nasal—antral perforation (Figure 3). A large, partially defined radiolucency measuring approximately 4 to 5 cm anteroposteriorly across the palatal midline and 1 to 3 cm in width. This large radiographic defect, in the absence of obvious swelling, necrosis, and discharge triggered an otolaryngologic referral for nasal endoscopy and laryngoscopy. Diagnostic computed tomography of the head was requested ahead of the patient’s scheduled otolaryngology appointment.

The history, the presentation, and the notable findings noted on plain radiography suggested the possibility of substance abuse—associated palatal perforation. The patient was contacted the day after his initial visit. He was asked again about any previous history of substance abuse. He admitted to a distant history of cocaine insufflation (>10 years) and reported being addiction free for over 10 years. He had been understandably reluctant to discuss this the previous day because his son had been present in the examination room.

Diagnostic computed tomography revealed perforation and destruction of the nasal floor, palatal vault, and nasal septum and diffuse lytic change involving the lateral nasal walls and turbinates (Figures 4A and B). Soft tissue sinus membrane thickening was noted in keeping with the patient’s history of sinusitis. The features were characteristic of midline destructive disease (MDL), which can be caused by a range of conditions, including cocaine abuse.

Following nasal endoscopy, laryngoscopy and a thorough otolaryngologic evaluation the above findings of MDL were confirmed. However, there was no evidence of necrotic tissue or mass on examination. The perforation was surrounded by mildly inflamed soft tissue but was described as being generally “clean.” A biopsy of the area was not indicated; further serologic tests were not performed. Further audiometry revealed left-sided hearing loss.

The clinical history, presentation, and radiographic findings provided sufficient evidence to arrive at a final diagnosis of palatal perforation associated with so-called cocaine-induced MDL (CIMDL). The patient’s previous history of cocaine abuse was responsible for the notable osseous destruction of the midface. The palatal perforation caused by eating a hot pizza slice was incidental and was the inciting agent that caused the mucosal defect. The mucosa overlying this large submucosal osseous defect was likely the only layer of integument separating the oral cavity from the floor of the nose. An acrylic obturator was fabricated to improve function in the patient. The patient was presented with the option of undergoing surgical reconstruction with a palatal flap, especially given that he had been drug free for more than 10 years. At his 6-month and 1-year follow-up visits,
he reported being happy with the acrylic obturator and elected to defer surgical reconstruction of the midface to a later date.

Discussion: The patient’s initial clinical presentation was a highly superficial manifestation of a substantially destructive process. The presence of a clean oronasal perforation triggered conventional radiographic and CT workup, which revealed the true extent of the loss of underlying tissue and generated a differential diagnosis for sinonasal midline destructive disease (MDL). The patient’s history of cocaine insufflation was sufficient to arrive at a final diagnosis of a cocaine-induced midline destructive lesion (CIMDL). This case underscores the importance of obtaining a thorough (past and present) and private social history (drugs, sexual history, etc.). It highlights the comparable clinical features of various MDLs. In particular, it provides an opportunity to review similarities in the pathogeneses of MDLs, especially those associated with vasculitis, ischemia, and immune-mediated destruction.

Cocaine (benzoylmethylecgonine) is a powerful nervous stimulant and highly addictive substance used in multiple forms (powder, leaves, infusions, etc.). In its purest form, cocaine hydrochloride is a white powder. However, “street cocaine” is frequently cut with fillers or enhancers, such as baking soda, quinine, sugars, local anesthetic, or, more recently, levamisole. The most frequently used route of self-administration of powdered cocaine is intranasal insufflation (snorting, sniffing, or blowing). Habitual cocaine insufflation often causes sinonasal mucosal necrosis and sinusitis. Osteocartilaginous destruction of the nose, sinuses, and palate is less common (CIMDL). It has been observed that CIMDL presents with characteristic centrifugal bone destruction: nasal septum (75%), turbinates (63%), lateral nasal wall (31%), nasal floor (<20%), and soft palate (<1%). This centrifugal pattern of destruction is not observed in patients with polyangitides. In addition, what seems to distinguish patients with CIMDL from those without is the presence of antineutrophil cytoplasmic antibodies (ANCA) in CIMDL. The predominant ANCA types in CIMDL are HNE-ANCA and PR3-ANCA (c-ANCA). Cocaine adulterated with levamisole is associated with increased p-ANCA and antiphospholipids in serology assays. The deposition of ANCAs along the blood vessels in the sinonasal passages causes destruction of blood vessels in the area, mediated by macrophages and T lymphocytes, and subsequent ischemia and necrosis. These patients do not respond to conventional immunosuppressive or modulatory therapy. Although CIMDL appears similar to the vasculitis observed in polyangitides, such as GPA or Wegener disease, the localized anatomic distribution (areas exposed to insufflated cocaine) and the subtle differences in the mechanisms involved set the two apart. Furthermore, the radiographic features described above and serologic findings help differentiate between CIMDL and MDL caused by immune-mediated polyangitides (GPA, microscopic polyangitides, etc.).

