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CLINICAL PATHOLOGIC CONFERENCE CASE 1: LESION PRESENTING AS A HEMORRHAGIC MASS OF THE ALVEOLAR RIDGE  SP Ngwenya, BK Bunn, University of Limpopo; University of Pretoria

Clinical Presentation: A 64-year-old man presented with a sessile, erythematous, hemorrhagic, lobulated, and ulcerated exophytic mass on the edentulous right maxillary ridge measuring 4.5 × 3 × 2 cm (Figure 1). The patient reported a 2-year history.

Differential Diagnosis: Careful examination of the clinical intra-oral photograph, together with consideration of the clinical history, revealed several diagnostically useful features. The lesion was of possible central or palatal origin. There appeared to be a degree of alveolar bone resorption, with abundant fresh hemorrhage within the oral cavity. Incidental findings of severe gingival recession on the upper canine and a root remnant of the upper right central incisor were noted. The premolars and molars in the region of the lesion were missing. There were no perioral or cutaneous lesions.

The diagnostic work-up of this case would have been greatly enhanced by further clinical information. A temporal history of the lesion was essential in this regard. The patient had reported a 2-year history at the time of presentation; it would have been significant to know whether the lesion had been slowly enlarging or if there was recent rapid enlargement. Reactive and benign lesions are generally slow-growing, while malignant lesions characteristically show rapid growth and local tissue destruction. Occasionally, a benign, slow-growing lesion or low-grade malignancy will undergo a spurt of growth activity in association with malignant transformation or dedifferentiation, respectively.

There was no history of functional disturbances related to the presence of the lesion, such as difficulty in eating or of any associated signs and symptoms (e.g., pain). The co-existence of systemic signs and symptoms are clinically significant in certain reactive and neoplastic processes. The patient did not know whether the loss of the upper right premolars and molars were related to the presence of the lesion. Furthermore, a history of the patient’s social habits, such as use of tobacco and consumption of alcohol, may have provided clinical clues as to the nature of the lesion. There was no history of preceding trauma, previous malignancy, or radiotherapy. There was no information regarding any co-morbid disease such as diabetes, HIV infection, or a bleeding disorder.

The age of the patient, apparent bone destruction, hemorrhage, and a 2-year history were suggestive of a chronic infectious lesion, low-grade neoplasm, or malignant transformation of a benign neoplasm. The clinical differential diagnoses include a wide spectrum of lesions ranging from localized reactive processes to neoplastic proliferations of epithelial, hematomlymphoid, vascular, odontogenic, and mesenchymal origin.

Polypoid to nodular soft tissue lesions with increased vascularity are frequently encountered in the oral cavity and represent a localized hyperplastic response to trauma, poor oral hygiene, or hormonal fluctuations. The differential diagnosis would therefore include lesions such as pyogenic granuloma (PG) and peripheral giant cell granuloma. PGs occur over a wide age range, with an increased incidence in younger patients. A slight female predilection is noted, possibly because of hormonal effects on the oral vasculature. PGs evolve rapidly, reaching their maximal size within a few weeks to months, after which they mature. At this stage, collagenization of the stroma results in a lesion with decreased vascularity and a firmer consistency, which is pale pink in color. The surface may remain ulcerated because of sustained trauma. The age of this patient, duration, and persistent vascular nature of the lesion do not correlate with the natural history of a PG. In addition, PGs seldom cause underlying bone destruction or resorption.

Peripheral giant cell granulomas are nodular, sessile masses exclusively involving the gingiva. Lesions may reach large sizes with surface ulceration, but characteristically have a more bluish to purplish hue. The histologic features reveal numerous multinucleated giant cells within a cellular stroma, intracellular hemorrhage and hemosiderin deposits. The possibility of a peripheral presentation of a central giant cell granuloma should be radiographically excluded. Central giant cell granuloma is rarely diagnosed in older patients, with most lesions occurring within the first four decades.

True neoplasms, both primary and metastatic, may present as maxillary alveolar ridge lesions. Oral squamous cell carcinoma (OSCC) should primarily be considered in a male patient of this age, particularly if a history of smoking and alcohol consumption is provided. Although the majority of OSCCs present as ulcerated, indurated lesions, occasional tumors may be more exophytic, nodular, and even polyloid, as is common for spindle cell carcinoma (SPCC). SPCC is a poorly differentiated, sarcomatoid variant of SCC in which the atypical spindle cell component is derived from overlying squamous epithelium. SPCC is a rare variant of OSCC occurring in older individuals, with a mean age of 65 years. Lesions have a propensity for alveolar ridge involvement and present as exophytic, ulcerated nodules or polyps. There is a strong etiologic association with tobacco usage, and alcohol consumption. Lesions may arise within previously irradiated fields. SPCC is aggressive and evolves rapidly, resulting in earlier presentation. Despite the close clinical resemblance, the long duration of this lesion makes SPCC unlikely.

Minor salivary gland adenomas and carcinomas may present as slowly progressive growths, presenting initially as submucosal masses that become ulcerated over time. Pleomorphic adenoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, and polymorphous low-grade adenocarcinoma are most prevalent at this site and may have indistinguishable clinical features. These tumors occur with increased frequency with advanced age and are unrelated to habits such as smoking. Sudden rapid growth of a previously innocuous lesion may signify malignant
Melanomas may occur within the oral cavity. Lesions are readily associated with pain at late stages of disease. Although a large proportion of lesions exhibit a degree of pigmentation, amelanotic melanomas may occur within the oral cavity. Lesions are readily misdiagnosed as reactive soft tissue proliferations or granulation tissue. Features in support of mucosal melanoma include the clinical appearance, site of involvement, patient age, and gender. Despite the obvious clinical similarities, the long duration and size of the present lesion are unusual for melanoma. Melanoma has also been reported to extrude from the sockets of recently extracted teeth.

