LOCALLY AGGRESIVE BENIGN PROCESSES OF THE ORAL AND MAXILLOFACIAL REGION

Eric R. Carlson, DMD, MD; Meredith August, DMD, MD; Salvatore L. Ruggiero, DMD, MD

INTRODUCTION

Pathologic processes of the oral and maxillofacial region are generally classified as benign or malignant based on specific histologic criteria, including the presence or absence of necrosis, mitotic figures as well as a basic understanding of the entity. The term *aggressive* has most commonly been reserved to describe malignant tumors because of their ability to grow quickly and invade surrounding structures, resulting in significant local growth, metastatic disease and possibly death of the patient. However, the oral and maxillofacial region is the site of many benign yet locally aggressive processes that can result in significant anatomic destruction, deformation and resultant loss of function (Fig. 1). Locally, aggressive benign processes can be distinguished from their malignant counterparts by a lack of skin invasion, a lack of epineural infiltration and the paradox of aggressive but slow growth. In some cases, many benign tumors of the oral and maxillofacial region can be more aggressive, destructive, and deforming than some malignant tumors, even though they grow less quickly.

Tissue masses are often referred to as tumors without specifically classifying their true pathologic nature or anticipated behavior.[1] A true appreciation for the specific type of pathology allows surgeons to propose scientifically sound treatment approaches. Simple growths (e.g., a fibroma caused by trauma or a pyogenic granuloma) have often been referred to as tumors, as have salivary gland tumors (e.g., pleomorphic adenoma and canalicular adenoma). Aberrant attempts at odontogenesis, including compound composite odontomas and ameloblastic fibro-odontomas have also been referred to as tumors.

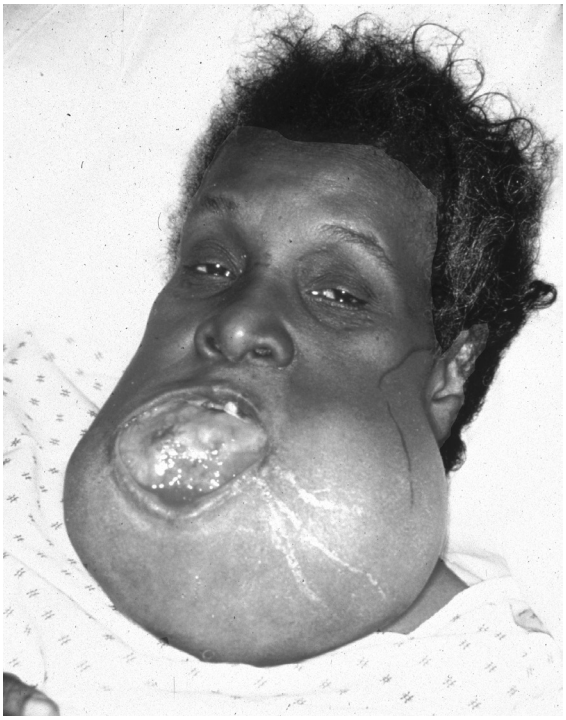

Figure 1: A very large ameloblastoma of the mandible exhibiting severe facial deformation.

These last two benign, yet non-neoplastic entities are more accurately described as hamar-

tomas. Hamartomas are defined as dysmorphic proliferations of tissue, native to its region of development, that are incapable of independent or autonomous growth. Instead, hamartomas cease growing at some point in their development, and they do not infiltrate cortical bone or surrounding soft tissues. This characteristic permits the surgeon to cure by performing enucleation procedures in bone or pericapsular excisions in soft tissues.

Choristomas are similar to hamartomas in being dysmorphic proliferations of tissue that are not capable of autonomous growth. However, they are derived from tissue not native to the site of development (e.g., lingual thyroids and osteomas of the tongue). Like hamartomas, choristomas may be removed in a relatively conservative fashion. Teratomas (e.g., benign cystic teratoma of ovarian derivation) are true neoplasms with the capacity for continual growth. Their origin is from all three germ layers, allowing for the production of hair, teeth and bone.

Benign neoplasms are dysmorphic proliferations of tissues that have the capacity for persistent, autonomous growth.

Benign neoplasms are dysmorphic proliferations of tissues that have the capacity for persistent, autonomous growth. These tumors have the ability to proliferate unless completely removed. Malignant neoplasms, in contrast, are dysmorphic proliferations of tissues that have the capacity for both autonomous growth and metastasis. Genetic alterations in malignant tumors allow a change in doubling times and for the development of metastasis where no previous capability existed.[2] The genetic alterations present in benign tumors are generally not susceptible to mutations, thereby conferring a relatively stable clinical course and typically prohibiting metastatic disease. This genetic stability produces a relatively consistent growth rate, degree of invasiveness vs. indolent infiltration of the surrounding tissues, and other clinical attributes.

Neoplasia is a cell-cycle disease.

Growth of a pathologic entity is a function of cell proliferation vs. apoptosis in the cell cycle. Neoplasia is, therefore, a cell-cycle disease.[3] A series of genetic alterations that control the cell cycle, involving both oncogenes and tumor suppressor genes, seem to be of critical importance in tumorigenesis. Normally, cell division is divided into four phases (Fig. 2): G1 (gap 1), S (DNA synthesis), G2 (gap 2), and M (mitosis). A key event is the progression from the G1 to the S phase. Genetic alterations that are unrepaired in the G1 phase may be carried into the S phase and perpetuated in subsequent cell divisions. The G1-S checkpoint is normally regulated by a complex, well-coordinated system of protein interactions whose balance and function are critical to normal cell division. Over-production of inducing proteins or under-production of inhibitor proteins can encourage the development of a tumor.

For example, p53 (located on chromosome 17p13.1) is normally a tumor suppressor gene. Normal p53 acts as a "molecular policeman" monitoring the integrity of the genome. If DNA is damaged, p53 accumulates and switches off

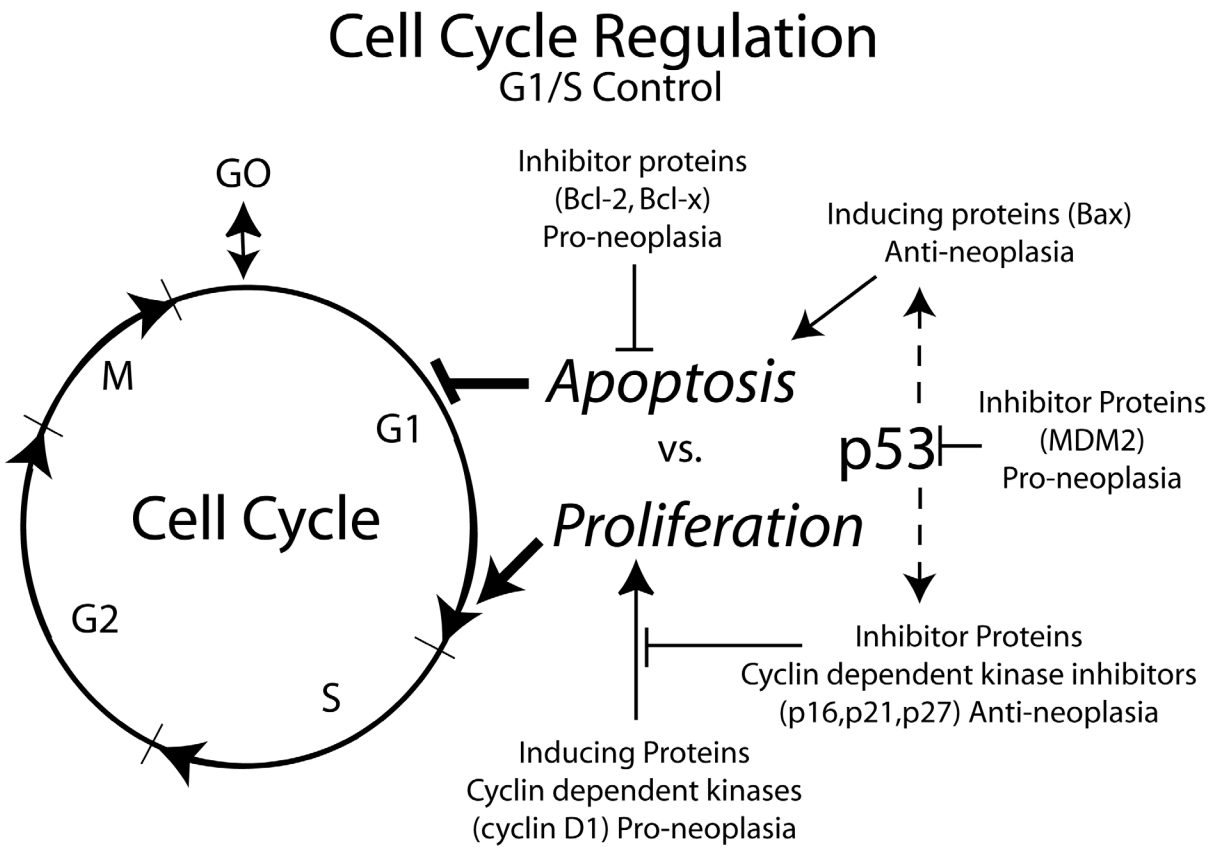

Figure 2: The cell cycle – a process of proliferation vs. apoptosis (programmed cell death). With permission Elsevier Science.

DNA replication, allowing extra time for repair mechanisms to act. If the repair fails, p53 may then trigger cell suicide (apoptosis).[4] In simplistic terms, normal p53 serves as a negative regulator at the G1-S checkpoint, but a mutation of p53 allows cells to proceed into the S phase of the cell cycle before DNA can be repaired, thus encouraging tumorigenesis.

In 1969, Li and Fraumeni reviewed medical records and death certificates of 648 childhood rhabdomyosarcoma patients and identified four families in which siblings or cousins had a childhood sarcoma.[5] These four families also had striking histories of breast cancer and other neoplasms, suggesting a new familial cancer syndrome of diverse tumors. Since the original description of the Li-Fraumeni syndrome, systematic studies and anecdotal reports have confirmed its existence in various geographic and ethnic groups. The spectrum of cancers in this syndrome has been determined to include breast carcinomas, soft tissue sarcomas, brain tumors, osteosarcoma, leukemia and adrenocortical carcinoma.[6] Possible component tumors of this syndrome include melanoma; gonadal germ cell tumors; and carcinomas of the lung, pancreas, and prostate. These diverse tumor types in family members characteristically develop at unusually early ages, and multiple primary

tumors are frequent. The molecular etiology of this syndrome is related to a germ-line mutation of one p53 allele. Patients have a 25-fold greater chance of developing a cancer by age 50 compared with the general population[7] because only one additional "hit" is needed to inactivate the second, normal allele.

Once believed to be unique, the understanding of neoplasia increased in 1997 with the discovery of another tumor suppressor gene called p73.[8,9] Located on chromosome 1p36, this gene encodes a protein that bears many similarities to p53 protein. Its DNA-binding domain resembles the corresponding region of p53, and it can also cause cell cycle arrest or apoptosis under appropriate conditions.[8,9]

of p53 and subsequent expression of MDM2. High levels of MDM2 may inactivate the tumor suppressor activity of p53 by forming a complex with it. Therefore, deregulation of MDM2 may be closely associated with tumorigenesis.

Proliferating cell nuclear antigen (PCNA) is a cell-cycle related antigen that has been used to evaluate the ability of many types of tumors to proliferate and recur. The detection of Ki-67 antigen using the monoclonal Ki-67 antibody is also a means of assessing tumor cell proliferation,[13] because the antigen is expressed in all proliferating cells during the G1, S, G2, and M phases of the cell cycle, but is absent in the G0 phase.[14] Low levels of PCNA and Ki-67 in

The surgical techniques for locally aggressive benign processes of the oral and maxillofacial region are dictated by the biologic behavior of the lesion.

The expression of Bcl-2 and Bcl-x (Fig. 2) can also encourage tumorigenesis by inhibiting apoptosis, and MDM2 may directly inhibit p53. The Bcl-2 proto-oncogene was initially discovered at the break point of the t(14;18) chromosomal translocation in patients with follicular lymphomas.[10] The Bcl-2 gene protects tumor cells by blocking post-mitotic differentiation from apoptosis. The Bcl-x gene, a Bcl-2 homologue, encodes two proteins: a long form, Bcl-x_L, that has anti-apoptotic activity and a short form, Bcl-x_S,[11] that promotes apoptosis by inhibiting Bcl-2. Bax gene, an additional Bcl-2 homologue, encodes a protein that induces apoptosis by interacting with Bcl-2 or Bcl-x_L proteins.

The MDM2 oncogene encodes a nuclear phosphoprotein that interacts with both mutant and normal p53.[12] Both proteins regulate each other, forming an autoregulatory feedback loop that in turn regulates the transcriptional function

nuclei of some locally aggressive benign tumors of the oral and maxillofacial region supports the notion of their slow growth. The concept of slow yet aggressive growth is a perceived paradox by clinicians.