Fig. 1. Oral examination revealed a 8-10 mm diameter, symmetric perforation in the left anterior hard palate. The surrounding mucosa demonstrates diffuse erythema.

Fig. 2. Panoramic radiograph. The palatal perforation is not properly appreciated.

Our patient presented with clinical and radiographic features that were consistent with CIMDL, although they occurred years after cessation of his cocaine habit. The tissues appeared otherwise intact on endoscopy. Further serologic tests were neither indicated nor obtained at the time of presentation. Although surgical management was an option, our patient elected to manage his defect conservatively.

In summary, it is apparent that CIMDL is a result of ischemic necrosis triggered by cocaine in a small subset of cocaine abusers, especially those that are predisposed to producing ANCAs (HNE, and PR3 types). This appears to be an emerging problem,
especially in individuals who use cocaine adulterated with levamisole. Recognizing this emerging pattern (clinical, social, radiographic, and serologic findings) is important, especially when trying to halt the disease process. Immunosuppressive therapy has limited therapeutic benefit, and only abstinence and careful debridement, in combination with conservative surgical or prosthetic management, appear to help patients with either active or past CIMDL.

References

Clinical Presentation: A 15-year-old male presented to his dentist with a well-circumscribed radiolucent lesion in the right posterior mandible (Figures 1 and 2). His medical
The differential diagnosis of a multilocular radiolucency in the posterior mandible in a young person involves consideration of a number of odontogenic, non-odontogenic, and other non-neoplastic lesions. Additional information about the patient, such as a history of injury, symptoms, or a family history of syndromes where lytic bone lesions are a component, would be helpful. In the absence of a comprehensive medical history, it is appropriate to consider a broad category of cysts or tumors. The most common odontogenic lesions with this presentation are odontogenic keratocyst (OKC; keratocystic odontogenic tumor), ameloblastoma, and odontogenic myxoma. Non-odontogenic lesions would include idiopathic bone cavity, aneurysmal bone cyst, osteoporotic marrow defect, and central giant cell lesion. It is also prudent to consider desmoplastic fibroma in the differential diagnosis given the patient’s age and the radiographic presentation.

Fig. 1. Right mandibular molar region showing well demarcated, multilocular radiolucency without cortical expansion.

Fig. 2. Radiographic image showing expansion and thinning of the mandibular buccal plate.

Fig. 3. Medium power microscopic view showing haphazard arrangement of fascicles of spindle-shaped cells (hematoxylin and eosin stain).

Fig. 4. Medium power microscopic view showing cytoplasmic positivity for smooth muscle actin (immunohistochemical stain).

The OKC is typically found in people between ages 10 and 40 years; Brannon reported a mean age of 37 years 9 months. Larger cysts may result in clinical expansion and palpable thinning of the overlying cortical plate of bone; and in this case, expansion is evidently absent.

Ameloblastoma and odontogenic myxoma are both odontogenic tumors, which are typically demonstrated as multilocular radiolucent lesions. Ameloblastoma is relatively rare in the 10- to 19-year age group, and myxoma is often encountered in those in the age group of 25 to 30 years. Moreover, the radiographic presentation of the lesion in this patient did not have a “soap bubble” appearance.