Primary lesions at this site often signify underlying immunosuppression, particularly in the setting of HIV/AIDS, where lymphoma is regarded as an AIDS-defining neoplasm. Lesions in this setting are rapidly fatal in the absence of appropriate therapy. Intra-oral lymphomas are typically non-Hodgkin lymphomas (NHL) of B-cell phenotype, most commonly diagnosed as diffuse large B-cell lymphoma or plasmablastic lymphoma. Lesions of the maxilla primarily involve the palate and gingiva. Oral cavity NHLs frequently present as rapidly enlarging, hemorrhagic masses. Intra-bony tumors mimic peri-odontal disease with sudden tooth mobility. Following tooth extraction, tumors extrude from the sockets as ulcerated, polypoid masses similar in clinical appearance to hyperplastic granulation tissue. Occasionally, NHL may present as non-specific oral ulceration that may be misdiagnosed as necrotizing ulcerative gingivitis or infective disease. Plasmablastic lymphoma is a distinct hemato-lymphoid neoplasm with a propensity for oral cavity involvement in the setting of HIV/AIDS. Plasmablastic lymphomas are highly aggressive, presenting as painful, rapidly enlarging masses with infiltration of adjacent bone. Lesions bear a striking resemblance to Kaposi sarcoma (KS). Although clinically similar to the lesion in question, the diagnosis of lymphoma is unlikely because of the lack of rapid growth, aggressive destruction, and constitutional signs and symptoms.

Kaposi sarcoma is a vascular malignancy of intermediate-grade malignant potential. The four epidemiological forms of disease are all associated with Human Herpes virus-8 infection. The most prevalent form, epidemic KS, occurs in the setting of HIV/AIDS and frequently involves the oral cavity. Isolated oral mucosal lesions of epidemic KS are seen in up to 22% of patients, while up to 71% occur concomitantly with cutaneous lesions. Oral KS lesions tend to be multifocal, although solitary masses are occasionally noted. KS is the most common malignant diagnosis in HIV/AIDS. Asymptomatic lesions in the early stages of HIV infection may remain clinically undetected for long periods of time before diagnosis, and in many instances are the first indication of underlying immune dysfunction. Early lesions are patch to plaque-like in appearance, with advanced lesions forming nodular proliferant masses, which are frequently ulcerated. The palate, tongue, and gingiva are frequent sites of oral involvement. The clinical impression in this case is most suggestive of a vascular lesion; thus, KS should be included in the clinical differential diagnosis. However, the solitary nature of this lesion and the associated fresh hemorrhage are not typical of KS. KS is also more frequently encountered in younger patients if associated with HIV/AIDS.

Angiosarcoma of the oral cavity is a rare vascular malignancy, with only 4% of all reported cases occurring intra-orally. Lesions evolve rapidly and are associated with pain and hemorrhage. The prolonged duration of this lesion, as well as the lack of associated pain, steers one away from this diagnosis. Tumors of odontogenic origin should always be considered for any primary jaw lesion. Odontogenic neoplasms account for up to 30% of oral lesions and occur most often in the second to fifth decades of life, with a distinct predilection for mandibular involvement. The majority of odontogenic tumors arise centrally within bone, with resultant bone expansion at the time of presentation. Malignant tumors have been reported as early as the second decade of life and typically cause pain and even paresthesia. Consideration of an odontogenic neoplasm is warranted in this case due to the site of involvement; however, the lack of bone enlargement may mitigate against this clinical diagnosis.

Osteosarcoma is the most common primary malignancy of bone, with 6.5% of tumors involving the jaws. Lesions have a tendency to occur in the third and fourth decades of life and...
frequently cause bone expansion.\textsuperscript{15} Imaging techniques reveal the extent of bone involvement. The non-specific radiographic changes reported in this case, together with the patient’s age, make the diagnosis of osteosarcoma unlikely.

With respect to the long duration of the lesion in this patient, a low-grade sarcomatous lesion warrants consideration. Low-grade myofibroblastic sarcoma (LGMS) is an example of such a neoplasm, which has a propensity for head and neck involvement.\textsuperscript{16} Furthermore, this tumor typically occurs in elderly patients, with a male predilection. While maxillary/paranasal sinus origin is unusual, rare cases have been reported at this site. The tongue and oral cavity proper are more favored sites of tumor occurrence. The apparently indolent nature of LGMS belies its sinister nature. Lesions may be present for a long time before diagnosis, but eventually result in metastatic dissemination if untreated. The lack of significant bone destruction and largely exophytic nature, together with the vascularity encountered in this case, are features that are not entirely concordant with those of LGMS.

Synovial sarcoma (SS), much like LGMS, may initially present as a slow-growing, deceptively innocuous lesion. Pain is a clinical feature in only 50\% of cases. SS accounts for 3\% of all soft tissue sarcomas of the head and neck and represents a rare oral neoplasm. The lesion in the current case is exophytic in nature, while most SSs are deep-seated masses. However, the patient’s age, vascular nature, and 2-year history are clinically compatible with a diagnosis of SS.\textsuperscript{17}

Soft tissue sarcomas are an important consideration for all head and neck tumors, although they constitute a mere 5\% of sarcomas in general. The typical presentation of a sarcoma is that of a painless, slow-growing mass. In this context, SS and malignant peripheral nerve sheath tumors should be considered separately, as these tumors are most likely to present as small, innocuous lesions of long duration that suddenly undergo rapid enlargement. In addition, both neoplasms are often hemorrhagic.\textsuperscript{18}

The most appropriate clinical work-up and diagnostic approach in the present case would ideally have involved clinical re-evaluation, imaging, and biopsy. It is imperative to obtain further clinical information, such as neural involvement and nodal status, as well as the presence of systemic signs and symptoms (e.g., a full blood count). Imaging modalities including radiographs and computed tomography scans are indispensable for determination of the lesional nature and extent of involvement.

\textbf{Diagnosis and Management:} An excisional biopsy of the ulcerated lobulated mass was performed. Gross examination of the specimen showed a yellowish-tan cut surface with areas of hemorrhage and surface ulceration. Microscopic examination showed an infiltrative, well-vascularized collagen-forming neoplasm composed of proliferating spindle-shaped and polygonal cells with cellular and nuclear atypia (Figure 2) arranged mainly in a storiform and fascicular pattern of growth with numerous pleomorphic giant cells and atypical mitotic figures (Figure 3) present. On immunohistochemical analysis, the cells stained negative for CD45, SMA, 34\beta E12, MNF116, S100, HMB45, and factor VIII protein, but showed strong, diffuse immunoreactivity with vimentin (Figure 4). CD68 (Figure 5) stained positive for background histiocytic cells (Dako, Glostrup, Denmark).