The surgical techniques for locally aggressive benign processes of the oral and maxillofacial region are dictated by the biologic behavior of the lesion. A true neoplasm must be removed with attention to linear margins and anatomic barrier margins, and these differ with the histopathologic diagnosis of the neoplasm. Because tumors extend beyond their clinical and radiographic margins, the surgical specimen should include quantifiably uninvolved soft and hard tissues around the tumor specimen, i.e., the linear margins. Anatomic barriers are soft and hard tissues that surround a tumor and delay its infiltration of uninvolved tissues. The best-known example is the capsule surrounding

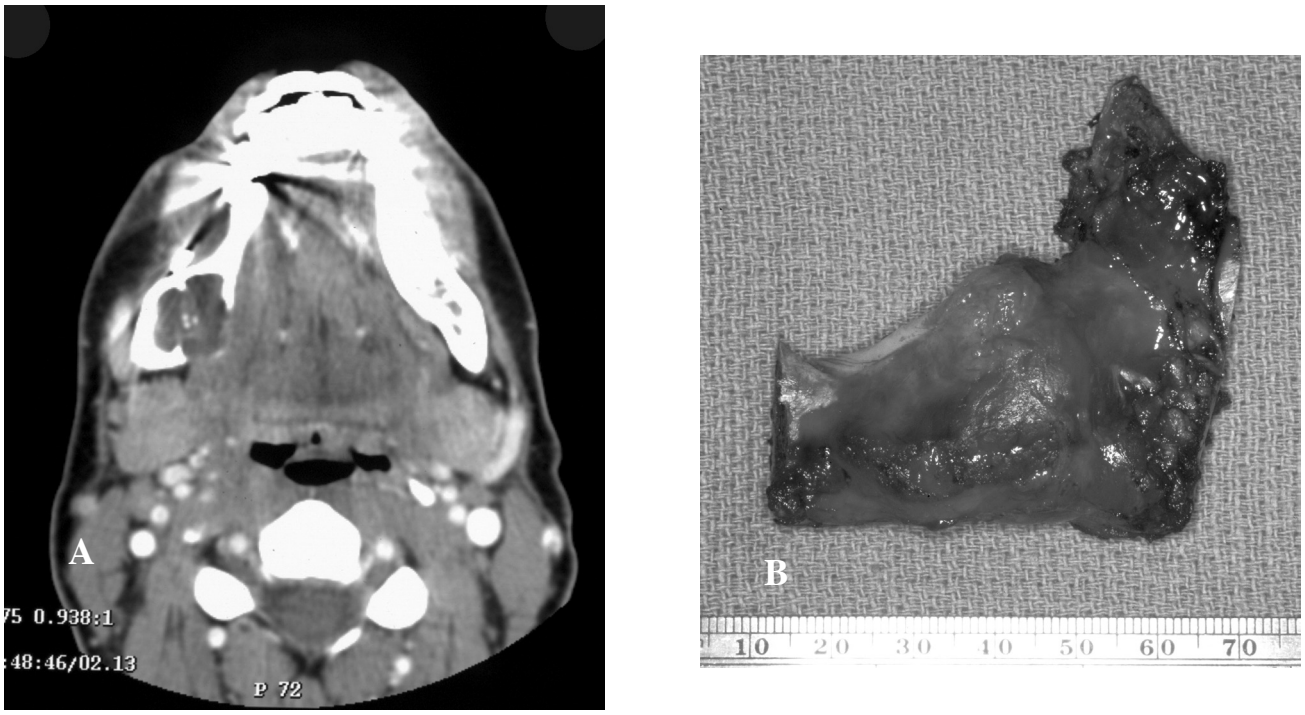

Figure 3: An ameloblastoma of the right mandible. **A.** The CT scans show perforation of the lingual cortex of the mandible. **B.** The anatomic barrier of periosteum is included on the medial aspect of the tumor specimen.

some, but not all, benign tumors. Other anatomic barriers include cortical bone, periosteum, muscle, mucosa, dermis and skin. The removal of one uninvolved anatomic barrier margin with the tumor specimen seems to ensure complete removal (Fig. 3). Hamartomas and choristomas do not require attention to linear margins and a pericapsular dissection suffices.

Unencapsulated benign neoplasms include the ameloblastoma and the pleomorphic adenoma. An ameloblastoma that appears to be confined to the medullary component of the mandible, for example, could be resected subperiosteally. However, the surgeon may wish to proceed with a supraperiosteal dissection, even when CT scans show intact cortical bone throughout, because the cortex may be perforated between CT slices. Sacrificing periosteum under such circumstances may prevent inadvertent spilling of tumor cells.

Locally aggressive benign tumors of the oral and maxillofacial region often grow so slowly that violation of the skin does not occur. Epidermal cells regenerate every eight days while a benign tumor's doubling time takes several months or years. Therefore, the skin is able to keep up with the developing tumor.

ODONTOGENIC TUMORS

Odontogenic tumors are a complex and diverse group of pathologic processes of great importance to oral and maxillofacial surgeons. While a majority of these processes are centrally located neoplasms, some are believed to more accurately represent hamartomatous prolifera-

tions, and some may occur peripherally in soft tissue. True odontogenic neoplasms demonstrate varying inductive interactions between odontogenic epithelium and odontogenic ectomesenchyme.*

Examples of aggressive odontogenic neoplasms include the ameloblastoma, odontogenic myxoma and the Pindborg tumor. Successful treatment of these true neoplasms requires attention to detail regarding their bony linear margins and the surrounding anatomic barriers when performing extirpative tumor surgery. Such attention is typical for benign tumor surgery of the jaws. These neoplasms also typify the paradoxical behavior of aggressive but slow local growth.

Ameloblastoma

The ameloblastoma is a benign tumor of the jaws and surrounding soft tissues that exemplifies the description, locally aggressive. (See *Selected Readings in Oral and Maxillofacial Surgery,* Vol. 2, #2) These neoplasms are capable of significant destruction and deformation of facial structures, and occasionally death.[15] Infiltration of surrounding soft and hard tissues of the face can be greater than that by some malignant neoplasms. Studies from North American authors find the ameloblastoma to comprise approximately 10% of all odontogenic tumors.[16,17] Although the solid or multicystic ameloblastoma is considered the most aggressive variant, the unicystic ameloblastoma is, at times, capable of significant destruction of the jaws, and should not be clinically underestimated. The peripheral ameloblastoma is, by contrast, innocuous and relatively indolent. The subclassification of ameloblastoma is not only pathologically specific, but clinically important, as well. A review of 3,677 cases of ameloblastoma found 2% to be peripheral, 6% to be unicystic and the remaining 92% to be solid or multicystic.[18]

Solid or multicystic ameloblastoma

The solid or multicystic ameloblastoma is the most common variant of ameloblastoma[18] and the most widely discussed.[19] In addition, its treatment is perhaps the most controversial. This tumor was identified well over a century ago,[3,19] with either Cassock or Broca being credited with its first scientific description in 1827 or 1868, respectively.[20]

Clinical and radiographic features

The solid or multicystic ameloblastoma is a tumor of adults, occurring predominantly in the fourth and fifth decades, with an average age of occurrence in the early 30's.[20] While this variant is rare in children, it can occur,[21,22] although the unicystic ameloblastoma is more common in children. The solid or multicystic ameloblastoma can occur anywhere in the maxilla or mandible, but has a predilection for the posterior mandible. In a study of 98 ameloblastomas by Mehlisch et al, 91 (93%) were located in the body or ramus of the mandible while 7% occurred at the symphysis.[23] Among 97 patiemts with mandibular ameloblastomas, Ueno et al. found 94 tumors in the molar region but only 28 tumors in the symphysis region.[24] Some patients had tumors in

*This ectomesenchyme was formerly referred to as mesenchyme because it was thought to be derived from the mesodermal layer of the embryo. It is now known and accepted that this tissue differentiates from the ectodermal layer in the cephalic portion of the embryo; hence, the designation ectomesenchyme.

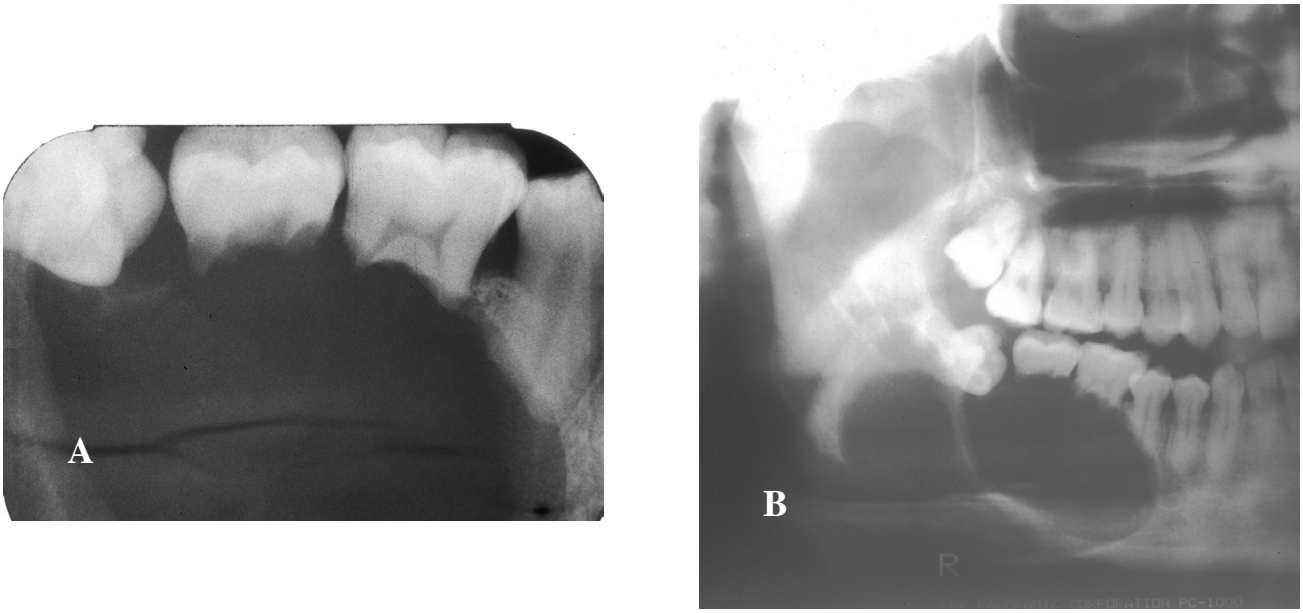

Figure 4: An ameloblastoma present in a 27-year-old male who presented with facial swelling and mobility of right mandibular teeth. **A.** Periapical radiograph obtained with the presumptive diagnosis of infection. Advanced root resorption was noted due to the presence of an aggressive neoplasm. **B.** Panoramic radiograph shows a multilocular radiolucency.

more than one mandibular site, but only 7 ameloblastomas occurred in the maxilla. The maxilla is an infrequent site for the solid or multicystic ameloblastoma,[25,26,27] where approximately 90% occur in the posterior maxilla.[20]

The solid or multicystic ameloblastoma is most commonly an asymptomatic painless mass, but pain, tooth mobility, and trismus can occur.[24] Routine panoramic radiographs may lead to serendipitous diagnosis. The solid or multicystic ameloblastoma most commonly appears as a multilocular radiolucency. (Fig. 4) Because they grow slowly, the radiographic margins are usually well defined and sclerotic.

Pathogenetic mechanisms of the solid or multicystic ameloblastoma include the expression of Bcl-2[11,28] and MDM2.[12] Of 12 unicystic ameloblastomas and 13 solid or multicystic tumors reviewed by Mitsuyasu et al,[28] all expressed Bcl-2, mainly in the outer layer of tumor cells. The stellate reticulum and squamoid cells were negative. In addition to inhibiting apoptosis, the Bcl-2 protein may play a role in maintaining stem cells in the peripheral layers of the tumor, from which proliferating cells are recruited. Kumamoto et al.[11] found Bcl-2 expression in the peripheral cells neighboring the basement membranes of various types of ameloblastomas. The Bcl-x protein was distributed more extensively than the Bcl-2 protein but in a similar fashion. Bax protein was quite low in ameloblastomas.

Carvalhais et al.[12] examined the expression of MDM2 in 13 ameloblastomas and a variety of other odontogenic lesions. The ameloblastomas showed higher MDM2 expression than did radicular cysts, but lower expression than

the two groups of odontogenic keratocysts. This not withstanding, MDM2 gene expression by ameloblastomas supports their pathogenesis.

Treatment and Prognosis

Treatment of the solid or multicystic ameloblastoma has been a source of controversy in the oral and maxillofacial surgery literature for decades. While most agree that this neoplasm is aggressive and deserves aggressive surgical management, several authors advocate conservative treatment initially and reserve radical surgery for recurrences.[29-31] Conservative surgical management of this variant of the ameloblastoma has historically included enucleation and curettage, while aggressive or radical surgery has involved resection.

Those who recommended curettage believe that ameloblastomas invade cancellous bone but not cortical bone.[32] Although cortical bone represents a competent anatomic barrier that might not be violated by a very small ameloblastoma, larger tumors show obvious clinical, radiographic and histologic evidence of cortical bone invasion.[2] Because the leading edge of the tumor is beyond the radiographic or clinical margin, a surgical linear margin, including both tissues, is required.

Curettage of this neoplasm also violates one of the first premises of tumor surgery: don't spill tumor. By definition, enucleation and curettage enters the tumor and will predispose the patient to persistent disease, often incorrectly referred to as "recurrent disease." In fact, when an ameloblastoma reappears following conservative surgery, it is because it was not properly treated from the outset. Such tumors should be referred to as persistent rather than recurrent. Conversely, resection of the ameloblastoma with negative soft and hard tissue margins should result in a cure of the patient.

When an ameloblastoma reappears following conservative surgery, it is because it was not properly treated from the outset.

Among 126 ameloblastoma patients treated in a variety of ways, Mehlisch et al. reported a "recurrence" rate of 90% for patients treated with curettage, and infrequent "recurrence" for those treated with resection. Sehdev et al. reviewed 92 ameloblastoma patients and found "local recurrence" in 90% of mandibular ameloblastomas, and 100% of maxillary ameloblastomas after curettage.[27] Equally worrisome was the finding that subsequent resection was able to control only 80% of mandibular tumors, and resection of "recurrent" maxillary ameloblastomas was ineffective in controlling the tumor.

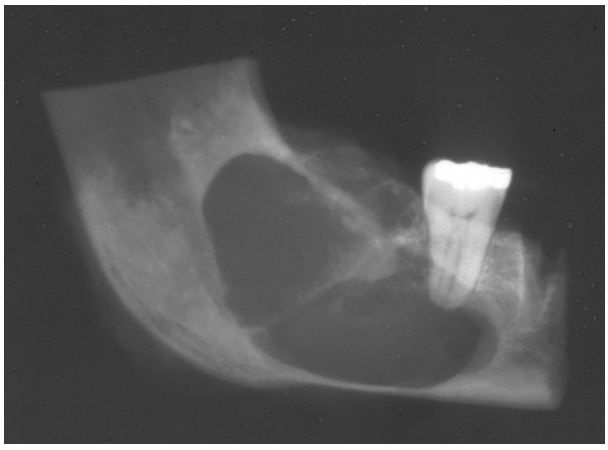

Figure 5: A specimen radiograph of an ameloblastoma resection showing 1-cm linear bony margins in the proximal and distal aspects of the resection.