Although this lesion is notably associated with the apices of several mandibular molar teeth, it is appropriate to consider non-odontogenic pathology in the differential diagnosis. The idiopathic bone cavity (simple, traumatic, or hemorrhagic bone cyst or solitary bone cavity) is most frequently encountered in patients in the 10- to 20-year age group. On radiographs, the classic appearance is that of a radiolucent lesion, which scallops between the apices of adjacent teeth; however, other lesions may show a partial fill with bone that will not scallop between teeth and therefore may resemble odontogenic cysts or tumors.
Focal osteoporotic marrow defect is a consideration, although these lesions typically occur in patients over the age of 40 years and more often in females.3

Giant cell tumors are histologically benign, yet expansile and possibly locally aggressive tumors formed by osteoclastic giant cells.2 Most patients who have a giant cell tumor are in the third or fourth decade of their lives.6 Although this type of lesion is a consideration, most of these tumors are more common in the anterior portions of the jaws, and mandibular lesions frequently cross the midline.3

Desmoplastic fibroma presents as an oval lytic defect that is well demarcated. No mineral occurs within the lesion, but if the cortex of the bone is unevenly affected or destroyed, areas of trabeculation may be apparent.5 This is an uncommon tumor of fibroblastic origin and yet occurs commonly in the mandible and is found in patients younger than 30 years of age.

Diagnosis: The final diagnosis in this case was solitary myofibroma, a benign proliferation of fibroblast-like cells, which ultrastructurally demonstrate the presence of cytoplasmic actin-like filaments. Two forms are recognized: (1) myofibromatosis represents a condition in which there are multiple lesions in infants and childhood; and (2) the solitary form is seen in older children and adults. This case represents the latter.

The solitary form is more common, and the head and neck region, including the mandible, tongue, buccal mucosa and lips, is often the site of occurrence.6 Typically, the alteration presents as a nonspecific, painless swelling and is most common during the first four decades of life. A clinical differential diagnosis includes a number of soft tissue or bone proliferations.

Microscopically, the tumor consists of a proliferation of spindle-shaped cells with eosinophilic cytoplasm, in which fascicles and swirls are formed (Figure 3). Immunohistochemistry in this case revealed the presence of cytoplasmic smooth muscle actin (Figure 4), but the cells were negative for desmin and S-100 protein.7 These markers are helpful in differentiating myofibroma from other connective tissue proliferations.8

Management: Treatment is conservative surgical excision. Recurrence is uncommon, although a small number may recur after excision.

References

CLINICAL PATHOLOGIC CONFERENCE CASE 4: A YELLOWISH SPECKLED PLAQUE OF BUCCAL MUCOSA Tania Jhamb, DDSa, Barry H. Frank, DDSb, Lee J. Slater, DDS, MS, bCase Western Reserve University, School of Dental Medicine, Cleveland, OH; bDesert Oral Surgery, Las Vegas, NV; bScripps Oral Pathology Service, San Diego, CA

Clinical Presentation: A 26-year-old man presented with an asymptomatic lesion of unknown duration (Figure 1). The 30 × 10 mm grayish-yellow, speckled plaque demonstrated subtle peripheral mucosal erythema. The surgeon’s clinical impression was hyperkeratosis and cheek biting, with possible sebaceous hyperplasia.

Differential Diagnosis: The clinical features were interpreted to most likely be indicative of an inflammatory or infectious process; a neoplastic condition was regarded as less likely. On the basis of the clinical presentation, several possibilities were considered in the differential diagnosis, including, from most to least likely, pyostomatitis vegetans, allergic contact stomatitis, infection, Langerhans cell histiocytosis of soft tissue, and squamous cell carcinoma.

Pyostomatitis vegetans, a rare condition, is an oral manifestation of inflammatory bowel disease and is more commonly seen in patients with ulcerative colitis or Crohn disease. It is

Fig. 1. A 26-year-old man had a speckled plaque demonstrating coalescing creamy-yellow papules.
characterized by multiple pustules on an erythematous base. These pustules can appear yellow or white in color, and as they erode, they form shallow “snail track” ulcers. The condition commonly affects multiple sites in the mouth, including the labial and buccal mucosa, the hard and soft palates, and the gingiva. The lesions are usually asymptomatic.1,2

Allergic contact stomatitis (hypersensitivity reaction) was also considered as part of the histopathologic differential diagnosis. The oral lesions may appear as an acute or chronic manifestation of an allergic reaction. The lesions are usually symptomatic, and patients often describe a burning sensation. Allergic contact stomatitis can show wide range of clinical patterns, and chronic cases may appear as erythematous or leukoplakic.3