Based on the immunohistochemical profile and microscopic features, a diagnosis of malignant fibrous histiocytoma (MFH)/undifferentiated pleomorphic sarcoma (UPS) was made.

Seven months post excision, the patient showed no evidence of recurrence.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Spindle and polygonal cell proliferation with numerous pleomorphic giant cells (hematoxylin–eosin stain; original magnification ×200).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{The collagen-forming tumor showed atypical mitotic figures, spindle-shaped and polygonal cells (hematoxylin–eosin stain; original magnification ×400).}
\end{figure}

\textbf{Discussion:} MFH was first described in 1963 by Stout et al as a morphologically distinct soft tissue sarcoma.\textsuperscript{20} The authors proposed the “facultative fibroblastic theory” after observations made in culture studies suggested the cell of origin to be a histiocyte capable of undergoing fibroblastic transformation and laying down collagen.\textsuperscript{20,22}

Advanced diagnostic techniques such as immunohistochemistry and electron microscopy have, however, have since established that a wide variety of soft tissue sarcomas and nonsarcomatous neoplasms show a similar morphologic pattern.\textsuperscript{19,21,22} This has led to a decrease in the incidence of diagnosis of UPS, which was once thought to be the most common soft tissue sarcoma subtype, representing 40\% of all adult soft tissue sarcomas. UPS has become a diagnosis of exclusion, with approximately 5\% of all soft tissue sarcomas presenting in adults.\textsuperscript{21-24,26,27} Currently, consensus exists that UPS demonstrates no evidence of histiocytic differentiation, and its histogenesis remains unresolved.\textsuperscript{22,31,32} Numerous hypotheses regarding the histogenesis of UPS have subsequently been proposed, which include an undifferentiated mesenchymal cell origin, a fibroblastic origin with facultative histiocytic differentiation, and a common final pathway in the dedifferentiation of sarcomas.\textsuperscript{22}
immunoreactivity for markers of differentiation. Molecular studies show complex karyotypes, heterogeneity, and genetic profiles similar to other sarcomas.

UPS most commonly presents in the retroperitoneum and extremities of elderly male patients as deep-seated lesions with progressive or rapid growth, the latter often associated with pain. Head and neck tumors are extremely rare and only contribute 15 to 3% of all undifferentiated soft tissue sarcomas. Etiology is poorly understood, with 2% to 3% of cases arising in sites of previous radiation and rarely in association with chronic repair processes. Approximately 5% of cases show distant metastasis at time of presentation. A 5-year survival rate of 50% to 60% has been reported for all UPSs. Head and neck UPS is associated with a poorer prognosis when compared with UPS of the trunk and extremities because of the increased risk of recurrences. Other prognostic factors include tumor size, depth, grade, histologic subtype, and necrosis. The treatment of choice is wide surgical excision with or without adjuvant radiation therapy.

In 2002, the WHO reclassified MFH and defined it as a small group of UPS with no definable line of differentiation and, in addition, recommended that MFH/UPS be used simultaneously. With the reclassification came the revision of the histologic subtypes. Previously there were 5 subtypes, namely the myxoid, angiomatoid, storiform-pleomorphic, giant cell, and histiocytic subtypes. Previously there were 5 subtypes, namely the myxoid, angiomatoid, storiform-pleomorphic, giant cell, and histiocytic subtypes. Previously there were 5 subtypes, namely the myxoid, angiomatoid, storiform-pleomorphic, giant cell, and histiocytic subtypes.

Fig. 4. Diffuse and strong immunoreactivity for vimentin (Dako; original magnification × 200).

Fig. 5. Background histiocytic cells immunoreactivity for CD 68 (Dako; original magnification × 400).

References


CLINICAL PATHOLOGIC CONFERENCE CASE 2: A DIFFUSE SWELLING AFFECTING SOFT PALATE AND OROPHARYNX

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Clinical Presentation: A 47-year-old woman presented with a 2-year history of odynophagia. Her medical, family, and social history were unremarkable. Dental history included full-mouth extractions because of extensive periodontal disease several years earlier. Head and neck extraoral physical examination was also unremarkable, with no evidence of asymmetry, trismus, or cervical lymphadenopathy. Routine panoramic radiographic examination failed to detect any osseous abnormalities. The intraoral examination revealed a 5 × 5-cm firm, diffuse, nontender submucosal mass in the left inferolateral portion of the soft palate (Figure 1) extending to the oropharynx and causing the displacement of the uvula and the lateral wall of the oropharynx medially (Figure 2).

Differential Diagnosis: Differential diagnosis of a diffuse soft-tissue mass affecting the posterior portion of the soft palate and lateral oropharynx comprises several different potential pathologies, including primary lesions of the palatal mucosa, such as minor salivary glands tumors (especially pleomorphic adenoma [PA] or low-grade mucoepidermoid carcinoma [MEC]) and benign mesenchymal tumors (BMT; most probably neurofibroma, lipoma, or leiomyoma).

Salivary gland tumors (SGTs) are considered uncommon lesions that account for approximately 3% of all head and neck tumors. Minor salivary glands tumors (MSGTs), in turn, represent up to 25% of all SGTs and may present with a myriad of histologic patterns. Overall, MSGTs mainly affect adult patients, especially in their third to fourth decades of life, and present a slight female predilection for both benign and malignant tumors. The palate is considered the most commonly affected site for both benign and malignant MSGTs, of which 33% to 75% occur in the palatal mucosa.

PA is the most common MSGT and the most common benign MSGT, while MEC is the most common malignant MSGT. The above-mentioned clinical and epidemiological characteristics are very similar to the currently described case. Intraoral PAs and MECs may be indistinguishable from a clinical point of view because both tumors tend to develop as asymptomatic slow-growing soft tissue nodules localized in the para-median regions of the hard palate, as well as in the transition area between hard and soft palate. Benign tumors and low-grade malignant tumors, such as PAs and MECs, are often submitted to excisional biopsy, probably because of their benign clinical aspect. Epidemiologically, well-delimited soft tissue swellings affecting the hard or soft palate have an approximately 50% chance of representing a malignant MEC (especially MEC). Thus, such lesions should be initially assessed by incisional biopsy or intra-oral FNAC, which would allow the histopathologic diagnosis and lead to adequate treatment. Most palatal MECs are low- or intermediate-grade lesions and present clinically as unsuspected soft tissue nodular lesions that, if untreated, may become large enough to cause facial asymmetry, speech impairment, and odynophagia.