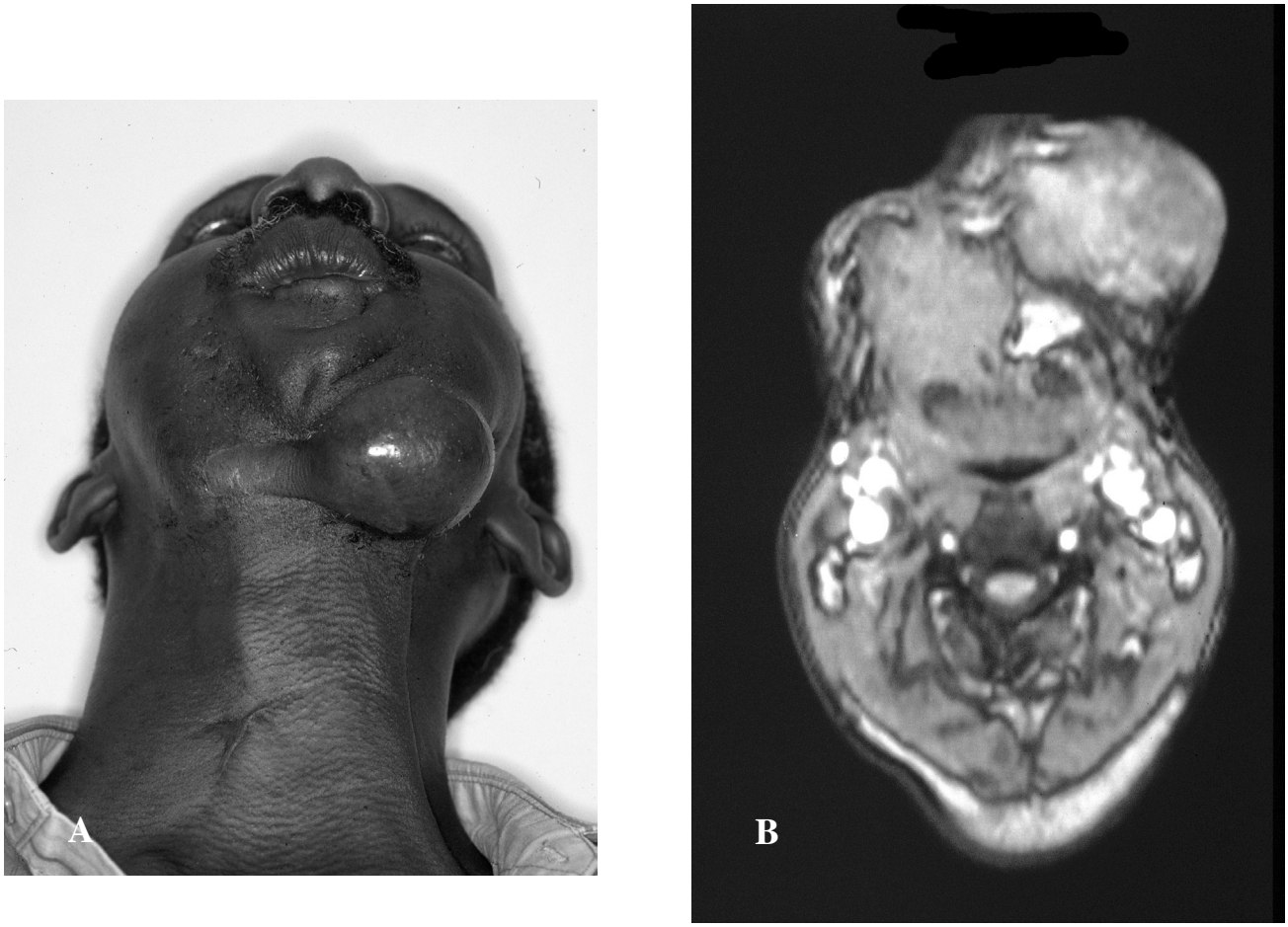

Figure 6: **A.** The clinical appearance, and **B.** MRI of a patient who underwent several enucleation and curettage surgeries for ameloblastoma of the mandible. At this time, he displays soft tissue persistence of his tumor in the facial skin. In addition, substantial floor of mouth and pharyngeal extension of the tumor was noted. The patient subsequently underwent wide excision of this persistent tumor, with the administration of postoperative radiation therapy.

In the final analysis, terms such as radical or conservative should probably not be used to describe the treatment of ameloblastoma. A scientific understanding of this tumor is that it is a slow-growing, aggressive benign neoplasm that is best controlled and cured with a resection using approximately 1.0 cm bony linear margins. The surgeon may wish to verify the bony linear margin with an intraoperative specimen radiograph (Fig. 5). Following resection, patients can be subsequently reconstructed and fully rehabilitated dentally. Attempts to control this tumor with more conservative measures compromise these objectives.

Salvage with radiation therapy has been described for the management of ameloblastoma.[33,34] Once thought to be radioresistant, the ameloblastoma has proved to respond to radiation therapy in limited series. Such therapy is valuable in those cases where a full surgical excision would be technically difficult because of tumor bulk and local invasion or where other medical factors, including age, would make radi-

cal surgery inappropriate.

In the review by Atkinson et al,[33] two of ten patients underwent incomplete excision in an attempt at surgical control of the tumors. Postoperative radiation therapy was offered, and the patients showed no evidence of disease at 30 and 60 months postoperatively. Of the remaining eight patients, six showed no evidence of disease one to ten years after radiation therapy without surgical intervention. In the remaining two patients, a residual mass was noted long after the conclusion of radiation therapy.

We believe that radiation therapy should not be required when surgery is executed properly. Radiation therapy may be of value, however, in postoperative management of relatively non-resectable tumors that were sub-therapeutically managed with enucleation and curettage surgeries (Fig. 6).

Unicystic ameloblastoma

In 1977, Robinson and Martinez reviewed 20 patients presenting with unilocular cystic lesions whose clinical, radiographic and growth features were those of dentigerous or primordial cysts.[35] The epithelial islands and portions of the lining epithelium seen in all 20 cases were indistinguishable from ameloblastic epithelium, based on characteristics described by Vickers and Gorlin.[36] However, Gardner and Corio[37] indicated that the basal cells are not remarkable and do not fulfill the criteria of Vickers and Gorlin for ameloblastoma.

Clinical and radiographic features

A review of the literature would suggest that the term "unicystic" developed from the observation that these lesions were most commonly radiographically unilocular. Regezi et al.[38] have recommended the term *cystic ameloblastoma* due to the identification of an occasional multilocular lesion. In any event, three well-accepted histologic subtypes of this variant of ameloblastoma have been noted: the luminal, intraluminal and mural subtypes. While the unicystic ameloblastoma can generally be treated conservatively with a high rate of cure, the mural subtype is inherently more aggressive[39] and should be treated similarly to the solid or multicystic ameloblastoma.[40]

The average age of occurrence for the unicystic ameloblastoma is the mid-twenties.[35,38,39,41] In general, this is younger than the average age for solid or multicystic ameloblastomas. This variant of the ameloblastoma has a definite predilection for the mandible, with the molar and ramus regions being most commonly affected (Fig. 7). This tumor is frequently associated with an impacted tooth.

Eversole et al. found six radiographic patterns in their review of 31 cases of unicystic ameloblastoma.[42] In all six patterns, the lesions were radiolucent and well defined. Three radio-

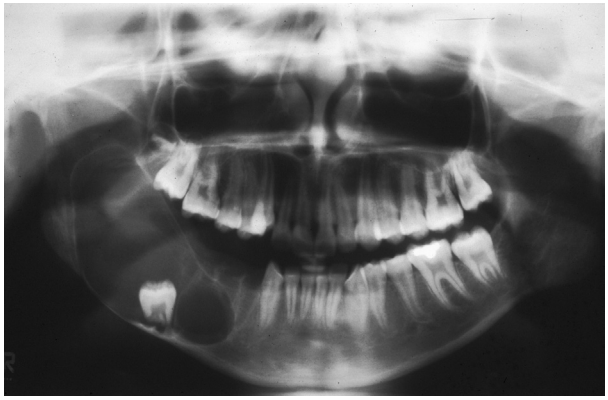

Figure 7: A large unicystic ameloblastoma of the right mandible presenting as a unilocular radiolucency of the mandible associated with an impacted tooth.

graphic patterns were observed in cases where the lesion was associated with impacted third molars, and three radiographic patterns were seen in cases not associated with an impacted tooth. Four of the six patterns were distinctly unilocular. Any large unilocular or multilocular radiolucency in a child, teenager, or young adult should cause the surgeon to suspect a unicystic ameloblastoma.

Treatment and prognosis

The unicystic ameloblastoma has a much lower rate of "recurrence" following curettage than do the solid or multicystic ameloblastoma. Robinson and Martinez[35] showed a 25% "recurrence" rate following curettage, and Gardner and Corio[38] reported a "recurrence" rate of 10.7% following curettage. In general, the luminal and intraluminal variants of the unicystic ameloblastoma are readily cured with enucleation and curettage (Fig. 8).

The mural variant of the unicystic ameloblastoma, due to its anatomic location, is less likely to be cured with this type of surgery. However, most of the papers discussing the unicystic ameloblastoma do not separate the mural subtype from the more easily treated luminal and intraluminal variants. Furthermore, the biologic behavior of the mural variant parallels that of the solid or multicystic ameloblastoma. We believe that the inclusion of the mural variant negatively impacts the overall cure rates of the unicystic ameloblastoma. While enucleation and curettage are effective treatments for the luminal and intraluminal variants, the mural subtype should be treated with resection.[31,40] (Fig. 9). However, the true diagnosis may be made following enucleation and curettage, and the surgeon may wish to adopt close follow-up rather than committing the patient to a return

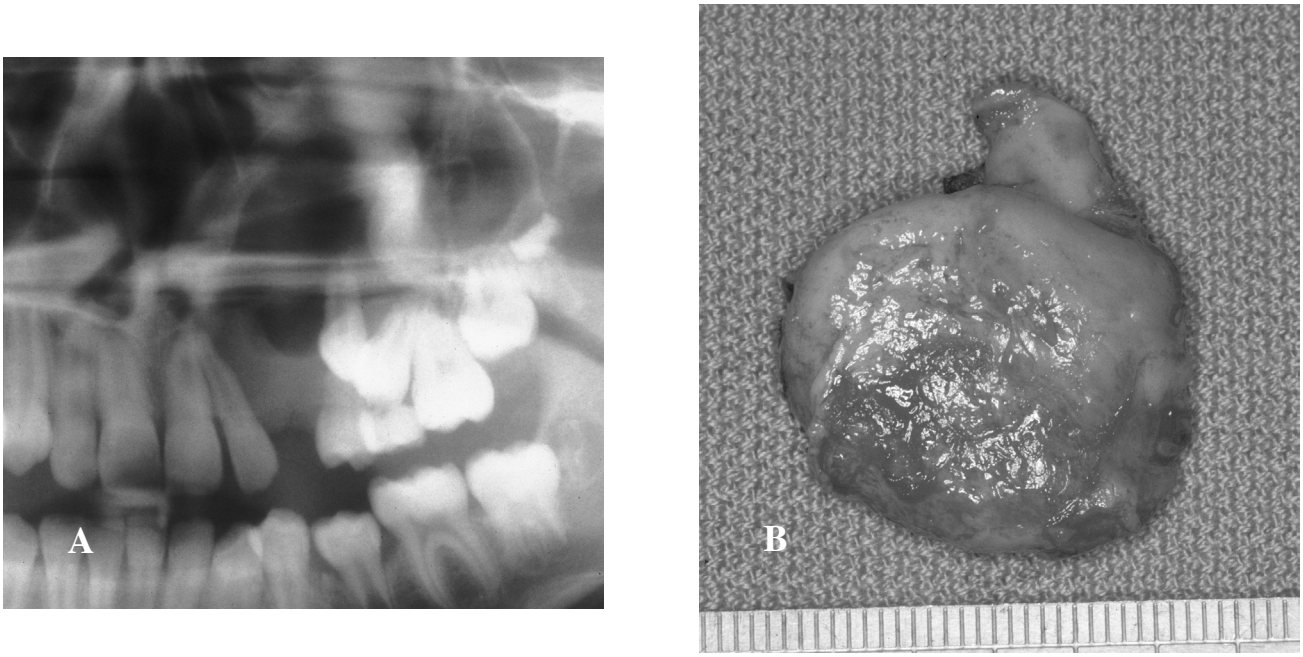

Figure 8: A unicystic ameloblastoma, intraluminal type, of the maxilla. **A.** Panoramic radiograph shows a unilocular radiolucency of the left maxilla. **B.** Curative treatment involves an enucleation and curettage of the tumor.

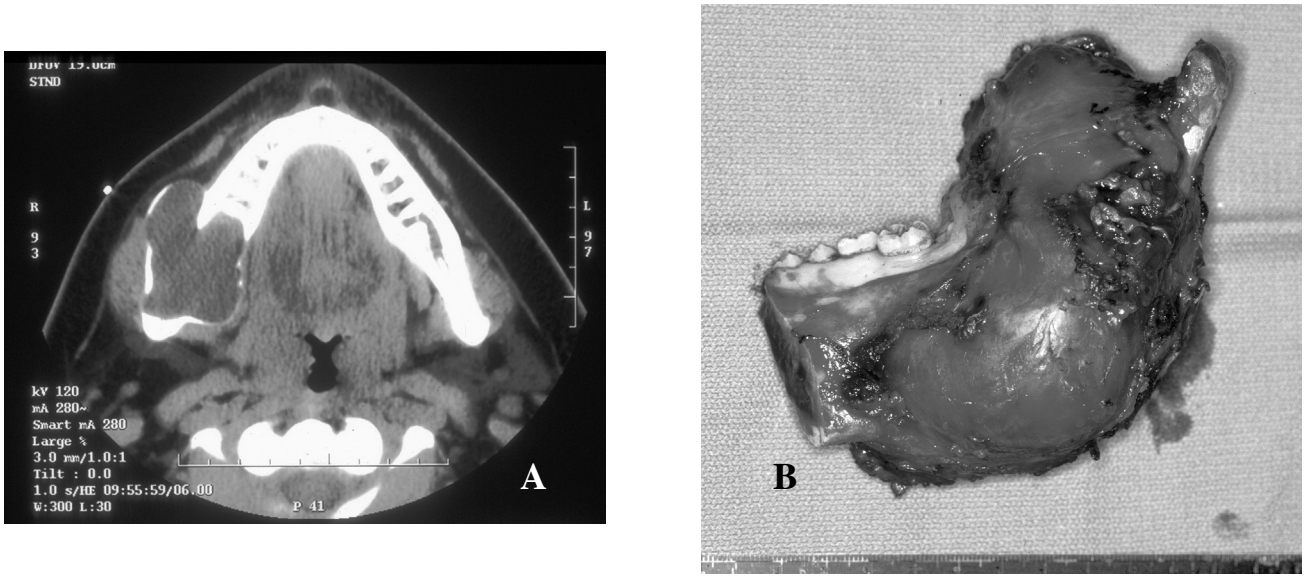

Figure 9: A unicystic ameloblastoma, mural subtype, of the mandible. **A.** CT scans show a destructive, expansile process of the right mandible. **B.** A disarticulation resection was required for curative therapy.

to the operating room for resection. If a mural subtype of the unicystic ameloblastoma is diagnosed on an incisional biopsy, we recommend primary aggressive management with resection.