The possibility that the lesion resulted from an infectious process was also considered. Oral manifestations of infectious disease may either represent the primary site of infection or may be secondary to widespread disease. Intraoral lesions can be caused by bacterial, fungal, or parasitic organisms (e.g., syphilis, tuberculosis, coccidioidomycosis, histoplasmosis, blastomycosis, and leishmaniasis). Clinically, infectious lesions may be solitary or multiple. They may have an erosive, erythematous, and granular appearance. Patients are usually symptomatic, presenting with varying degrees of pain.4-7

Langerhans cell histiocytosis of soft tissue exhibits variation in appearance. Accordingly, lesions may appear leukoplakic or erythematous. Lesions may be solitary or multiple and may present as ulcerated or boggy. In one third of cases, lesions are seen in oral soft tissue structures, with or without simultaneous intraosseous involvement.8

Squamous cell carcinoma of buccal mucosa comprises 10% of intraoral carcinomas in the United States and Europe. However, its incidence is higher in Asia because of the habit of betel nut chewing. It is also associated with tobacco chewing or snuff dipping. Clinically, it usually appears as a white, verrucous-like lesion. Minimal pain may be present during the early growth phase.9,10

**Diagnosis and Management:** An incisional biopsy demonstrated evidence of candidiasis, with pseudohyphae focally colonizing the parakeratotic layer. A strikingly distinctive histologic finding was the presence of eroded superficial pustules that contained prominent eosinophils. A myriad of conditions can manifest with increased eosinophils,11-13 but their unusual distribution in subcorneal eosinophilic pustules, together with a possible immunodeficiency-associated candidiasis, evoked consideration of hyperimmunoglobulin E syndrome (HIES) (Figures 2A and B). The surgeon confirmed that the patient had a history of HIES (Job

![Fig. 2. A, Buccal mucosal biopsy exhibiting an eroded hyperparakeratotic surface covered by a “smudged” fibrinous exudate showing entrapped leukocytes (predominantly eosinophils); spongiosis with transmigrating eosinophils and lymphocytes; and, in connective tissue, a dense polymorphic inflammatory infiltrate of lymphocytes, plasma cells, and eosinophils. B, Surface epithelium displaying a plethora intraepithelial degranulating eosinophils between keratinocytes of the superficial spinous layer. C, Degenerating degranulated eosinophils entrapped in a fibrinous exudate covering eroded surface epithelium (an eroded eosinophilic pustule).](image-url)
syndrome); it manifested in the patient predominantly as recurrent lung infections. Therefore, the buccal mucosal lesion was diagnosed as an oral manifestation of HIES.

The patient has been under the care of his physician, and no significantly debilitating features of HIES have been manifested.

**Discussion:** HIES, or Job syndrome, was first described by Davis et al. in 1966. It is a complex primary immunodeficiency associated with extremely high serum immunoglobulin E (IgE) levels and susceptibility to infections with extracellular bacteria. It has no known associations with race, ethnicity, or gender. It is characterized by eczematosid rashes, skin abscesses, recurrent sinopulmonary infections, mucocutaneous candidiasis, and malignancies, along with craniofacial, musculoskeletal, dental, and vascular abnormalities.

This autosomal dominant condition is caused by mutations in the gene STAT3 (signal transducer and activator of transcription 3) located on chromosome 17 q21. STAT3 is integral to signal transduction for multiple cytokines, including interleukin (IL)-6, IL-10, IL-11, IL-17, IL-21, IL-22, and IL-23. This pathway controls both the proinflammatory and anti-inflammatory aspects of the immune response. Furthermore, mutations in STAT3 lead to failure of T helper 17 (Th17) CD4 cell differentiation, which is STAT3 dependent; this may lead to higher susceptibility to infection seen in HIES.

Clinical features of HIES include rashes that may resolve or persist and are consistent with eczematosid dermatitis driven by Staphylococcus aureus infection. The skin infections lack warmth and erythema and thus are appropriately named “cold” abscesses, which are a universal feature of the disease. Another commonly seen feature of HIES is recurrent sinopulmonary infections, predominantly caused by S. aureus, which result in bronchiectasis and pneumatoceles. High rates of mucocutaneous candidiasis are also commonly seen in the condition. Therefore, HIES is a disease of both excessive inflammation (exuberant purulence seen in pneumonias) and scant inflammation (presence of cold abscesses).