Benign soft tissue tumors may also appear in the oral cavity as asymptomatic, nodular, long-standing stable lesions, generally covered with tissue of normal coloration. Thus, BMTs...
originating from neural, adipocytic, and muscle tissues were also considered during the clinical diagnosis algorithm. Among benign neural tumors, neurofibromas usually affect the palate of young females and present as slow-growing asymptomatic masses of variable size, with clinical features similar to the case in question. Among BMTs, neurofibroma was considered to be more probable because of its higher frequency and predilection for the palate. A lipoma was also briefly considered because these typically present in the oral cavity as slow-growing and well-defined masses. However, lipomas rarely affect the palate and lateral wall of the oropharynx and often present with a yellowish covering surface, which contrasts with the present case. Leiomyomas are seldom diagnosed in the oral mucosa and oropharynx, however, when involving the oral cavity, the palate is the most frequently involved site. As in the case described here, oral leiomyomas present as slow-growing and well-defined masses that develop in young adults without causing major symptoms. Taking this into consideration, this was considered as a possible, albeit unlikely, diagnostic hypothesis.

When taking together, the clinical features of this patient, the demographic data, as well as the prevalence of all the lesions described, MSGT was considered the most likely diagnostic hypothesis.

**Diagnosis and Management:** The clinical presentation of the lesion prompted intra-oral fine needle aspiration cytology (FNAC). Cytologic examination was inconclusive, but a few clusters of acinar differentiated cells could be identified and were suggestive of an acinic cell carcinoma (ACC).

Subsequently, a computed tomography scan (CT) with intravenous contrast was performed and revealed a large expanse well-circumscribed oval soft tissue mass located medially to the mandibular angle, projecting within the left parapharyngeal space (Figure 3). The lesion was in connection with the deep portion of the left parotid gland and presented a central hypodense area suggesting necrosis (Figure 4). Taking into account the clinical presentation of the lesion, the cytopathologic findings from the FNAC and the CT, suggesting a massive ACC affecting the deep lobe of the parotid gland and involving the left parapharyngeal space with extension to the oral cavity, it was decided to refer the patient to a head and neck surgeon.

The disease was clinically and radiographically staged as T3N0M0 and the patient was treated with a total parotidectomy using a transcervical-transparotid approach. The facial nerve was identified and dissected, and a superficial parotidectomy was performed. The deep lobe of the tumor was identified, mobilized and removed (Figure 5). The intraoperative findings confirmed the connection of the tumor with the deep lobe of the left parotid gland.

On macroscopic examination, the surgical specimen included the superficial portion of the parotid gland and an ovoid well-circumscribed tumor measuring $5.5 \times 4.1 \times 2.1$ cm and weighing 32g (Figure 6). The cut surface showed heterogeneous brownish areas and central tan to reddish areas containing soft and friable necrotic material. On microscopic analysis, the tumor presented a dense and homogenous proliferation of well-differentiated large and polygonal serous acinar cells (Figure 7) with small eccentric nuclei and abundant basophilic zymogen-like cytoplasmic granules (Figure 8), which were found to be positive with periodic acid-Schiff (PAS) stain and resistant to diastase digestion (Figure 9). Focal areas of vacuolated and clear cells were also observed throughout the tumor (Figure 10). Atypical mitoses and cellular atypia were absent. The tumor cells were arranged in a solid pattern, confirming the diagnosis of an acinic cell carcinoma (solid-type) of the deep lobe of the parotid gland involving the left parapharyngeal space.
space. Parotid-associated lymph nodes were free of tumor cells; however, the tumor fibrous capsule revealed areas of rupture and tumor invasion. Thus, the patient underwent postoperative head and neck radiotherapy to a total dose of 60 Gy.

The patient is doing well after a 60-month follow-up with no signs of recurrent disease or any other complication (Figure 11).

**Discussion:** The parapharyngeal space is a complex anatomic site that contains several different tissue components, including major blood vessels, cranial nerves, minor and major salivary gland tissue, bone, and lymph nodes. Tumors arising in this location may get large enough to displace the soft palate and the lateral wall of the oropharynx medially, causing an intraoral lesion and rendering the mass palpable through the oral cavity. Parapharyngeal space tumors (PSTs) must present at least 2.5 cm in diameter to be able to push the lateral pharyngeal wall toward the oral cavity, which is considered a very uncommon clinical phenomena.  

PSTs encompass a huge variety of tumors, of which up to 90% are benign. In general, the differential diagnosis of masses in the parapharyngeal space include MSGTs originating from ectopic minor salivary glands, tumors affecting the deep lobe of the parotid gland, neurogenic lesions (Schwannomas, neurofibromas, and paragangliomas), vascular lesions (hemangioma, lymphangioma, and internal carotid aneurysm), and miscellaneous tumors, including lymphomas, desmoid tumors, leiomyomas, liposarcomas, and metastatic disease. Generally speaking, the most frequent tumor affecting the parapharyngeal space is the PA of minor salivary gland origin (35%), followed by neurilemomas (18%), lymphomas (13%), and paragangliomas (12%).

Usually, PSTs represent a diagnostic challenge because they present in a nonspecific manner, frequently achieving large dimension before diagnosis, generally without causing symptoms. However, advanced stage lesions, such as the one presented herein, may be associated with dysphagia, dyspnea, trismus,
unilateral hearing loss, and neurological disorders, including Vernet syndrome and Horner syndrome. When there is clinical evidence of PFTs, a detailed head and neck examination combined with high-resolution radiographic examinations, including CT and magnetic resonance imaging (MRI), is recommended for diagnosis. Similar to many other head and neck tumors, preoperative intraoral FNAC may assist with the diagnosis of PSTs.\textsuperscript{19,20}

ACCs represent approximately 5% of all parotid gland epithelial tumors and 12% of all parotid carcinomas, and rarely involve the parapharyngeal space. The overwhelming majority of ACCs occur in the parotid gland and some may occasionally be found in major salivary glands or in the seromucous glands of the oral mucosa and aerodigestive tract.\textsuperscript{5,21} Similarly to the current case, the majority of ACCs present in the fourth to sixth decades of life, with a slight predilection for women.