Odontogenic myxoma

The odontogenic myxoma is an uncommon benign neoplasm that is thought to be derived from ectomesenchyme and histologically resembles the dental papilla of the developing tooth. These tumors represent between 3% and 5% of all odontogenic tumors.[16,17]

Clinical and radiographic features

Odontogenic myxomas usually occur in the second and third decades but have been reported from 5 to 72 years of age,[43] and one very unusual case was reported in a 17-month-old child.[44] The odontogenic myxoma may occur in any area of the jaws with some studies identifying more tumors in the maxilla, and some reporting more tumors in the mandible.[40,43] In radiographs, large, multilocular tumors are commonly seen, with characteristic very fine or wispy bone trabeculae, often at right angles to one another, within the radiolucent defects (Fig. 10). This feature is not pathognomonic for the odontogenic myxoma, but is highly suggestive.

Treatment and prognosis

Odontogenic myxomas have the same degree of aggressiveness; ability to infiltrate normal, surrounding tissues; and ability to persist if treated conservatively as the ameloblastoma. For these characteristics, there are no differences between the odontogenic myxoma and the solid or multicystic ameloblastoma. Therefore, we recommend resection, including a 1-cm linear bone margin, confirmed by intraoperative specimen radiographs (Fig. 10).

Treatment should be based on the known biologic behavior of a tumor, a genetically determined attribute. Conservative curettage has been recommended for the treatment of the

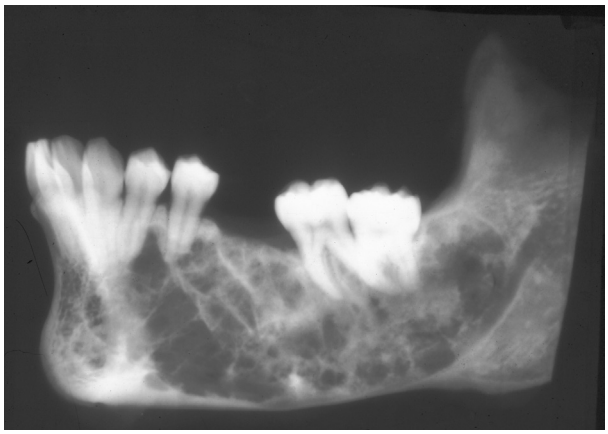

Figure 10: A specimen radiograph of a segmental resection of the mandible for odontogenic myxoma. Note the characteristic radiographic pattern of bone trabeculae at right angles to one another.

odontogenic myxoma when the tumor is small, with resection reserved for larger tumors. Treating a small odontogenic myxoma with a conservative surgery while treating a larger tumor with resection is a misconception of tumor surgery that fails to appreciate the biologic behavior of such a tumor. A small tumor has the same potential biologic behavior as a large tumor of the same diagnosis. The difference is only time. Resection of a small tumor is prudent because it provides curative therapy for the patient, while committing that patient to a smaller reconstruction, either immediately or later.

A small tumor has the same potential biologic behavior as a large tumor of the same diagnosis.

The pathogenetic mechanisms of the odontogenic myxoma are less well known than those of the ameloblastoma. One scientific paper assessed the overexpression of apoptotic proteins and matrix metalloproteinases in 26 odontogenic myxomas.[45] When tested for anti-apoptotic proteins, an average of 6.5% of specimen cells were positive for Bcl-2 and 10.4% for Bcl-x, while control tissue showed only 1.1% of cells positive for Bcl-2 and 1.2% for Bcl-x. The proapoptotic proteins Bak and Bax were not detected in tumor or control cells. Ninety percent of tumor cells stained positively for MMP-2 compared with 10% of controls. Both specimen and control tissues were negative for MMP-3 and MMP-9.

Pindborg Tumor

The calcifying epithelial odontogenic tumor, or Pindborg tumor (after the oral pathologist who first described the neoplasm) shares numerous features with the ameloblastoma and odontogenic myxoma. The tumor is distinctly locally aggressive, and accounts for about 1% of all odontogenic tumors.[16,17] Microscopically, the presence of amyloid is one feature that distinguishes the Pindborg tumor from either the ameloblastoma or odontogenic myxoma.

Clinical and radiographic features

The Pindborg tumor is seen in patients ranging in age from the second to the tenth decade, with a mean age of about 40 years.[3] There appears to be no gender predilection, and the mandible is affected about twice as often as the maxilla. Like the ameloblastoma, the molar and ramus regions are the most common sites of occurrence of this tumor. Painless expansion of the jaws, often noted serendipitously, is the most common symptom. Radiographically, the tumors are often associated with impacted teeth and may be unilocular or multilocular. A mixed radio-opaque/radiolucent pattern is most typical (Fig. 11).

Treatment and prognosis

Treatment recommendations for the Pindborg tumor have ranged from simple enucle-

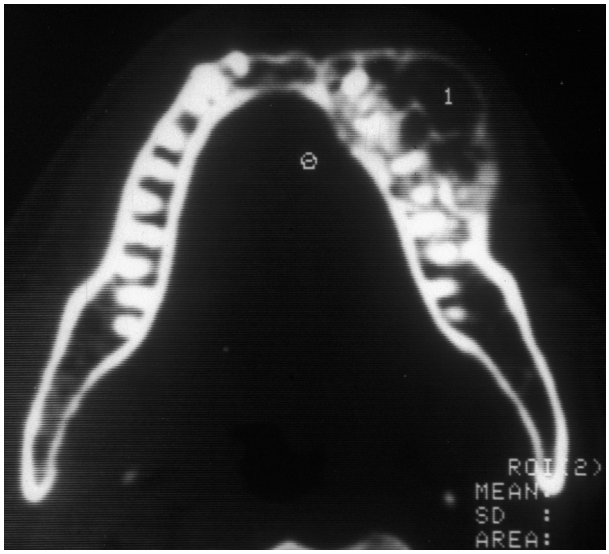

Figure 11: The typical mixed radiolucent-radiopaque pattern of the Pindborg Tumor. The destructive and expansile nature of these tumors can be seen on this radiograph.

ation and curettage to resection. In 1976, Franklin and Pindborg reported on 113 cases of this tumor.[46] Follow-up information was available for 79 cases. Sixteen recurrences were noted, most commonly in those patients who were treated conservatively with curettage only, enucleation only, or incomplete removal. More aggressive removal with resection resulted in infrequent recurrence.

LANGERHANS CELL HISTIOCYTOSIS

Langerhans cell histiocytosis (LCH) is a rare disorder in which lesions contain cells with features similar to the Langerhans cells of the epidermis. Formerly referred to as histiocytosis X, LCH comprises three morphologically similar lesions: eosinophilic granuloma, Hand Schüller Christian Disease, and Letterer-Siwe Disease. The term *histiocyte* refers to two groups of immune cells: (1) macrophages, the primary antigen-processing cells; and (2) dendritic cells, the primary antigen presenting cells, each of which contributes to an immunocytologic continuum.[47] Recent nosology of the histiocytic disorders places LCH in the category of dendritic cell-related diseases of varied biologic behavior, together with juvenile xanthogranuloma and the histiocytomas. Although there are rare malignancies featuring cells with the LC phenotype, malignant LCH is not recognized.[48] The extraordinarily rare malignant disorders are referred to as dendritic cell-related histiocytic sarcomas, Langerhans cell type.[47] Clinical and radiographic assessment of patients with Langerhans cell histiocytosis allows for classification of the disease as follows:

Eosinophilic granuloma – monostotic or polyostotic involvement without visceral involvement.

Hand-Schüller-Christian disease – involvement of bone, skin, and viscera

Letterer-Siwe disease – prominent cutaneous, visceral and bone marrow involvement occurring mainly in infants.

Letter-Siwe Disease is a highly lethal form of LCH that affects young children and has a rapidly declining course. Its cardinal clinical features include hepatosplenomegaly and anemia. Head and neck manifestations are less common than those noted in eosinophilic granuloma and Hand Schüller Christian disease, therefore Letterer-Siwe Disease will not be reviewed here. Furthermore, since eosinophilic granuloma represents the prototypical form of LCH in the jaws, only this variant will be discussed in this review.

The etiology of LCH is somewhat obscure. Some recent studies have demonstrated a clonal proliferation of Langerhans cells, supporting the concept of a neoplastic process.[49] It has also been suggested that the disease may

result from exuberant reactions to an unknown antigenic challenge. Evidence is emerging that some patients with LCH may exhibit defects in certain aspects of the cell-mediated arm of the immune system. A deficiency of suppressor T lymphocytes, as well as low levels of serum thymic factor, suggest the presence of a thymic abnormality in this disease.

Eosinophilic granuloma

Clinical and Radiographic Features

Eosinophilic granuloma of bone is a disease with an incidence of one new case per 350,000 to 2 million per year.[48] Most patients are younger than 20 years of age when the diagnosis is made. Common locations are the ribs, the spine and the skull. Tenderness, pain and swelling are common patient complaints. Loosening of teeth in the affected alveolar bone is commonly noted. Radiographically, the jaws may exhibit solitary or multiple radiolucent, destructive lesions (Fig. 12). The lesions generally affect alveolar bone, giving the appearance of teeth "floating in air." Jaw lesions may be accompanied by bone involvement elsewhere in the skeleton.

Although LCH may be encountered in patients over a wide age range, more than 50% of cases are seen in patients under age ten.[50] There seems to be a definite male predilection. Children younger than age 10 most often have skull and femoral lesions, while patients over age 20 more often have lesions in the ribs, shoulder girdle and mandible.

Treatment and prognosis

Lesions of the maxilla and mandible are usually treated with surgical curettage. Low doses of radiation may be employed for less accessible lesions, or incompletely removed lesions in bone. The potential for induction of malignant disease secondary to radiation therapy is a concern in younger patients, and it should be used with caution. Intralesional corticosteroid administration can be effective in some patients with localized bone lesions. Long-term follow-up is essential to rule out recurrent disease.

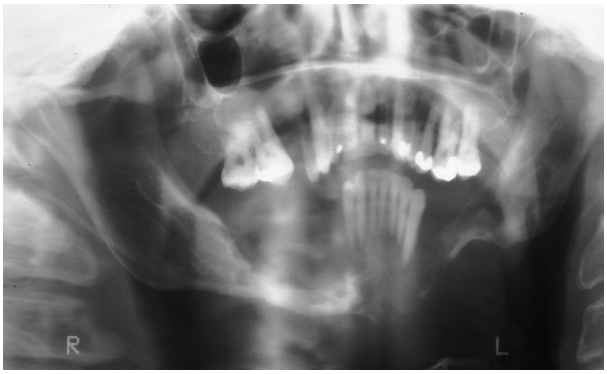

Figure 12: Panoramic radiograph of an eosinophilic granuloma of the mandible. Note the destructive process of the mandible, with "teeth floating in air."

FIBRO-OSSEOUS NEOPLASMS OF THE FACIAL BONES

The nomenclature of fibro-osseous lesions (FOL) of the facial bones can be confounding, and oral pathologists often rely upon radiological and clinical information in addition to histologic material to render a diagnosis. (See also *Selected Readings in Oral and Maxillofacial Surgery, Vol. 3, #1)* Charles Waldron has stated that "in the absence of good clinical and radiologic information, a pathologist can only state that a given biopsy is consistent with a fibro-osseous lesion."[51] In general terms, these lesions are composed of fibrous connective tissue of varying cellularity admixed with osteoid, mature bone or cementum-like structures. Dysplastic and hamartomatous processes such as fibrous

dysplasia and cemento-osseous dysplasia are part of an inclusive list of FOLs. The cemento-ossifying fibroma and its variants, including the more aggressive juvenile and psammomatoid types as well as the desmoplastic fibroma will be included in this discussion.

Ossifying Fibroma (Cementifying Fibroma, Cemento-ossifying Fibroma)

Clinical and radiographic features

Ossifying fibroma (OF) is the most common fibro-osseous neoplasm diagnosed in the jaws. It is essentially identical to lesions designated as cementifying fibroma and cemento-ossifying fibroma. It is a benign intraosseous lesion that is characterized radiographically and microscopically as being sharply demarcated from the surrounding uninvolved bone. In its non-aggressive form, it is generally treated conservatively with minimal likelihood of recurrence.[52] Histologically, the lesion can look identical to fibrous dysplasia and thus, its clinical and radiologic features are critical to the rendering of a correct diagnosis. A recent review by Voytek et al. demonstrated isolated jaw lesions that showed components of both fibrous dysplasia and cemento-ossifying fibroma within the same lesion.[53]

Ossifying fibroma (OF) is the most common fibro-osseous neoplasm diagnosed in the jaws.

The radiologic appearance of the OF depends upon its stage at diagnosis.[54] Early lesions may be primarily lucent and misdiagnosed as an odontogenic cyst or ameloblastoma. They are frequently unilocular and associated with a smooth and corticated border. With maturation, a mixed radiolucent/radio-opaque pattern is common. The borders in both cases are distinct and growth appears symmetrical and concentric. Tooth displacement and root resorption are commonly found, and a thin lucent rim often surrounds the mass. In the mandible, a characteristic downward bowing of the inferior border is often noted.

OFs occur most frequently in the mandible but other sites in the craniofacial skeleton can be involved.[55] A female predilection is reported with peak incidence during the third and fourth decades of life. Most lesions are slow growing and are rarely associated with pain or paresthesia. The clinical behavior of these lesions in and around the paranasal sinuses and orbits is often reported as being more expansile and aggressive.[56] In these sites, the lesion is also more likely to contain cementum-like (psammomatous) bodies within a fibrous stroma that may be highly cellular. Several investigators have recommended reservation of the term "cementum" only for the bone-like substance attached to tooth roots and consider these cementum-like bodies to derive from bone.[57,58] Jaw OFs are thought to arise from cellular elements within the periodontal ligament space, although similar lesions are found in extragnathic bones and, therefore, other cellular sources are probable.[59]

A variety of histologic patterns are found in OFs.[60] The microscopic appearance is largely dependent upon the stage at diagnosis. Most commonly, the lesion is composed of a cellular, relatively avascular stroma characterized by spindle-shaped cells with bland nuclei. Focal multinucleated giant cells are often found. The

calcified tissue consists of trabeculae of woven bone and occasionally lamellar bone. Deposits of basophilic calcifications resembling cementum may also be found. It is the presence of these bodies that has led to the synonymous use of cemento-ossifying fibroma and cementifying fibroma for these lesions.[61] However, identical cementum-like bodies have also been noted in extragnathic sites and therefore these bodies are unlikely to be cemental in nature.[62]

Hyperparathyroidism-jaw tumor syndrome is an autosomal dominant disorder characterized by multiple well-circumscribed ossifying fibromas. Renal anomalies and other tumors are found in these patients.[63] Another unusual manifestation of the cemento-ossifying fibroma is its occurrence in multiple quadrants within the jaws. These lesions may mimic polyostotic fibrous dysplasia both clinically and radiographically. Both familial and non-familial cases have been reported.[64]

Treatment and prognosis

Treatment of OFs is dependent upon their size, clinical behavior and associated symptoms.[65] Small and asymptomatic lesions can be followed. Because the lesion is frequently well demarcated from the surrounding bone, removal is expedited. Often, the lesion shells out intact or in large fragments from the surrounding bone. However, incomplete removal is associated with a variable rate of recurrence. Those lesions demonstrating aggressive features (e.g., a history of rapid growth, multiple episodes of recurrence, problematic anatomical location) may require a more radical approach for complete removal.