Patients with HIES may have cutaneous abscesses and may exhibit eosinophilic spongiotic dermatitis. Other histopathologic findings included eosinophilic folliculitis, superficial and deep perivascular dermatitis with abundant eosinophils, and abundant eosinophils extending into the subcutaneous fat.

The condition is associated with an increased risk of malignancies, such as non-Hodgkin lymphoma, predominantly of B-cell origin. In HIES, nonimmunogenetic features include increased interalar distance, prominent forehead and chin, coarse skin, and facial asymmetry that becomes apparent in late childhood and early adolescence. Musculoskeletal abnormalities include hyperextensibility, scoliosis, minor trauma fractures, and osteopenia. Vascular abnormalities lead to aneurysms, dilation and tortuosity of middle-sized arteries, and lacunar infarctions.

Dental manifestations of autosomal dominant HIES include retention of deciduous teeth, delayed eruption of permanent teeth, and double dentition. Once deciduous teeth are removed before the teenage years, permanent teeth erupt normally. Patients also show high, arched palate, cleft lip and palate, midline sagittal clefts in the middle third of the tongue and multiple mucosal fissures. Oral superinfections of the mucous membrane (usually mycotic) result in lesions, erythema, and atrophy.

Laboratory abnormalities in HIES include eosinophilia and IgE levels usually elevated above 2000 IU/mL. HIES should be suspected in individuals with elevated IgE in addition to immunologic and somatic features. A scoring system developed by Grimbacher et al. is useful in the diagnosis of HIES and aids in predicting who is likely to have STAT3 mutations.

Treatment of HIES is limited to proper skin care and prevention and aggressive treatment of infections. Several treatment modalities have been proposed for HIES, such as bone marrow transplantation, interferon-γ, intravenous IgG, disodium cromoglycate, isotretinoin, and double-filtration plasmapheresis. The data supporting the use of these are preliminary, and none of the treatment modalities offers a cure.

**References**


Clinical Presentation: A 28-year-old male Navy diver presented with a chief complaint of oral and skin lesions following an underwater port-cleaning mission that occurred following the Haiti earthquake in January 2010. He reported numerous cause-and-effect factors for the lesions and stated that they could be controlled by diet and the use of a tanning bed. At the time of examination, he was applying gentian violet and ioniczole nitrate to the lesions. On examination, the patient exhibited multiple impressive craterlike ulcers and erosions of the skin of the face and ears (Figure 1), the chin, and the back of the head. Intraoral erosions of the buccal, labial, and vestibular mucosa were also present (Figure 2), along with fissures and surface erosions at the corners of the mouth (Figure 3). An additional medical examination revealed lesions on the back of the neck, anus, penis, and scrotum in various stages of healing.

Differential Diagnosis: On the basis of the history of spending a significant amount of time in the water, the differential diagnosis for this case should include conditions that develop upon exposure to infectious organisms as well as hazardous materials or toxic substances released into the environment following an earthquake. High on this list would be bacterial or fungal infections, which could manifest as both mucosal and skin ulcerations. This would include *Mycobacterium tuberculosis*, a particularly hardy microorganism that can infect multiple tissues, leading to ulcerations from long-term granulomatous inflammation. There are many reported cases in the literature documenting oral infections, with one case in particular closely resembling the oral lesions exhibited by the current patient. However, the patient was not suffering from any systemic symptoms as might be expected.