Several histomorphologic growth patterns are described: solid/lobular, microcystic, papillary-cystic, and follicular. PAS-positive (diastase-resistant) cytoplasmic zymogen-like granules are the hallmark of these tumors. Apart from the classic polygonal acinar-type cells, sheets of vacuolated and clear cells are also frequently seen.\textsuperscript{22,23}

Lymph node involvement is not a common finding in ACCs, and the main aim of therapy is to perform complete tumor removal during the first surgical approach. Well-delimited tumors involving the deep lobe of the parotid gland and the parapharyngeal space are preferentially surgically removed by means of a transcervical approach with facial nerve dissection and total parotidectomy.

ACC presents a low risk for lymph node metastasis; therefore, neck dissection is reserved for management of clinically suspicious nodes. Postoperative radiotherapy is recommended only for cases with residual disease or capsular rupture.

All patients diagnosed with ACC must be submitted to long-standing clinic follow-up because late recurrences (even 20 years after treatment) are often seen.\textsuperscript{24,25}

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References


CLINICAL PATHOLOGIC CONFERENCE CASE 3: A CHALLENGING CASE OF AN ENLARGING SWELLING OF THE MAXILLA

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Clinical Presentation: A 32-year-old Nigerian female presented to a local dentist with a 2-month history of an enlarging swelling of the upper left labial sulcus, extending from the central incisor to the canine area. The patient had never attended a dentist before this.

Panoramic tomography (Figure 1) showed a radiolucent lesion in the anterior aspect of the left maxilla at the level of the alveolus. This lesion was predominantly well-circumscribed, but on the right side, close to the apices of the incisors and canine, the borders were indistinct. The lesion also appeared to be extending into the right side and midline of the nasal septum. Although predominantly osteolytic, there were a few sclerotic foci toward the left side. The hard palate appeared thinned but not resorbed. The lesion was not corticated and there was marked irregular erosion of the tooth roots of the first and second incisors and of the apical area of the canine (Figure 1, inset).

Differential Diagnosis: Although the clinical symptoms were present for only 2 months, the radiographic findings are compatible with a lesion of long duration, with a rather slow but progressive rate of growth. Therefore, the entities to be discussed in the differential diagnosis should include benign but locally aggressive tumors (odontogenic and non-odontogenic), malignant lesions (mainly of the low-grade type), and inflammatory/infectious conditions.

Among the benign odontogenic tumors, desmoplastic ameloblastoma (DA) can be considered because it manifests as a painless swelling of the jaw, usually located in the anterior region. The slow rate of growth is consistent with movement of tooth roots and root resorption, as seen in this case. Radiographically, DA has ill-defined borders. Although our case is partly ill-defined and infiltrative, it is mostly well-circumscribed. Additionally, DA often has a mixed radiolucent-radiopaque pattern, similar to a fibro-osseous lesion, which was not seen in the present case.

Odontogenic fibroma (OF) and calcifying epithelial odontogenic tumor (CEOT) are also included in the differential diagnosis. OF has a female predominance and, when present in the...
maxilla, tends to affect the anterior portion.\(^2,3\) However, CEOT is more commonly noted in the premolar-molar region of the mandible. Both OF and CEOT usually present as slowly enlarging painless expansion of the jaws that, on imaging, can present as radiolucent lesions with evidence of tooth displacement and resorption.\(^2,4\) OF is often very well-demarcated or corticated; CEOT often presents as a mixed radiolucent-radiopaque lesion on imaging (Figure 1).

Among the malignant odontogenic tumors, ameloblastic carcinoma\(^6\) and clear cell odontogenic carcinoma\(^6\) may be considered. Ameloblastic carcinoma and clear cell odontogenic carcinoma can show an expansile intra-osseous radiolucency with ill-defined borders and root resorption. Perforation of the bone cortices and infiltration into adjacent structures can also be present. However, these lesions are mainly located in the mandible; additionally, pain and/or paraesthesia may also be expected.\(^3\) None of the latter symptoms were present in our case.

The central giant cell lesion (CGCL) in most cases is asymptomatic and can show swelling and loosening of teeth in young adult patients (average age, 25 years). On imaging, CGCL presents as a multilocular or unilocular radiolucent lesion with non-corticated borders. Disappearance of the lamina dura, root resorption, tooth resorption, nasal obstruction, and penetration of the jaw cortex have been described in CGCL.\(^5,6\) However, the majority of cases are located in the mandible.

Sinonasal schwannoma is a rare tumor constituting only \(~4\%\) of all head and neck schwannomas.\(^9\) It can be painless, even when tumors are large and extend into adjacent structures.\(^9\) In long-standing lesions, cystic change can occur and this may confer a radiolucent appearance in a background of increased radiopacity.\(^10\) as in the present case. Tooth movement and root resorption have been documented in schwannomas of the jaws.\(^11,12\)

Sinonasal lymphoma is the second most common malignancy of the sinonasal tract, following squamous cell carcinoma, with B-cell lymphomas, being the more frequent type found in the paranasal sinuses.\(^12,14\) The radiographic features usually demonstrated a poorly demarcated lesion with expansion into adjacent structures, bone destruction, and root resorption and widening of the periodontal ligament of adjacent teeth. Some of these features were evident in the present case. Similar radiographic features can be encountered in osteosarcoma of the jaws.

Sinonasal squamous cell carcinoma\(^15\) and sinonasal adenocarcinoma\(^16\) are not favored diagnoses because they usually arise higher in the sinonasal region and are expected to be symptomatic, especially in advanced stages. The patient in the present case was asymptomatic, despite the advanced stage of the tumor.

Of the inflammatory/infectious conditions, rhinoscleroma could be considered because it is a chronic, progressive process with potential to destroy and extend into adjacent structures, including the oral cavity.\(^17\) However, this is a less likely diagnosis in the present case, as the patient is not known to reside in an area endemic for rhinoscleroma.