Juvenile Ossifying Fibroma (JOF)

Clinical and radiographic features

This relatively uncommon lesion may be distinguished from other FOLs of the jaws by the age of the patient at time of diagnosis, its clinical presentation and its potentially aggressive behavior.[66] The term was coined in 1952 by Johnson (cited in Johnson et al.,[67]) and further established as additional cases were reported and described. In 1991, a review of 112 cases collected at the Armed Forces Institute of Pathology over a 45-year period further codified the nomenclature, although a plethora of synonymous terms certainly adds to the diagnostic confusion the JOF has generated.[67]

JOF is most often diagnosed before the age of 15 and tends to show a male predilection.[68] Due to rapid proliferation, associated facial swelling is common (Fig. 13). Localization to the facial bones is reported in 85% of cases, the calvarium in 12% and non-craniofacial sites in 4%.[69] The facial bony lesions most commonly arise in areas contiguous with the paranasal sinuses (90%) but jaw lesions have been described in 10% of cases. Johnson et al. hypothesized that the JOF arises from an overproduction of the myxofibrous cellular stroma normally involved in the development of the nasal septum and the sinuses as they enlarge.[67] Similarly, overproduction in sutural lines in the skull may also account for the tumor's localization to those sites. The etiology of the jaw lesions is less clear, but some authors speculate that maldevelopment of tissue septa between the roots of teeth can contribute.[70]

Common presenting complaints, in addition to facial swelling, can include nasal obstruction, proptosis and rarely, intracranial extension. The tumor frequently erodes the bony septa of

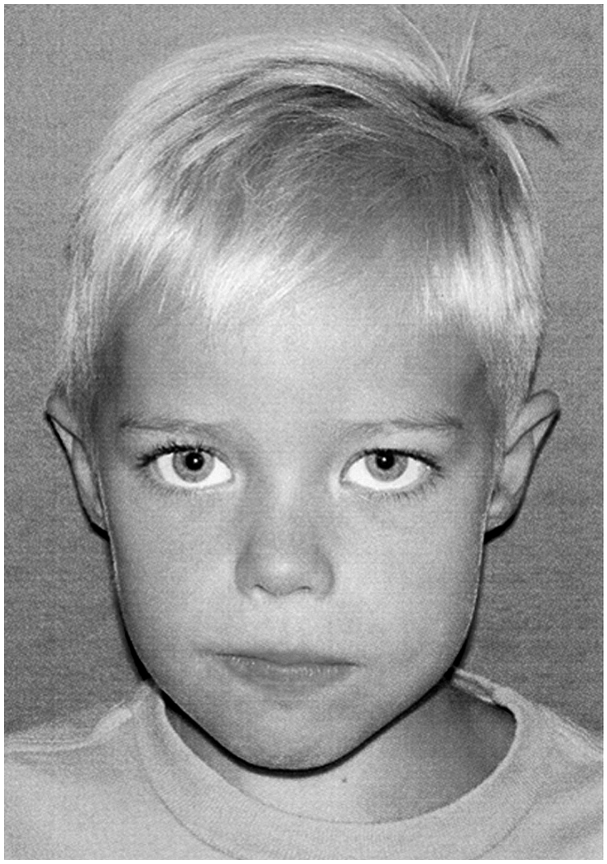

Figure 13: Facial photograph of a 6-year-old boy with a rapidly expanding juvenile ossifying fibroma of the left maxilla. Note the associated facial swelling and deformation of the nasolabial region. (from Kaban, Troulis eds. ***Pediatric Oral and Maxillofacial Surgery***, Saunders, Philadelphia, 2004, with permission)

the sinuses and leads to encroachment upon the orbit, nose and skull. Impaired sinus drainage with associated mucocele formation is common. Visual loss from optic nerve compression can occur. Because the dura is an effective barrier to brain invasion, other neurologic signs are uncommon.[71]

Radiographically, the features of JOF are relatively non-specific. The lesions may be uni- or multilocular and generally have irregular

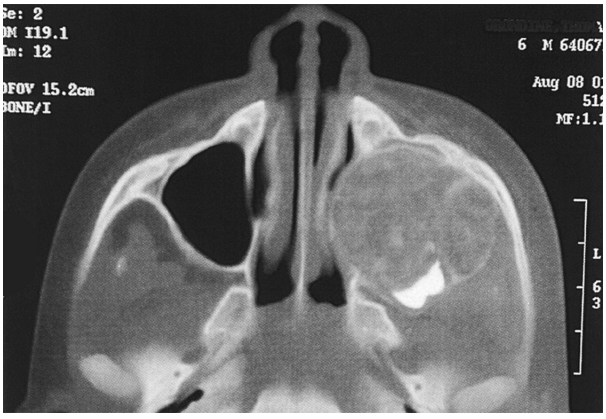

Figure 14: Axial CT image of a juvenile ossifying fibroma of the left maxilla demonstrating bony expansion, obliteration of the maxillary sinus and tooth migration. (from Kaban, Troulis eds. ***Pediatric Oral and Maxillofacial Surgery***, Saunders, Philadelphia, 2004, with permission)

borders. Cortical thinning and perforation are frequently identified. Maxillary tumors tend to obliterate the sinuses.[72] CT scans often show these lesions widening and filling the medullary space of bone (Fig. 14). The degree of associated ossification is variable.[73] MR images are hypointense on both T1 and T2 weighted sequences. If cystic spaces are present within the tumor, these will image as hyperintense on T2. Visualization of the tumor is enhanced with the use of gadolinium contrast.[74]

Two variants of JOF (trabecular and psammomatoid) are recognized although controversy still exists as to whether the latter should be considered a cemento-ossifying fibroma.[75] Both variants occur most frequently during the first and second decades of life. Approximately 75% of the psammomatoid variants develop in the orbits, paranasal sinus region and the skull.[76] They are less common in the jaws where the trabecular variant predominates.[77] Some authors prefer to restrict the designation juvenile ossi-

fying fibroma to those lesions characterized by the presence of osteoid strands (the trabecular variant) and consider the psammomatoid variant to be a cemento-ossifying fibroma.[78,79]

The growth pattern of JOF can be variable and the clinical signs depend upon the anatomic site of origin. Because of the clinical presentation and radiographic findings, these lesions must be distinguished from craniofacial malignancies such as osteosarcoma, fibrosarcoma and Ewings sarcoma.[80] In addition, aggressive benign jaw neoplasms (both odontogenic and non-odontogenic) should also be included in the differential diagnosis.

On gross examination, JOFs are whitish in coloration and often have a gritty consistency. Distinguishing features of JOF may include the following: morphologic heterogeneity compared to the generally uniform pattern describe for the cemento-ossifying fibroma, areas of dense cellularity within a myxomatous stroma, and uneven distribution of bone and calcified structures within the tumor. Within the gross tumor itself, cystic spaces with blood breakdown products are often found.

Histologically, these lesions may closely resemble the cemento-ossifying fibroma, and there is an overlap between the trabecular and psammoosteoid variants.[81] JOFs are characterized by a highly cellular stroma without notable mitotic activity. Embedded within the stroma are numerous mineralized structures (ossicles, chondricles and cementicles) (Fig. 15). Vascularity is only prominent at the periphery of the tumor. Reactive bone may also be found at the periphery, and the lesion often infiltrates the surrounding normal bone, making complete removal difficult.[82]

Treatment and prognosis

Conservative surgical excision is the treatment of choice. However, the recurrence rate for JOF treated with local excision or curettage can be between 30%-58%.[51] Thus, if conservative treatment is selected, careful longitudinal follow-up is imperative. In cases with cortical expansion, periosteal elevation or frank bony perforation such treatment is ill advised. Wide resection with complete surgical resection is associated with a lower rate of recurrence.[83] Despite the aggressive nature of JOF, malignant transformation over time has not been described.

Desmoplastic Fibroma
(Aggressive fibromatosis;
Central fibroma, desmoid type)

Clinical and radiographic features

Desmoplastic fibroma (DF) is an unusual benign tumor, of connective tissue origin, that

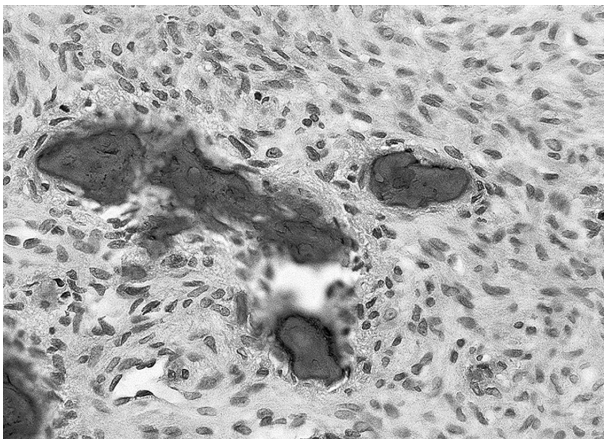

Figure 15: Histologic section (X 400) of a juvenile ossifying fibroma demonstrating a highly cellular stroma without mitotic activity and containing numerous mineralized structures (from Kaban, Troulis eds. ***Pediatric Oral and Maxillofacial Surgery***, Saunders, Philadelphia, 2004, with permission).

has most commonly been described in the metaphyseal region of the long bones.[84] Its name derives from the fact that histologically it closely resembles desmoid tumors of the abdominal soft tissue.[85] This entity within soft tissue has also been referred to as aggressive fibromatosis.[86] First recognized by Jaffe in 1958, isolated cases occur within the jaws and paraoral soft tissue. The ramus-angle region of the mandible appears to be the most common site of involvement.

Clinically, the tumor presents with bony expansion and extension into surrounding soft tissue. For those lesions predominantly involving soft tissue, surface resorption of the underlying bone is common. The majority of patients in both the intrabony and soft tissue cases are younger than 30 years of age. The etiology is unknown although there may be an association with previous trauma, endocrine abnormalities and genetic factors.

Histologically, the lesion is composed of thick bundles of collagenized fibrous tissue and aggregates of elongated, spindle-shaped cells with hyperchromatic nuclei. Little or no mitotic activity is noted (Fig. 16). However, the clinically aggressive nature of this tumor, coupled with the fact that it is non-encapsulated and poorly demarcated from the surrounding bone, make distinguishing it from a well-differentiated fibrosarcoma imperative.

A recent review of 63 jaw cases by Hopkins et al.[87] described the lesion's characteristics. Fifty-four cases originated in the mandible, nine in the maxilla. No sexual predilection was found. The mean age of patients was 14 years (range 1-46 years). The radiographic findings were nonspecific and included both uni- and multilocular lucencies with variability in marginal regularity and sclerosis. Its aggressive bony destruction, as stated above, can mimic malignancy (Fig. 17). The histology in these cases consistently demon-

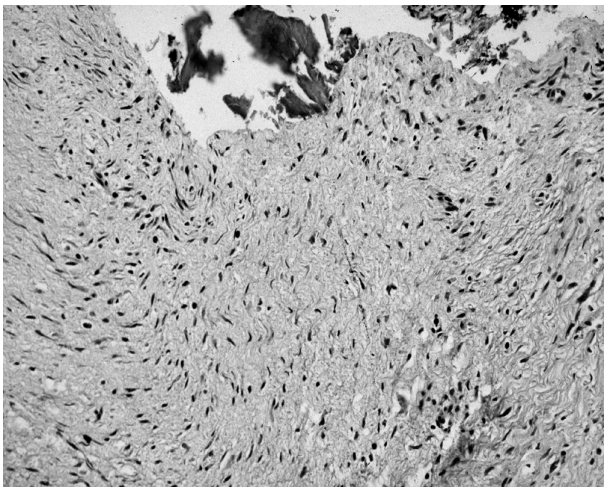

Figure 16: Histologic section of a desmoplastic fibroma (X 400) demonstrating bundles of collagenized fibrous tissue with associated spindle-shaped cells containing hyperchromatic nuclei without evidence of mitoses.

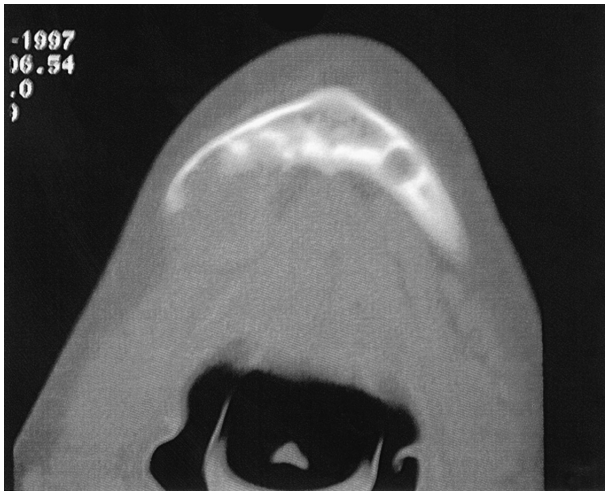

Figure 17: Axial CT image of a mandibular desmoplatic fibroma demonstrating extensive bony destruction and expansion into soft tissue (from Kaban, Troulis, eds. ***Pediatric Oral and Maxillofacial Surgery***, Saunders, Philadelphia, 2004, with permission).

strated mature fibrous tissue, absent mitoses and an abundant collagenous stroma. These lesions differ from FOLs by being non-encapsulated and lacking calcifications.

Treatment and prognosis

Although benign, this tumor is locally aggressive and conservative therapy with curettage is associated with a recurrence rate as high as 35%.[78] Therefore, wide surgical excision is the recommended treatment. Many authors describe the difficulty in obtaining adequate margins due to invasion of surrounding bone by the tumor.[79,88] If the tumor has eroded the bone and extends into the surrounding soft tissue, an even wider resection will be required. Radiation therapy and chemotherapy appear to have little role in primary treatment.