Diphtheria should also be considered, since it can cause oral cavity lesions, similar to those shown in Figure 2, as well as skin lesions in the cutaneous form. What favors this diagnosis is the fact that systemic toxic manifestations are uncommon among those who have been immunized, so the patient would not be expected to experience any physical illness or the acute-phase reaction common to bacterial infections. Although high on the differential list, the oral lesions of diphtheria are usually located more posteriorly, and the skin ulcerations would be much larger, with raised, rolled borders and necrotic centers. Finally, infection with *Bacillus anthracis*, the organism that causes anthrax, can manifest as both cutaneous and oropharyngeal ulcers. However, once again, in this condition, the ulcerations would be more alarming, with red, raised, highly inflamed borders and a black necrotic base. The

Clinical Pathologic Conference Case 5: A Male Navy Diver with Oral and Skin Lesions Basile J*, J.T. Castle, CAPT, DC USN®, “University of Maryland Dental School, Baltimore, Maryland, USA; Naval Medical Center Portsmouth, Portsmouth, Virginia, USA
skin ulcerations exhibited by the current patient, although slightly
inflamed, were flat and not likely necrotic. It also must be noted
that transmission of bacteria through contaminated seawater, as
implied by the history, would be rather unlikely.

Vesiculobullous disorders also need to be considered. Since
the patient is suffering from both skin and mucosal lesions,
 pemphigus vulgaris would be high on the differential list, although
this condition affects an older population, usually related to he-
redity (European Jewish and Mediterranean populations) and has
not been known to arise acutely. Paraneoplastic pemphigus can

Fig. 1. Craterlike ulcer on cheek and erosion of tragus and helix
with re-epithelialization of the antitragus.

Fig. 2. Maxillary labial vestibular mucosa demonstrating multi-
ple erosive areas extending to the wet–dry line.

Fig. 3. Multiple skin ulcers and erosions in varying stages of
healing, some showing scale crust formation, others with um-
bilicated borders and peripheral erythema.

Fig. 4. Incisional biopsies of oral mucosa revealed acute and
chronic inflammation. A, Low magnification. B, High magnifi-
cation. (hematoxylin and eosin stain).

arise acutely, but this disease generally affects older females, and
the patient does not have a history of a neoplasm. More closely
related to an environmental factor would be erythema
multiforme, which could account for the skin lesions. The lack
of a history of “target” lesions and labial crusting and the fact
that erythema multiforme favors skin over mucosa, whereas this
patient has extensive aphthae-like oral lesions, rule out this diagnosis. Another factor that rules out all of these conditions is that there is no specific history of blisters that ruptured to form the current lesions.

Contact dermatitis or mucositis should also be considered, as the patient could have come into contact with some toxic substance during his dives, perhaps multiple times, and eventually developed the reaction that brought him to the clinic. The varied, irregular appearance of the skin lesions, which could have started as a rash, ulcerations, or both, rather than blisters, as well as the oral ulcerations, might be a result of an exuberant immune reaction that can manifest in any number of ways.

Diagnosis and Management: Incisional biopsy of the skin demonstrated parakeratosis, acute and chronic inflammation, and polarizable foreign material, and prior biopsy had demonstrated psoriasis. Direct immunofluorescence studies were negative. Incisional biopsy of the oral mucosa revealed acute and chronic inflammation (Figures 4A and B), and once again, direct immunofluorescence was negative. The results of basic metabolic panels to include magnesium and phosphorus, as well as a complete blood count with differential, were within normal limits. Fungal cultures of selected skin lesions showed no growth. The patient additionally stated that he had removed a worm from a lesion of his face and was concerned that these worms were tracking through his brain. Following this admission, the patient was referred for a psychological consultation, where he was diagnosed as suffering from schizophrenia and delusional disorder with concomitant Munchausen syndrome and was placed on olanzapine (Zyprexa), aripiprazole (Abilify), and valproic acid (Depakote).

Discussion: On January 12, 2010, an earthquake measuring 7.0 on the Richter scale struck Haiti, the strongest ever recorded in that country’s history. The earthquake inflicted significant damage to a population already suffering from a series of hurricanes and tropical storms that occurred in 2008. The poorest country in the western hemisphere, Haiti’s already weak infrastructure, including basic utilities, such as power, water, and sanitation, was almost completely destroyed, creating an environment favorable for the development of hygiene-related and foodborne illnesses and diseases associated with overcrowding, which might be expected with population displacement and relocation to shelters. In addition to these immediate concerns of wounds and injuries, the World Health Organization (WHO) anticipated that several vectorborne and communicable diseases, including pandemic influenza A (H1N1) 2009, diphtheria, dengue, hepatitis, leptospirosis, tuberculosis, typhoid, measles, and pertussis, would arise under these conditions.