Finally, metastasis to the jaws cannot be excluded. However, the current patient is relatively young to have metastatic disease. The majority of the patients with metastases to the oral cavity and jaws are older than 50 years of age.\(^18\) Breast, prostate, and lung cancers are the most common primary tumors presenting with jaw metastasis.\(^18,19\) Other primary sites of origin of metastases reported in the jaws are cancers of the colon, liver, rectum, thyroid, uterus, and parotid gland.\(^18,19\)

**Diagnosis and Management:** The macroscopic features of the incisional biopsy consisted of irregular pieces of tan-colored tissue with a maximum dimension of 15 mm. Hematoxylin and eosin-stained sections showed a densely cellular spindle cell tumor (Figure 2) arranged in interlacing fascicles that in places resembled a herringbone pattern. Cytologically, the cells were fusiform and spindled with mild pleomorphism. Scattered within the lesion were infrequent small islands of irregular osteoid (Figure 2). Some of these osteoid structures were surrounded by large mildly pleomorphic cells consistent with osteoblasts.

The histopathologic differential diagnosis was broad and initially included tumors such as monophasic synovial sarcoma, fibrosarcoma, fibroblastic osteosarcoma, chondrosarcoma (there was no evidence of chondroid tissue), and phosphaturic mesenchymal tumor. However, given the areas of osteoid formation, the histopathology was most suggestive of a malignant mesenchymal tumor consistent with osteosarcoma. Immunohistochemistry for a broad sarcoma panel that included cytokeratins, EMA, S100, desmin, CD34, and CD31 was negative. Patchy positivity for SMA, CD99, and CD117 was seen. The Ki67 proliferation rate was about 15% of the tumor cells.

The case was referred for management to the Royal National Orthopaedic Hospital and the University College London Hospital. Both institutions agreed with the diagnosis of a fibroblastic osteosarcoma.

Following the diagnosis, computed tomography of the head and neck was obtained (Figure 3). This showed the main bulk of the tumor was in the left maxilla with extension across the midline to involve the right maxilla, upper lip, and premaxillary soft tissues. The lesion displayed irregular boundaries and contained small flecks of mineralization.

The patient was given preoperative chemotherapy followed by a subtotal maxillectomy (Figure 4) at the University College Hospital, London in 2009. The resection specimen included most of the left maxilla, anterior part of the right hard palate, upper lip, and anterior part of the nose.

The histology from the resection specimen showed features similar to the incisional biopsy. However, there were numerous markedly pleomorphic cells associated with areas of mineralized
osteoid (Figure 5). Despite the preoperative chemotherapy, there was a significant amount of viable tumor. The final diagnosis of the resection specimen was of a high-grade osteosarcoma of fibroblastic type. The tumor showed a poor response to neo-adjuvant chemotherapy (<90% tumor necrosis). The resection margins were clear of tumor by at least 5 mm. Despite the serious diagnosis, this patient had a recent pregnancy and there has not been any evidence of recurrence in almost 3 years since the initial resection.

Discussion: This is an interesting case of a fibroblastic osteosarcoma of the jaws. The incidence of osteosarcoma of the jaws has been estimated at around 0.7 per million. Osteosarcomas of the jaws tend to occur during the third and fourth decades of life, which is about a decade or two later than conventional osteosarcoma of the long bones. In the jaw bones, the chondroblastic and the osteoblastic types of osteosarcoma are the most frequently encountered histopathologic variants. Fibroblastic osteosarcoma is rarely reported in this location.

According to the WHO guidelines, the fibroblastic osteosarcoma is of “a high grade spindle cell malignancy with minimal amounts of osseous matrix with or without cartilage.” This variant of osteosarcoma appears to be more frequent in the extremities of children younger than 5 years of age.

In general, the radiographic findings of osteosarcoma of the jaws vary from osteolytic to osteosclerotic to mixed lesions, the latter being the most frequent. Irregular resorption of tooth roots, variable radiopacities, obliteration of the normal trabecular bone, and sunray and sunburst appearance are all features associated with osteosarcomas of the jaws. Given the lack of substantial calcification of the osteoid in fibroblastic osteosarcoma, it is not surprising that radiographically this lesion most often presents as an osteolytic lesion, as seen in our case (Figure 1). The irregular resorption of the tooth roots in the present case reflects the infiltrative and osteolytic nature of this tumor and, at the same time, suggests some chronicity of the lesion.

Some studies of large series of osteosarcomas of the jaws have shown a predilection for the mandible. However, when present in the maxilla, there appears to be a predilection for the canine-premolar area. A previously reported case of fibroblastic osteosarcoma was also described in the maxilla, involving the canine to the molar region. In our case, the canine was also involved but the tumor was more anteriorly located around the incisor area (Figure 1).

The current case and the previously described case of fibroblastic osteosarcoma both presented as an expansile lesion of the maxilla. Swelling with bony expansion of the cortical plates is the most common clinical presentation of osteosarcoma of the jaws. Symptoms that have been associated with osteosarcoma of the jaws are include painful nasal obstruction, epistaxis, loosening of teeth, paraesthesia, and numbness.

Another interesting point about this case is that, despite the diagnosis of a high-grade osteosarcoma, the patient has not shown any recurrences or metastasis after 3 years. This might be because of the clear tumor margins achieved in the resection specimen.
However, some have reported a more favorable prognosis in survival of 60% to 80% in osteosarcoma. Resection with clear margins is well-recognized as a favorable prognostic factor in osteosarcomas of the jaws.31,32

There is no evidence of any prognostic significance between the different histopathologic variants of osteosarcoma.24 However, some have reported a more favorable prognosis in chondroblastic osteosarcomas of the jaws.25 Although the current case has not shown evidence of recurrence or metastasis, the previously described case of fibroblastic osteosarcoma showed rapid growth and recurrence after 6 months.28

In conclusion, this was a rare case of a fibroblastic osteosarcoma that presented with a relatively indolent clinical history. The initial radiographic features showed worrisome osteolytic and infiltrative features. The prognostic significance of fibroblastic osteosarcoma of the jaws still remains to be elucidated; however, it appears that, as in other osteosarcomas, early diagnosis with multi-modality therapy that includes clear margins are associated with a better prognosis.