VASCULAR LESIONS OF THE HEAD AND NECK

A biologically based classification scheme outlined by Glowacki and Mulliken[89] has been invaluable in the diagnosis and understanding of vascular lesions. The first determination for any vascular lesion is whether it is a malformation or a hemangioma. The differences are based on cellular kinetics and are correlated with the natural history and biologic behavior of each. (See also, *Selected Readings in Oral and Maxillofacial Surgery, Vol. 5, #3*)

A hemangioma is a true neoplasm of endothelial cells and is characterized by hyperplasia and cellular proliferation. Hemangiomas usually appear early in infancy and undergo rapid growth during the first years of life. This growth subsequently slows and the lesions involute during the subsequent 5-6 years. In contrast, malformations are associated with a normal endothelial turnover. For vascular malformations the flow characteristics of the lesion (low or high) must be determined. Low-flow malformations are further subdivided into capillary, lymphatic or venous. High-flow malformations are generally composed of mixed arteriovenous components and often contain shunts. Malformations do not demonstrate cellular hyperplasia. They are present at birth and grow proportionately with the child.[90]

The hallmark of the hemangioma is its rapid growth during the neonatal period

Hemangiomas

Clinical and radiographic features

Hemangiomas are true neoplasms of endothelial cells and are diagnosed in infancy. The most common site of occurrence (>60%) is the head and neck region. They generally appear during the first month of life and are more than three times more common in females. Unlike vascular malformations, true intrabony hemangiomas have not been described. Mulliken notes that secondary skeletal changes are unusual with hemangiomas and only minor underlying bony deformations have been noted.[90]

The hallmark of the hemangioma is its rapid growth during the neonatal period (the so-called proliferative phase). Unlike vascular malformations, the growth rate is much faster than the child's normal growth. During the proliferative phase, mast cells appear to play a major role in angiogenesis.[91] They increase

up to 30-fold and then return to normal levels during involution. In addition to active growth, the coloration of the hemangioma may also deepen during the proliferative phase. Vascular malformations, on the other hand, tend to have a persistent coloration. The hemangioma has a firm and somewhat rubbery feel compared to the soft and compressible nature of the vascular malformation. Despite these differences, diagnostic uncertainties are common, especially between hemangiomas and lymphatic malformations.

Radiologic investigation can help distinguish hemangiomas from vascular malformations. CT with contrast during the proliferative phase of a hemangioma will demonstrate homogeneous enhancement of the tumor that generally appears as a well-circumscribed mass.[92] Vascular malformations, on the other hand, appear heterogeneous and may show intralesional calcifications and cystic channels. Angiographic evaluation of hemangiomas is rarely indicated.

Various complications are associated with hemangiomas, especially during the proliferative phase.[93] With rapid growth, the overlying skin may ulcerate and result in recurrent bleeding that is seldom brisk or life-threatening. Depending upon the location of the tumor, obstruction and impingement of contiguous anatomic structures can occur. For example, periorbital tumors may obstruct the visual axis and prevent retinal development in infants.[94] Obstruction of the nasal airway can also be a problem because infants are obligate nasal breathers.

Practitioners must also be aware of the possibility of bleeding abnormalities in children with hemangiomas. (See *Selected Readings in Oral and Maxillofacial Surgery, Vol. 8, #6*) The Kasabach-Merrit syndrome is the result of severe thrombocytopenia associated with a large and proliferating hemangioma or multiple hemangiomas (hemangiomatosis).[83] Such cases may result in acute hemorrhage as well as a rapid increase in the size of the tumor. Petechiae and ecchymoses are commonly seen. Consumptive coagulopathies have also been described in patients with hemangiomas and are more likely in the face of complicating clinical infections. High output cardiac failure can also occur.[95] The hemangioma, with its low-resistance channels, acts as a large arteriovenous shunt in such cases. Emergent embolic intervention or surgical treatment may be required if the congestive heart failure cannot be controlled medically.

Treatment and prognosis

Following the proliferative phase, the hemangioma generally stabilizes and begins to grow commensurately with the child. Spontaneous involution is the rule. One of the earliest signs that this is occurring is a fading of color, and the surface begins to look mottled and the lesion feels less tense. Commonly, the last coloration is gone by the fifth year of life. The overlying skin becomes atrophic and paler than the surrounding skin. Complete resolution of hemangiomas is reported in more than 50% of cases by age 5 and in more than 70% of cases by age 7. Thus, an expectant attitude toward treatment is most appropriate. Mulliken and Young report that the rate and the completeness of involution do not correlate with the initial size of the tumor and are difficult to predict.[90]

Appropriate treatment of hemangiomas has been actively debated over the centuries and continues to be an area of investigation and

controversy. Despite the well-documented history of spontaneous regression and resolution, these tumors can become large and deforming, causing anguish to parents and families. During the proliferative phase, frequent examinations and reassurances are required.

Systemic steroids, used in selective cases, and have been found to hasten the onset and rate of involution of hemangiomas.[96] When they have been used the tumor is causing unacceptable facial distortion, recurrently bleeding, ulcerating or becoming infected, or interfering with normal function. Similarly, in cases of severe thrombocytopenia and refractory congestive heart failure, steroid trials are often undertaken. Unfortunately, not all tumors are responsive to steroids, and decisions on dosing should be based on signs of responsiveness. Chemotherapy and radiation therapy have also been used in life-threatening situations. In cases of congestive heart failure, lack of response to medications may require embolic or surgical therapy.[97]

More recently, interferon-alfa has been used in the treatment of severe hemangiomas of infancy.[98] Such therapy is reserved for steroid-resistant lesions that, due to their size and anatomic location (periorbital, glottic), may be vision- or life- threatening. The treatment protocol most commonly involves subcutaneous administration of interferon-alfa in a dose of 3 million units/m^2/day for a variable duration of time (ranging from 2-14 months). Due to its anti-angiogenic properties, interferon impedes endothelial proliferation in these rapidly growing hemangiomas and accelerates regression. Generally good results are noted with arrested growth in most cases and accelerated regression in many. However, interferon use is not without side effects. The reported flu-like symptoms are generally self-limiting and do not require cessation of therapy. However, more serious neurologic side effects (including depression, somnolence, confusion, memory impairment and visual changes) may occur. The long-term effects in infants are, as yet, unknown. Therefore, this therapy is appropriately reserved for steroid-resistant tumors of alarming and threatening proportions.[99]

Lymphatic Malformations

Clinical and radiographic features

Lymphatic malformations (LMs) in the head and neck region are thought to arise from a defect in the embryologic development of primordial lymphatic channels. They usually present during the first year of life, and more than 90% are evident by age two. Because of their localization in the cervicofacial region, airway compromise becomes an early concern. They occur with equal frequency in both sexes.[100]

Various descriptive classification schemes exist for LMs.[101] Traditionally, they have been classified into three categories based on their microscopic appearance: (1) capillary (containing a network of small lymphatic channels), (2) cavernous (containing networks of dilated lymphatics that tend to infiltrate the soft tissue) and (3) cystic hygromas (large uni- or multiloculated channels lined by a single layer of endothelium and containing abundant proteinaceous fluid). Smith et al. proposed a slightly different classification scheme (microcystic, macrocystic or mixed) that was based upon the response of these lesions to sclerotherapy.[102] A third classification system by de Serres et al. is based on the location and extent of involvement of the LM in relation to the hyoid bone and whether the lesion is bi-

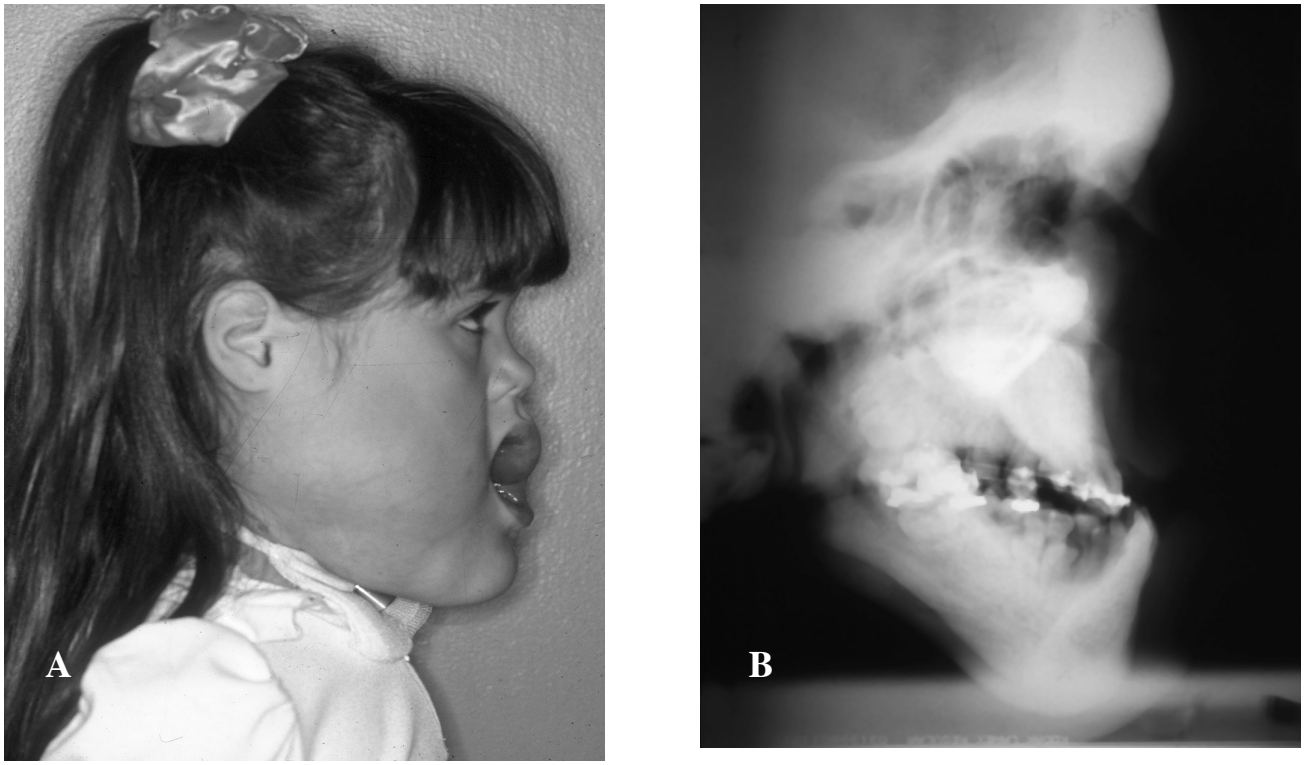

Figure 18 **A.** Lateral facial photograph, and **B.** Lateral cephalometric radiograph demonstrating a large cervicofacial lymphatic malformation with associated bony overgrowth.

lateral or unilateral.[103]

Histologically, these lesions are generally composed of cystic channels lined by a single layer of flattened endothelium. The surrounding walls can be of variable thickness and are fibromuscular.[104] Areas of hemorrhage and thrombi are found. The surrounding connective tissue often contains abundant lymphocytes as well as germinal centers.

LMs can be diverse in their clinical presentation, from tiny cutaneous blebs to large, cystic lesions that increase commensurately as the child grows. They can result in deformation of contiguous structures and secondary overgrowth of underlying bone.[105] LMs are generally soft to palpation and the overlying skin can be thin and atrophic.

Hemorrhage, fibrosis and secondary infection are frequently associated with LMs of the head and neck. A history of sudden enlargement is often reported in cases of concurrent infection such as URIs and also secondary to hemorrhage. Bacterial infection and associated cellulitis of the overlying skin are frequent complications.[106]

Underlying skeletal hypertrophy has been reported in 80% of cervicofacial lymphatic malformations (Fig. 18). In the jaws, this can lead to progressive development of malocclusions such as prognathism and open bite. Isolated lymphatic malformations of the tongue can also cause occlusal disharmony (Fig. 19).

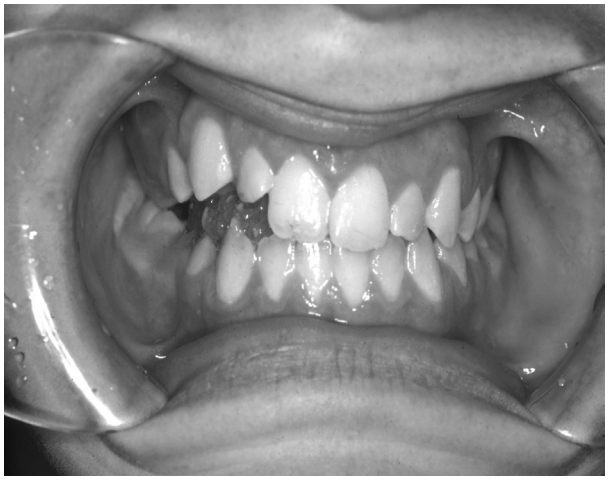

Figure 19: Intraoral photograph of an isolated lymphatic malformation of the tongue resulting in a lateral open bite.

Treatment and prognosis

Multiple treatments have been recommended for lymphatic malformations. Various intralesional sclerosing agents have given largely disappointing outcomes.[107,108] More recently, promising results have been reported with the use of OK-432.[109] This agent is a lyophilized mixture of low-virulence streptococcus strains incubated with penicillin G. It is described as a potent immunostimulant, and has been found to cause immunologic up-regulation, activation of neutrophils, macrophages and T-cells and to elevate the concentration of tumor necrosis factor and IL-6 in the cystic fluid contained in LMs. The solution of OK-432 is directly injected into the cystic spaces of the LM after the cyst contents have been drained. It has, thus, found most utility in macrocytic LMs. Preliminary studies report a decrease in LM volume in the range of 86%, where a successful response to therapy is defined as a greater than 60%.[110]

Drainage procedures, especially in neonates, are only temporary measures used to treat airway compromise and aspiration risk.[111] Mulliken and Young caution that the variety of clinical presentations of these malformations make specific treatment recommendations difficult.[90] In lieu of doing harm, often the best therapy is to do nothing. Secondary infections must be treated aggressively with appropriate antibiotics.

If surgical excision is contemplated, it must be well timed and carefully executed. The non-neoplastic nature of lymphatic malformations must be kept in mind. Although they are expansive and deforming, they do not infiltrate adjacent normal tissue. Removal of cervical malformations requires identification of the important nerves in the neck (e.g., the vagus and cervical sympathetic chain). Lymphatic malformations in and around the parotid gland require complete exposure of the facial nerve.[112] In the case of very large lesions, resection will often be incomplete, and with each repeated attempt at removal, the resection becomes increasingly difficult because of scar tissue formation and deformation of the normal anatomy.

Rowley et al. have divided LMs into subtypes based on the appropriate timing of surgery.[109] Type I LMs are located below the level of the mylohyoid muscle and generally can be safely resected within the first 12 months of life. In such cases, sharp dissection is the preferred mode and a single procedure is often sufficient. In contrast, Type II LMs are above the level of the mylohyoid muscle and more commonly are diffuse and poorly defined. Complete surgical resection of these lesions is very challenging. The use of carbon dioxide or Nd:YAG lasers may be helpful in the removal of disease not amenable to sharp dissection. These resections are generally done later than Type I LMs. Traditionally, giant lesions are removed via staged resection.[113]

Low Flow Venous and Combined Malformations

Clinical and radiographic features

Much like the lymphatic malformations but distinct from hemangiomas, these vascular anomalies are non-neoplastic and do not exhibit endothelial proliferation. They most commonly occur in true form or may be mixed with capillary and lymphatic elements.[90]

The clinical presentation of venous malformations is variable, ranging from small, dilated varicosities to large and complex lesions permeating tissue planes. Most commonly, the overlying skin or mucosa has a bluish hue (Fig. 20). The lesions are soft and non-pulsatile and often enlarge with Valsalva maneuvers or changes in head position. They grow at a similar rate as the child but may have episodes of rapid enlargement secondary to trauma, clinical infection or to hormonal changes such as those seen during puberty and pregnancy.[114] Thrombus formation within the lesion is common and may be associated with tenderness.