In the case presented here, the most unfortunate aspect was the fact that the patient sought out many providers at multiple medical facilities who believed his fictitious report. None of these providers who saw the patient early on in his presentations (October 2011) were able to put together the fact that U.S. Navy operations ceased in Haiti in June 2010 and therefore his oral and skin lesions were unrelated to his diving missions. The delay in the detection of the truth about his condition was understandable, as it was a difficult task, although addressing the issue in a nonfrontational and accepting manner can facilitate the patient taking the initial step toward resolution, whether that may be through pharmaceutical therapy, supportive psychotherapy, or hospitalization psychiatric care. Long-term results in these patients are hard to predict and quantify, as many relapse after treatment has been completed. Understandably, substantial morbidity and mortality exist with this disorder.

Although it may be a delayed finding, cutaneous Munchausen syndrome should be considered when skin manifestations are spectacular and difficult to diagnose and the findings are normal with routine or basic testing.

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References


Clinical Presentation: A 77-year-old male presented with an asymptomatic, exophytic mass of the left posterior maxilla. The patient had first noticed the mass 3 months before presentation. His medical history was significant for benign prostatic hyperplasia and cataracts. Medications included lisinopril, hydrochlorothiazide, nepafenac, and tamsulosin. The patient had been smoking at least one cigar a day for the past 40 years. Extraorally, the patient’s left face showed fullness and asymmetry, which extended posteriorly to the cheek. The left eye was displaced superiorly and asymmetry, which extended posteriorly to the cheek. The left eye was displaced superiorly. The left nostril had mucous secretions (Figures 1A and B). Intraorally, on the left posterior maxilla, there was a large, erythematous mass, which extended onto the buccal and palatal alveolar mucosa. The patient’s left maxillary molars had been extracted many years before the development of the lesion. Mandibular teeth were occluding against the mass, creating a wear pattern across the surface of the lesion (Figure 2). Cone beam computed tomography (CBCT) of the head revealed a soft tissue mass occupying the entire left maxillary sinus. The mass had remodeled and eroded the orbital floor and had destroyed the lateral and medial walls of the sinus to occupy the left maxillary sinus, creating a wear pattern across the surface of the lesion. The mass obstructed sinonasal drainage. The ethmoid air cells were completely opacified. The mass extended inferiorly to the alveolar process and had replaced the cancellous bone of the left maxillary molar region. The buccal cortex of the left maxillary molar region was lost. The palatal cortex and floor of the left nasal cavity were grossly intact, but there were pinpoint breaks along the palatal cortex (Figures 3A and B).

Differential Diagnosis: Given the clinical and radiographic findings, the mass was consistent with a malignancy. Malignancies that most frequently affect the maxillary sinus in the older adult population include carcinomas and hematopoietic malignancies. Squamous cell carcinoma and salivary gland adenocarcinomas were considered. Sinonasal undifferentiated carcinoma was considered less likely, as some bone remodeling was evident in the CBCT scan, a radiographic feature not typically present in highly aggressive malignancies. Metastatic carcinoma, lymphoma, multiple myeloma, and plasmacytoma were considered because they cause pin-point breaks along cortices.

Diagnosis and Management: Incisonal biopsy of the intraoral lesion was performed and the specimen submitted for histopathologic examination. Initial examination revealed a clear cell neoplasm with a prominent vascular component. The overall features were highly suspicious for metastatic clear cell renal cell carcinoma (RCC). After further communication with the

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Fig. 1. A & B. Extra-oral photographs show left facial fullness and asymmetry. The left eye has been superiorly displaced. The left nostril is filled with mucous secretions.

Fig. 2. Intraoral photograph shows a large, erythematous, exophytic mass of the left maxillary molar region.
submitting surgeon, it was learned that the patient had no prior history of malignancy. The neoplasm exhibited a solid growth pattern infiltrating the connective tissue (Figure 4A). Formation of prominent ductlike structures that resembled renal tubules, with intervening thin-walled, delicate blood vessels, was noted (Figure 4B). Many of the vessels were congested with erythrocytes. The individual tumor cells had abundant clear cytoplasm, with round, uniform basophilic nuclei.