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References
CLINICAL PATHOLOGIC CONFERENCE CASE 4: A 15-YEAR-OLD BOY WITH RADIOGRAPHIC CHANGES IN THE LEFT MANDIBLE

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Clinical Presentation: A 15-year-old boy who experienced pain on chewing was referred regarding mobility of his mandibular left molar teeth. He was otherwise in good health with no relevant medical history. Radiologic examination of the mandible revealed several dental and bony changes: widening of the left ramus of the mandible with a diffuse increase in bone density, the left body of the mandible was vertically enlarged, the third molar crown was deformed and the root was rudimentary or absent, the roots of the mandibular left second molar tooth were shortened, and the second premolar root apex was also slightly foreshortened (Figure 1). A 99mTc MDP (methoxyisobutylisonitrile) bone scan showed extensive uptake in the left mandible (Figure 2). Full blood count was normal.

Differential Diagnosis: Based on the clinical and imaging findings, a variety of differential diagnoses were considered.

Chronic osteomyelitis of the mandible encompasses a spectrum of clinical entities including proliferative periostitis (Garre’s osteomyelitis), which is a non-suppurative condition with low-grade diffuse inflammatory reaction, usually associated with a periapical infection, characterized by thickening of the periosteum and subperiosteal deposition of bone, resulting in enlargement of the affected region.

Chronic non-specific sclerosing osteomyelitis/osteitis is currently considered to be an auto-inflammatory disorder that may affect the mandible and is characterized by patchy areas of sclerosis and radiolucency on imaging that may cause mandibular enlargement. The changes represent the manifestation of a chronic inflammatory reaction in both the cortex and medulla, with associated endosteal and periosteal thickening. Subsequent diffuse cortical thickening and narrowing of the medullary canal occurs. The process may occur at any age, although it is most frequent in late childhood and adolescence. There is a slight female predominance and is characterized by relapses and remissions.

Systemic symptoms are rare, along with mild fever and mild elevation of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The process may be unifocal or multifocal and may be recurrent. Non-specific chronic inflammation, which includes plasma cells with reactive sclerosis, is noted histologically. There are no sequestrae, abscess formation is not identified, and culture is negative. Associated cutaneous skin disorders may occur (‘SAPHO’ syndrome).

Intraosseous vascular malformations of the maxillofacial region sometimes give rise to dental emergencies because of proximity of the teeth to the intramedullary lesion. Those near the alveolar bone often present with pericoronal bleeding, mobile teeth, and sometimes occlusal anomalies. In contrast to our case, vascular malformations in the mandible and maxilla usually produce a poorly defined, radiolucent lesion with a honeycomb or soap bubble appearance. Root resorption has been observed, creating an appearance of teeth floating in the adjacent alveolar osseous erosion.

Mandibular fractures during childhood may result in altered permanent tooth development and eruption, dependent on the stage of development at the time of fracture. Mandibular growth can be affected in an unpredictable manner and the presence of infection will also have a significant effect. There was no such history in this case.

Based on the presence of a sclerotic lesion, matrix producing tumors including osteoma, osteoid osteoma, osteoblastoma, ossifying fibroma, and fibrous dysplasia were considered. These entities are usually more clearly delineated and well-circumscribed on imaging. Osteosarcoma could be entertained based on the presence of a poorly defined alternating sclerotic and radiolucent lesion, although overt aggressive features are the norm.

In this age group and at this site, chondrosarcoma was considered highly unlikely. Langerhans cell histiocytosis may occur at any age, and the jaw is the second most common site of involvement in the head and neck region. In contrast to our case, these are usually characterized by a radiolucent appearance, frequently involving one or more areas in one or more quadrants, with loosening of the associated teeth. Finally lymphoma may rarely be associated with bone sclerosis.

Diagnosis and Management: A biopsy of the region was performed and the tissues fixed in 10% buffered formalin. The fragments comprised pieces of hard and soft tissue measuring up to 10 mm in size. All were processed in a routine fashion with decalcification of the hard tissue components. On light microscopy there were multiple fragments of tissue, one of which comprised a portion of dental follicle. Multiple separate fragments of fibrous tissue and bone were present. Within the fibrous tissue, crushed hyperchromatic poorly preserved cells were present. In the bony tissue, better preserved sheets of atypical cells with a high nuclear-to-cytoplasmic ratio...
and mildly variable, enlarged slightly convoluted nuclei were noted. The cytoplasm was inconspicuous. Nucleoli were small and the chromatin evenly distributed and bland. Rare mitoses were noted. The accompanying osseous tissue comprised predominantly woven bone lined by the atypical cells, also noted in osteocyte lacunae. Occasional fragments of immature lace-like/filigree-type osteoid production by tumor cells was seen, focally surrounding and encasing pre-existing mature host lamellar bone characterizing a destructive permeative process (Figure 3).

Histopathologic features were those of a small, round, blue cell tumor with immature tumor osteoid production. Although this prompted consideration of Ewing sarcoma (ES), the presence of atypical/malignant osteoid production in this setting is characteristic of small cell osteosarcoma.

This diagnosis was supported by the presence of distinct sclerosis on imaging.

Immunohistochemical stains showed distinct strong membrane staining for CD99 and FLI1 nuclear positivity was noted (Figure 4). Cytokeratins AE1/AE3 and CAM 5.2, chromogranin, synaptophysin, CD45, CD43, TdT, CD117, CD1a, and myeloperoxidase were all negative.

Subsequent FISH analysis was performed using LSI EWSR1 (22q12) dual-color break-apart rearrangement probe (Vysis, Abbott Molecular, Des Plaines, IL) which split (rearranged) EWSR1 signals in 94% of cells scored. This is molecular cytogenetic evidence of a translocation involving the EWSR1 gene at 22q12 such as the t(11;22) or t(21;22) (Figure 3). Although the constellation of histopathology and imaging is in keeping with small-cell osteosarcoma, the positivity for CD99 and FLI-1 raises the possibility of a rarely documented possible variant of Ewing tumor. This was confirmed by FISH testing, in which translocation involving the EWSR1 gene at 22q12 was identified.