Venous malformations within the jaw most often appear during the second decade of life as a slowly growing mass. They are commonly associated with tooth mobility, cortical expansion and a history of gingival bleeding. The first indication of their presence may be hemorrhage during a dental extraction.

Plain radiographs often show a localized radiolucency of "honeycomb" appearance. Tangential films may demonstrate spicules of bone radiating in a "sunburst" pattern.[115] CT scanning is very helpful in documenting the degree of cortical expansion and the extent of the lesion.

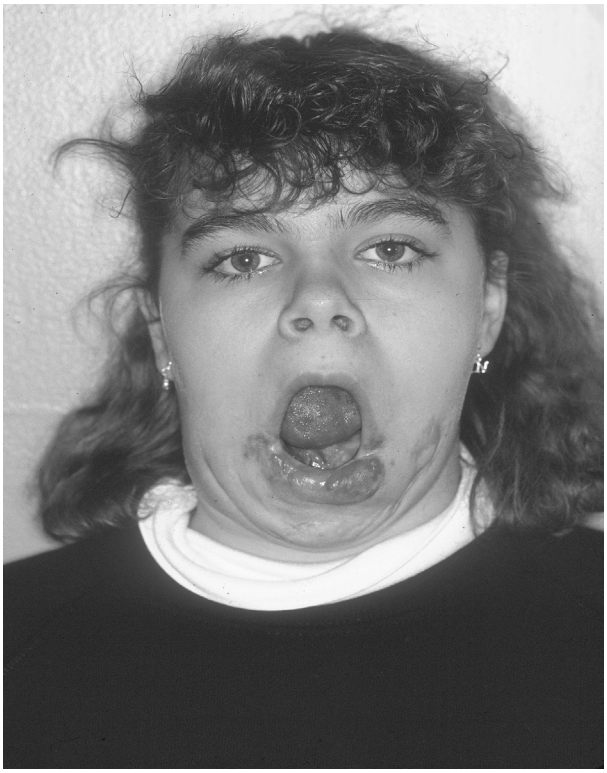

Figure 20: Facial photograph of patient with a low-flow venous malformation. Note the extensive skin and mucosal discoloration.

Treatment and prognosis

Most venous malformations are asymptomatic and should be treated conservatively. Successful treatment planning requires a thorough understanding of the anatomic boundaries and flow characteristics of the lesion as well as an assessment of coagulation parameters. Venography helps to document the anatomy of the lesion. Direct percutaneous injection of contrast material may be required to assess the lesion's full extent.[116]

Large venous malformations are often associated with coagulopathies. In addition to evaluating an INR and PTT, fibrin split products, fibrinogen and platelet number should

be requested. (See *Selected Readings in Oral and Maxillofacial Surgery, Vol. 8, #6*) Coagu-lopathies must be corrected if surgery is contemplated.[117]

Total removal of extensive venous malformations is often limited by anatomic constraints. A sub-total resection can reduce bulk and improve facial contour and aesthetics, but can also be associated with post-operative expansion of the remaining venous channels.

Intralesional sclerosing agents remain a viable treatment option for venous and mixed capillary-venous malformations. Ethibloc®, so-

Large venous malformations are often associated with coagulopathies

dium tetradecyl sulfate and ethanol have shown some success. Photocoagulation using various lasers is most effective for small and superficial lesions.[118] (See also, *Selected Readings in Oral and Maxillofacial Surgery, Vol. 3, #5*)

Arteriovenous malformations (A-V malformations)

Clinical and radiographic features

A-V malformations are characterized by an abnormal communication between arteries and veins, bypassing the normal capillary beds. They can occur at any level of the vascular tree, and the length of the channels between the arteries and veins can vary widely.[90]

A-V malformations of the head and neck may grow for years before their high-flow nature becomes threatening.[119] Murmurs, thrills or bruits are associated with these lesions, and the sound may be heard in an amplified manner by the patient. The overlying skin is often warm to the touch (Fig. 21). Destruction of adjacent bony structures is found.[120] Jaw lesions may be asymptomatic or associated with pulsatile swelling, pain or sudden hemorrhage (Fig. 22). Radiographically, these lesions are generally ill defined and may be multilocular. Much like proliferating hemangiomas and venous malformations, large A-V malformations may be associated with disseminated intravascular coagulation and consumptive coagulopathies.

Treatment and prognosis

Many surgical and non-surgical methods have been used alone or in combination for the treatment of A-V malformations. Non-surgical methods have included radiation therapy, injection of sclerosing agents and various embolization techniques. Surgery, for accessible lesions, has included both limited and wide extirpation. In general, the long-term outcomes of all treatments have been disappointing, and recurrences

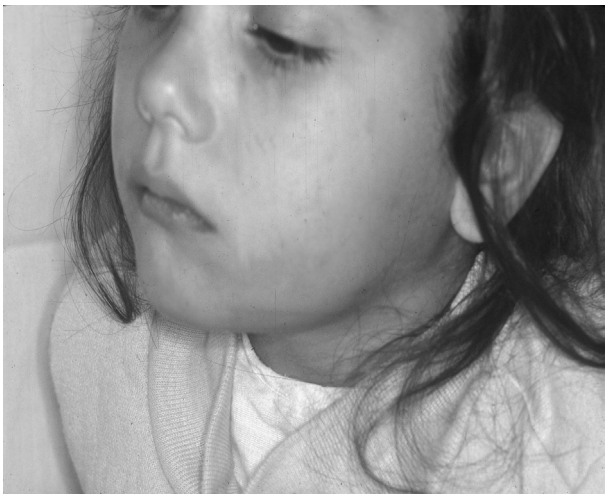

Figure 21: Facial photograph of a patient with a high flow arteriovenous malformation. The overlying skin demonstrates a faint blush and is warm to the touch and pulsatile.

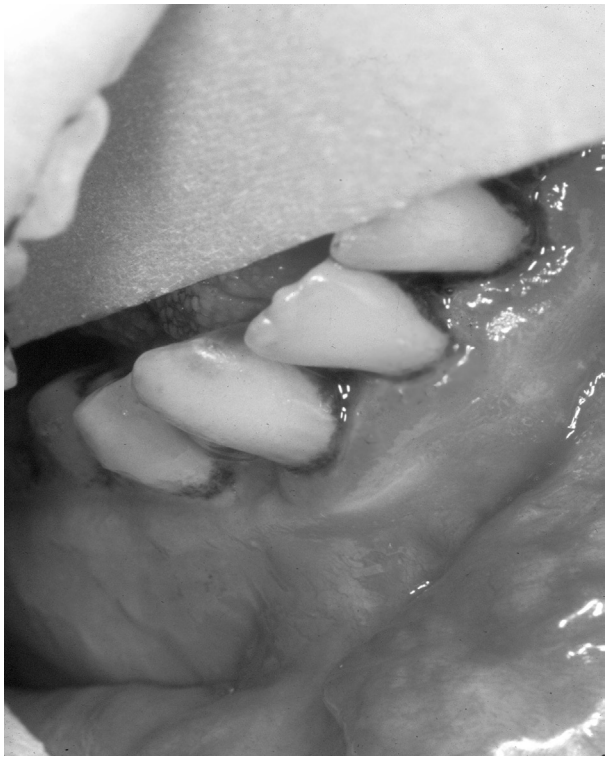

Figure 22: Intraoral photograph of a patient with a high flow arterio-venous malformation of the mandible with associated hemorrhage around the necks of the mandibular teeth.

are common. Ligation of the external carotid artery is not an effective treatment because recruitment of collateral vessels invariably occurs from the internal carotid and vertebral systems as well as from the contralateral external carotid artery. Because these malformations are extensive, complete removal is rarely possible.[121]

Depending upon the nature and the anatomy of the lesion, embolization can be accomplished via superselective angiography using intra-arterial catheters (arterial embolization) or through direct puncture techniques with embolization directly within the lesion (transcutaneous transosseous embolization).[122] Improvements in angiographic techniques and catheter technology now allow precise delivery of embolic material to targeted sites, thereby minimizing neurological and other complications. Other improvements include digital subtraction techniques, biplane arteriography and miniaturized and flow-guided catheters. Several sessions may be required.

Arterial embolization is the best treatment for high-pressure malformations with associated fistulae. The direct puncture technique is most commonly employed for low-flow venous malformations and intrabony malformations. Because there is no dominant flow toward the lesion in these cases, the catheter must be brought as close to the lesion as possible by inserting it into one of the venous collections.

Various embolic materials have been used, including Gelfoam®, Spongel®, Ethibloc®, autologous muscle and coagulated blood, lyophilized dura, various wire coils, coils with associated wool strands, polyvinyl alcohol and cyanoacrylate. Sclerosing agents such as ethanol have also been used. Coils must be deposited directed into the varix of the malformation.[120] Conceptually, they decrease blood flow, increase turbulence and promote clot formation and obliteration of the varix. Over time, the coagulum surrounding the coils will be remineralized and new bone commonly forms at the lesion site.

When endovascular therapy is being performed for cure or palliation, permanent materials are generally chosen. If embolization is being done in anticipation of surgical resection, either absorbable or permanent materials are appropriate. Potential complications associated with embolic therapy include: arterial spasm, vessel rupture, adverse reaction to the substance used, contiguous tissue necrosis and pulmonary emboli secondary to escape of material into the

are common. Ligation of the external carotid artery is not an effective treatment because recruitment of collateral vessels invariably occurs from the internal carotid and vertebral systems as well as from the contralateral external carotid artery. Because these malformations are extensive, complete removal is rarely possible.[121]

Depending upon the nature and the anatomy of the lesion, embolization can be accomplished via superselective angiography using intra-arterial catheters (arterial embolization) or through direct puncture techniques with embolization directly within the lesion (transcutaneous transosseous embolization).[122] Improvements in angiographic techniques and catheter technology now allow precise delivery of embolic material to targeted sites, thereby minimizing neurological and other complications. Other improvements include digital subtraction techniques, biplane arteriography and miniaturized and flow-guided catheters. Several sessions may be required.

Arterial embolization is the best treatment for high-pressure malformations with associated fistulae. The direct puncture technique is most commonly employed for low-flow venous malformations and intrabony malformations. Because there is no dominant flow toward the lesion in these cases, the catheter must be brought as close to the lesion as possible by inserting it into one of the venous collections.

Various embolic materials have been used, including Gelfoam®, Spongel®, Ethibloc®, autologous muscle and coagulated blood, lyophilized dura, various wire coils, coils with associated wool strands, polyvinyl alcohol and cyanoacrylate. Sclerosing agents such as ethanol have also been used. Coils must be deposited directed into the varix of the malformation.[120] Conceptually, they decrease blood flow, increase turbulence and promote clot formation and obliteration of the varix. Over time, the coagulum surrounding the coils will be remineralized and new bone commonly forms at the lesion site.

When endovascular therapy is being performed for cure or palliation, permanent materials are generally chosen. If embolization is being done in anticipation of surgical resection, either absorbable or permanent materials are appropriate. Potential complications associated with embolic therapy include: arterial spasm, vessel rupture, adverse reaction to the substance used, contiguous tissue necrosis and pulmonary emboli secondary to escape of material into the venous circulation. Because of its flow characteristics cyanoacrylate can penetrate deeply into the lesion but is also associated with an inflammatory response and can glue the catheter tip to the walls of blood vessels.

Many of the following authors have advocated the combined use of superselective embolization followed by surgical resection as the treatment of choice for vascular malformations of the maxilla and mandible. However, long-term outcome studies are sparse due to the limited number of these lesions reported.

Persky et al. reported the outcome of treatment for 31 vascular malformations of the head and neck.[92] Eighty-one percent were treated with embolization alone and 19% had preoperative embolization followed by resection. When the malformations were isolated to the mandible without soft tissue extension, all patients were cured by the treatment. A lower cure rate (46%) was reported for maxillary lesions. None of the patients with combined maxillary and mandibu

of uninvolved bone is the treatment of choice. In such cases, subsequent reconstruction will be required. Resection of the involved bone with immediate replantation of the cortical shell is another treatment option described.[125]

Larson and Peterson advocate exposure of the ipsilateral external carotid artery at the time of resection, wide access to the entire lesion and proceeding with the anterior osteotomy cut first.[124] The risk of hemorrhage can be reduced by using controlled hypotension, rapid surgical technique, and preoperative embolization of the main vessels supplying the malformation, followed by surgery within 72 hours.

GIANT CELL LESIONS OF THE JAWS

Giant cell lesions of bone represent a broad category of entities. (See also *Selected Readings in Oral and Maxillofacial Surgery, Vol. 5, #5*) For the purpose of this review, we will limit our discussion to those central giant cell lesions that affect the maxillofacial region. Most, if not all, of the initial reports regarding giant cell lesions are found in the orthopedic literature. This is not unexpected given the high incidence of such lesions in the appendicular skeleton. In 1953, Jaffe was one of the first to distinguish giant cell lesions of the long bones from those that occur in the jaws.[126] His preference was to characterize the jaw lesions as a "reparative processes" resulting from local hemorrhage as opposed to a true neoplasm. Although he did not deny the existence of a true giant cell tumor occurring in the jaw, he believed their occurrence in this location was very rare.