On the basis of the classic features identified, a small panel of immunohistochemical markers, including the renal cell carcinoma (RCC) marker and CD10, also called common acute lymphoblastic leukemia antigen, was selected. Each of these markers is sensitive for neoplasms derived from renal proximal tubules, including clear cell and papillary RCCs. Both markers were positive within the tumor cells. RCC is a 200-kD glycoprotein found in normal kidney along the brush border of the pars convoluta and pars recta segments of the proximal tubules. According to Ozcan et al, RCC marker is expressed in 72% to 85% of primary clear cell RCCs and 35% to 46% of metastatic clear cell RCCs. The current tumor exhibited positive expression of RCC along the luminal surfaces of the ductlike structures and also extended along some cytoplasmic membranes (Figure 5A). Expression of CD10 was more profoundly positive within the same locations (Figure 5B). CD10 has been shown to be strongly expressed by normal proximal tubular cells. CD10 has been found to be expressed in approximately 93% of primary clear cell RCCs and 100% of metastatic tumors, although these figures are based on a small sample size.

A diagnosis of clear cell carcinoma was rendered, with an extended comment that further systemic workup was recommended, as the features were consistent with metastatic RCC. The patient was subsequently referred to an oncologist and was diagnosed with stage IV RCC. Abdominal CT revealed two hyperdense lesions within the lower pole of the left kidney, measuring 4.8 cm in diameter and the other measuring 1.8 × 1.0 cm. An additional 1.2 × 1.4 cm hyperdense lesion was identified within the right kidney. No biopsy of the lesions was performed; however, the interpretation of
the radiologist was that the lesions in the left kidney were highly suspicious for malignancy. The patient received 10 sessions of radiation for the maxillary tumor and was placed on oral sunitinib, 37.5 mg daily for 4 weeks on and 2 weeks off, for approximately 9 months. At 7 months after diagnosis, the oncologist noted that the left maxillary facial swelling and gingival lesion showed significant resolution. No oral lesion was detectable 1 year and 7 months after initiation of treatment, and follow-up abdominal CT examination revealed a decrease in the size of all three renal lesions.

Discussion: The lesion in the current case is believed to have metastasized from the kidney to the bones of the left maxilla and eroded into the oral cavity, and filling the maxillary sinus and eroding the floor of the orbit. This was the initial presentation of an occult primary tumor, as has been reported to be the case in 23% to 25% of previously reported oral metastases. In men, the most common malignancies that metastasize to the oral cavity are lung, kidney, liver, and prostate cancers, whereas in women, the most common primary sites are the breast, female genital organs, kidney, and colon or rectum. When presenting as intrabony involvement, regardless of the type of primary tumor, the most common clinical findings are swelling and pain, paresthesia, or both. If metastasis to oral soft tissues occurs, findings typically consist of a fast-growing, hemorrhagic lesion with an ulcerated appearance resembling a pyogenic granuloma. In a relatively small study cohort, Murillo et al. found that 50% of their patients (8 of 16) presented with both soft tissue and bone involvement.

Although the histopathologic features in this case were strongly suggestive of metastatic clear cell RCC, not every case is as straightforward and can represent a diagnostic challenge. In these cases, immunohistochemical markers are of utmost importance in establishing the diagnosis. In addition to the already described markers, RCC and CD10, PAX-2 has been reported to be a useful marker in metastatic RCCs. A member of the paired box gene family, it is involved in development of the kidney. RCC tumor cells exhibit nuclear staining with PAX-2. Ozcan et al. reported that 74% of all metastatic RCCs exhibited positivity with PAX-2, which is significantly higher than the 35% to 46% of metastatic RCCs positive with RCC marker.

The prognosis of patients with metastatic RCC is poor, with the 5-year survival rate reported to be less than 10%. Hirschberg et al. reported in their review of metastases to the oral cavity that the average survival time was 7 months from diagnosis, whereas Cohen reported that the median survival for metastatic RCC is 13 months. This case highlights the possibility of an occult primary tumor, although rare in the oral cavity, initially presenting as a metastatic lesion in the oral cavity.

References

Fig. 5. A, Medium power (×20) photomicrograph of immunohistochemical marker renal cell carcinoma revealing positive expression along the luminal surfaces of the duct-like structures, as well as extending along some cytoplasmic membranes. B, Medium power (×20) photomicrograph revealing expression of CD10 within the same locations described in (A).