The patient was treated with compressed Ewing protocol, which comprised 10 cycles of vincristine, cyclophosphamide, doxorubicin, ifosfamide, and etoposide. Resection and reconstruction with a free vascularized graft was successfully performed after 7 cycles of chemotherapy.

A complete response to chemotherapy was achieved on examination of the resection specimen and a further 3 cycles of chemotherapy ensued.

Discussion: Small-cell osteosarcoma (SCO) is a rare variant of high-grade osteosarcoma with clinical features and distribution similar to conventional osteosarcoma but characterized by small, round, blue cells similar to ES, in which at least focal atypical, non-reactive osteoid production is identified. It is usually not associated with the presence of ES translocation and is therefore considered to be a unique entity. SCO can rarely be positive for CD99, but a negative result supports the diagnosis of SCO.10 Thus far, FLI 1 expression has not been identified in typical forms of SCO.11

The ES/primitive neuroectodermal tumor (PNET) family of tumors comprises a group of small round cell tumors genetically defined by a specific reciprocal chromosomal translocation between chromosomes 11 and 22. The t(11;22)(q24;q12) is present in about 85% of cases.12 The rearrangement results in the translocation of the 3’ portion of the friend leukemia virus integration site 1 (FLI1) gene from chromosome 11 to the 5’ portion of the Ewing sarcoma (EWS) gene on chromosome 22.13 Occasionally, alternative translocations are observed involving chromosomes 22q12 and either 21q22 (10%) or 7p22 and 17q12. Rearrangements of EWS with FLI or a FLI-related gene

Fig. 1. Radiologic findings. An orthopantomogram revealed widening of the left ramus of the mandible with a diffuse increase in bone density. The left body of the mandible was vertically enlarged. There was relative radiolucency in several regions. The third molar crown was deformed and the root was rudimentary or absent. The roots of the mandibular left second molar tooth were shortened. The second premolar root apex was also slightly foreshortened.

Fig. 2. 99mTc MDP (methoxydiphosphonate) bone scan showed extensive increased uptake in the left mandible.
characterize 98% of all ES. Some cases of CD99-positive ES/PNET do not have chromosome 22 aberrations and may be associated with an alternative gene fusion. Additional structural changes have also been identified in ES/PNET.

Very few cases with findings similar to ours are documented. A recent review identified only 4 similar cases:

A 20-year-old man with large tumor of the right acromion with the morphology of a small-cell osteogenic sarcoma. Pulmonary metastases developed 10 months after chemotherapy, in which features of SCO were confirmed. Standard G banding showed t(11:22)(q24:q12). A possible relationship between ES and SCO was mooted.

A 37-year-old man with multiple intraperitoneal tumors in which the morphology was that of SCO. CD99 was positive and RT-PCR (reverse transcription-polymerase chain reaction) detected EWS-FLI1 fusion gene. The abdominal location was highly unusual for SCO and the possibility of overlap between these entities was suggested.

A 12-year-old girl with multifocal SCO in multiple bones considered primary in the seventh thoracic vertebra. The histology was that of SCO; however, interphase FISH detected ES breakpoint region 1 (EWSR1) gene rearrangement. RT-PCR identified a novel fusion transcript EWSR1-CREB3L1. This transcript is also found in low-grade fibromyxoid sarcoma.

A mixed therapeutic regimen was used, but the patient died after 3 years. The authors suggested that FISH alone may not be a reliable method to differentiate between ES and SCO in clinical practice and that molecular and cytogenetic findings must be interpreted in the context of the combined clinical and pathologic findings. The EWS gene is promiscuous and associated with a variety of disparate neoplasms.

A 17-year-old boy with SCO of the right proximal fibula in which strong diffuse positivity for CD99 and FLI1 was noted and interphase FISH-detected EWSR1 gene rearrangement. The FISH pattern was atypical in 41% of cells and the breakpoint for the rearrangement was distal (telomeric) to those usually detected.

Fig. 3. A, Hematoxylin and eosin-stained section at low power showing the bony tissue with associated sheets of atypical cells. A portion of dental papilla is included in the right upper. B, The dense fibrous connective tissue contains irregularly distributed hyperchromatic cells with extensive crush artifact. C, In regions sheets of malignant cells are present, devoid of matrix production. D, Elsewhere abundant woven bone with an immature pattern is seen. Note the atypical cells in some of the osteocyte lacunae. The arrows show original mature lamellar trabeculae (confirmed on polarization) covered by atypical osteoid. E, The cells have a high nuclear-to-cytoplasmic ratio with slightly variable, enlarged, and convoluted nuclei. The nucleoli are small and the chromatin is evenly distributed and bland. The cytoplasm is inconspicuous.
in tumors with a t(11;22). There was a poor response to chemotherapy and amputation was performed. The authors speculated that ES and SCO may share an early common pathway of tumor development at the cytogenetic level before the accumulation of additional genetic alterations causes their divergence.21

ES may show variable morphology and simulate many other tumors. As such, it is classified into 3 groups according to their principal morphological criteria: Classical ES, PNET, and atypical ES (which includes all other subtypes).22,23 This includes tumors with sclerosis, adamantinoma-like areas, large cells, epithelioid cells, clear cells, spindle cells, hemangiopericytoma features, and synovial sarcoma-like features.22-28 The diagnosis ultimately depends on identification of EWSR1 translocation established by FISH and preferably also by RT-PCR analysis.24

This is an unusual case of a small round cell tumor with the morphology of SCO and the cytology and molecular footprint of ES. Whether these reflect SCO with Ewing’s translocation or atypical ES with osteoid production is not yet clear.

Malignant osteoid remains the hallmark of SCO, while the presence of an EWSR1 translocation with the specific gene fusions is typical of ES family of tumors. In a number of cases, however, the distinction between these two entities is blurred.

Similar tumors have been described previously in the literature. The findings in these cases suggest that these tumors may share an early common pathway.

Management is problematic. SCO is usually treated with conventional osteosarcoma therapy, which differs from that recommended for ES. As such, in these apparently overlapping cases, modification of therapeutic regimens may be necessary. This patient responded very well to the ES protocol, with complete tumor response, which contrasts with some of the previous reports described as “small cell osteosarcoma with Ewing translocation.”

Therefore, the classification and the ideal treatment for these most unusual tumors remain to be elucidated.

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References