Since then there have been many case reports of giant cell lesions in the craniofacial skeleton[127-137] that have raised questions about the "benign nature" of these jaw lesions. Many of these series included distinct examples of aggressive giant cell lesions of the jaw that were not distinguishable from the giant cell neoplasm of long bones. In Waldron and Schafer's[129] series of 38 cases of giant cell lesions of the jaw, six cases fulfilled the histologic and clinical criteria of giant cell tumors. It was their position that "giant cell tumors" of the long bones and "giant cell reparative granulomas" of the jaws are in fact one and the same entity, but they may differ in presentation and histology because of a variation or difference of degree within the spectrum of a single disease process. They argued that because these giant cell reparative granulomas are "non-odontogenic" one would expect such bone lesions to also present in the axial skeleton. Earlier, Shklar and Meyer reported ten such cases.[127]

Currently it is felt that these jaw lesions are characterized by variable clinical behavior and histologic presentation. The literature regarding giant cell lesions of the jaws can be somewhat confusing because some authors have included both central and peripheral lesions in their series. Although there are many series of central giant cell jaw lesions, only three major reviews exist, representing a compilation of 208 cases of central giant cell lesions of the jaw.[130,132,136] Austin et al.[130] reported on 34 cases and Andersen et al.[132] reported on 32 cases of central giant cell lesions of the jaw. The remaining cases in those two series all represented peripheral lesions. However, Whittaker and Waldron[136] point out that the clinical presentation and behavior of peripheral giant cell lesion differs from that of the central lesion. For the purposes of this review, only the central lesion will be discussed.

be requested. (See *Selected Readings in Oral and Maxillofacial Surgery, Vol. 8, #6*) Coagu-lopathies must be corrected if surgery is contemplated.[117]

Total removal of extensive venous malformations is often limited by anatomic constraints. A sub-total resection can reduce bulk and improve facial contour and aesthetics, but can also be associated with post-operative expansion of the remaining venous channels.

Intralesional sclerosing agents remain a viable treatment option for venous and mixed capillary-venous malformations. Ethibloc®, sodium tetradecyl sulfate and ethanol have shown some success. Photocoagulation using various lasers is most effective for small and superficial lesions.[118] (See also, *Selected Readings in Oral and Maxillofacial Surgery, Vol. 3, #5*)

Arteriovenous malformations (A-V malformations)

Clinical and radiographic features

A-V malformations are characterized by an abnormal communication between arteries and veins, bypassing the normal capillary beds. They can occur at any level of the vascular tree, and the length of the channels between the arteries and veins can vary widely.[90]

A-V malformations of the head and neck may grow for years before their high-flow nature becomes threatening.[119] Murmurs, thrills or bruits are associated with these lesions, and the sound may be heard in an amplified manner by the patient. The overlying skin is often warm to the touch (Fig. 21). Destruction of adjacent bony structures is found.[120] Jaw lesions may be asymptomatic or associated with pulsatile swelling, pain or sudden hemorrhage (Fig. 22). Radiographically, these lesions are generally ill defined and may be multilocular. Much like proliferating hemangiomas and venous malformations, large A-V malformations may be associated with disseminated intravascular coagulation and consumptive coagulopathies.

Treatment and prognosis

Many surgical and non-surgical methods have been used alone or in combination for the treatment of A-V malformations. Non-surgical methods have included radiation therapy, injection of sclerosing agents and various embolization techniques. Surgery, for accessible lesions, has included both limited and wide extirpation. In general, the long-term outcomes of all treatments have been disappointing, and recurrences are common. Ligation of the external carotid artery is not an effective treatment because recruitment of collateral vessels invariably occurs from the internal carotid and vertebral systems as well as from the contralateral external carotid artery. Because these malformations are extensive, complete removal is rarely possible.[121]

Depending upon the nature and the anatomy of the lesion, embolization can be accomplished via superselective angiography using intra-arterial catheters (arterial embolization) or through direct puncture techniques with embolization directly within the lesion (transcutaneous transosseous embolization).[122] Improvements in angiographic techniques and catheter technology now allow precise delivery of embolic material to targeted sites, thereby minimizing neurological and other complications. Other improvements include digital subtraction techniques, biplane arteriography and miniaturized and flow-guided

(88%) were less than 4 cm. This is consistent with a series reported by Eisenbud et al. where 63% of the lesions were less than 4 cm.[134]

Although most cases present with well defined borders, the perimeter is not usually corticated. In Whittaker and Waldron's series of 142 lesions[136] and Horner's study of 26 cases[138] only 19% and 8%, respectfully, demonstrated a well corticated border. Cortical thinning and expansion are also seen (Fig.23 C). Thirty-eight percent of the lesions reported by Horner displayed radiographic evidence of cortical expansion and thinning.[138] Waldron and Shafer described the cortical expansion as a localized "bossing" effect rather than a diffuse expansion.[129] Although cortical perforation is not common, it has also been reported.[133] Some authors have correlated the existence of cortical perforation and root resorption with a more aggressive clinical course.[135,136] However, there is no single radiographic feature that is pathognomonic for a giant cell lesion.

Histologically, a giant cell lesion is dominated by two types of cells: stromal cells and multinucleated giant cells. The predominant histologic pattern is a loose fibrous connective tissue stroma containing a variable amount of collagen (Fig. 24). This stroma is typically interspersed with numerous small vascular

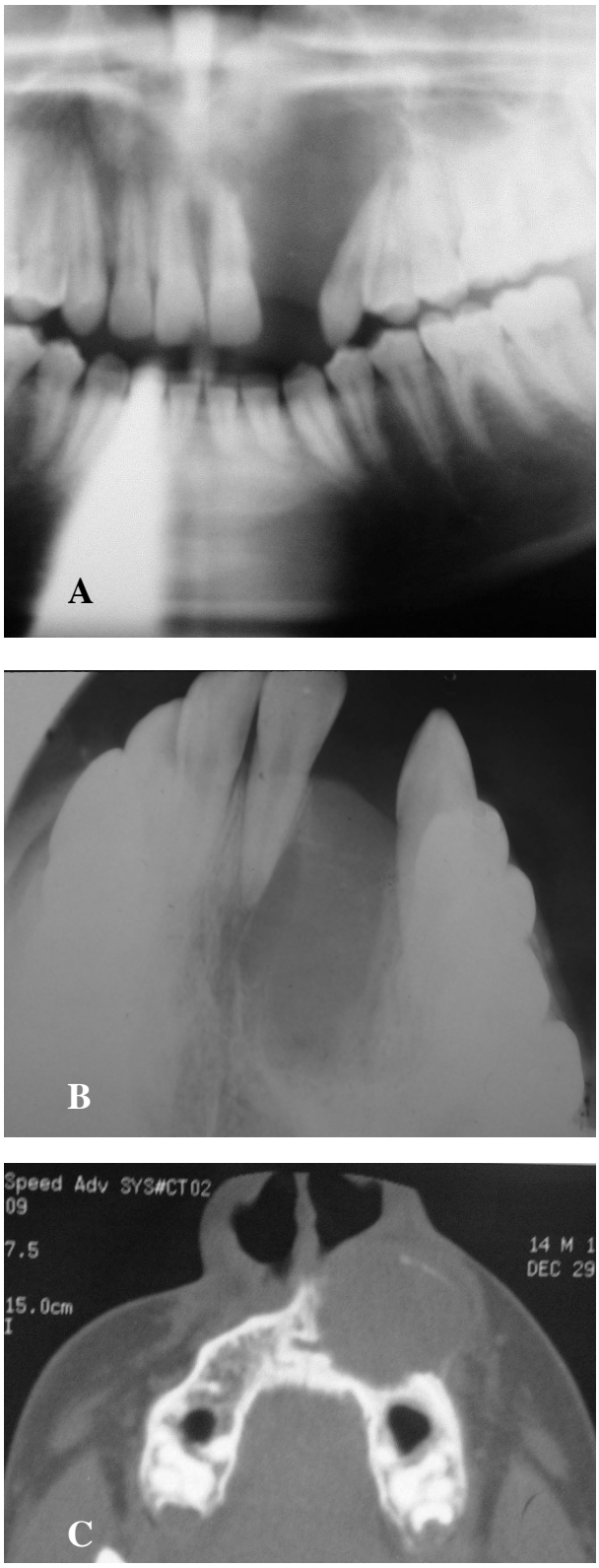

Figure 23 **A.** Panoramic radiograph of a giant cell lesion in the left maxilla of a 13-year-old patient. The lesion presents as a radiolucent lesion in the anterior maxilla with displacement of the teeth; **B.** Maxillary occlusal radiograph demonstrating the osteolytic lesion in the left pre-maxillary region; **C.** Axial computed tomographic radiograph of the anterior maxillary giant cell lesion. This is a well-defined radiolucent lesion with considerable bony expansion, cortical thinning and osteolysis.

channels and many proliferating spindle-shaped cells.[145-148] The histologic field is usually highly vascular with many intravascular and extravascular red blood cells. Consequently large numbers of extravasated red blood cells and hemosiderin-laden macrophages are commonly seen, often focally, throughout the lesion. Based on ultra-structural observations[149] and the analysis of phenotypic cell markers,[150] these stromal cells are most likely of fibroblast/myofibroblast origin.[151]

The large amount of extravasated red blood cells has prompted some investigators to examine the vasculature in these lesions more closely. Andersen et al.[152] examined the ultra-structure of these vessels and determined that gaps of varying sizes allowed direct continuity between the intravascular space and perivascular tissue. More recent studies have provided immunohistochemical and ultra-structural evidence confirming significant alterations within the vasculature of these lesions.[152] Specifically, the vessels were structurally incomplete or defective in the deeper regions of the lesion and were associated with an abundant amount of extravasated red blood cells and multinucleated giant cells. However, the vessels at the periphery of the lesion were intact. These authors speculated that a relationship exists between the presence of perivascular multinucleated giant cells and the anomalies found within the vasculature. Others have hypothesized that giant cell lesions are part of a spectrum of mesenchymal angiogenic tumors and, therefore, should be considered as a proliferative vascular lesion.[153, 154]

The other prominent cell type found in this lesion is the multinucleated giant cell. Usually of varying size, number, shape and distribution they contain a varying number of nuclei from cell to cell and case to case. These giant cells typically aggregate around vascular channels.

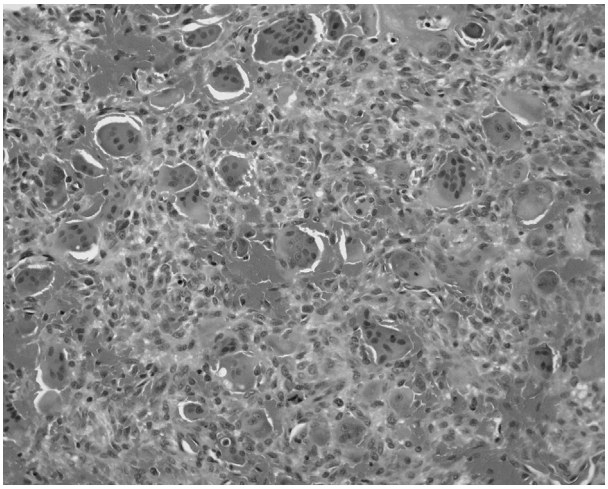

Figure 24: Photomicrograph of a typical central giant cell lesion of the mandible characterized by numerous multinucleated giant cells and extravasated red blood cells within a loose fibrous connective tissue stroma.

Many theories have been proposed for the origin of the giant cells in these lesions. Many cell lines have been implicated in the histogenesis of the giant cells including macrophages,[155-157] osteoclasts[158-161] and myofibroblasts.[149] Three current theories suggest origin from: 1) circulating progenitor cells that are identical to osteoclasts, 2) reactive, fully differentiated end cells derived from stromal macrophages and 3) cells formed as a result of an intracellular fusion of local myofibroblasts.

The analysis of apoptotic regulatory proteins and cellular proliferation markers has established that multinucleated giant cells are reactive rather than proliferative in nature and display an increased level of apoptosis compared to stromal cells.[150, 162, 163] The giant cells may also play an important regulatory role in these lesions. In vitro data from giant cells in tumors

from long bones suggest that tumor necrosis factor-alpha (TNF-α), secreted by multinucleated giant cells, modulates the expression of certain metalloproteinases (MMP-9) in stromal cells.[164] This is significant in light of other data that has established a potential role for matrix metalloproteinases in tumor invasion and metastasis.[165]

The clinical behavior of these lesions can range from a small, slowly growing asymptomatic mass that responds well to simple curettage to a very large and aggressive tumor that produces pain and can recur frequently. Some investigators have reported true malignant giant cell tumors of the jaw that produce distant and local metastases.[166-169] This wide spectrum of clinical presentation has inspired a search for certain histologic parameters that might predict the biologic and clinical behavior of these entities.

In 1988, Chuong et al. retrospectively studied 17 cases of central giant cell jaw lesions and compared the fractional surface area of the giant cells, relative sizing, stromal characteristics, mitotic index, the number of inflammatory cells and the hemosiderin content between aggressive and non-aggressive lesions.[137] They demonstrated two significant findings: 1) the giant cells in aggressive lesions had a high relative size and 2) the giant cells in recurrent lesions had a high relative size and fractional surface area. Aggressive lesions also occurred more frequently in younger age groups.

Ficarra et al,[135] utilizing the method of Chuong et al,[137] classified two patient groups as having either aggressive or non-aggressive lesions. Computer assisted image analysis was then used to examine the number of giant cells, mean number of nuclei per giant cell, fractional surface area and relative size between the two groups. Aggressive giant cell lesions had a significantly greater number of giant cells and a significantly greater fractional surface area than the less aggressive lesions. Whittaker et al. utilized a silver staining technique of nucleolar organizer regions to demonstrate a significant difference between giant cells from recurrent lesions versus those from non-recurrent or non-aggressive lesions.[170]

In another study, Whittaker and Waldron reviewed 142 cases of central giant cell lesions and found statistically significant histologic differences in the distribution of giant cells and the presence of osteoid between recurrent and non-recurrent lesions.[136] Conversely, Eckart[171] examined the nuclear DNA content of the giant cells using image cytometry and found no significant difference between aggressive and non-aggressive variants using these parameters. Auclair[172] was also unable to establish a quantitative or qualitative histologic difference between recurrent and non-recurrent giant cell lesions.

Certain cell cycle proteins (p53, Ki-67) are currently used as markers to establish proliferative indices for human tumor cells. Analysis of the expression of these cell cycle proliferative proteins failed to show a significant difference between aggressive and non-aggressive giant cell lesions.[150]

It seems, therefore, that while certain histologic criteria may be helpful in alerting a clinician to the potential aggressive behavior of giant cell lesions, no definitive histologic parameter exists that accurately predicts clinical behavior. The clinician must continue to rely on clinical

long-term follow-up in order to adequately manage these lesions.[173]

Treatment and Prognosis

Surgery is the main treatment for giant cell lesions of the jaws. However, there is some degree of variability regarding which surgical procedure should be employed. Some of this variability undoubtedly results from confusing terminology in the literature, i.e., what is one surgeon's "simple curettage" is another surgeon's "aggressive enucleation". Nevertheless, the most important aspect of any surgical treatment is to ensure that the entire lesion is removed. In most large series of giant cell lesions involving the jaws, surgical curettage is the most common procedure employed.[128,130,132,134,137] For certain clinical scenarios this may require that soft tissue (i.e. mucosa and periosteum) must also be removed (aggressive curettage)[128,130,135] or an extended bony margin obtained (curettage with peripheral ostectomy).[134] Large and clinically aggressive lesions with extensive involvement of the maxilla or mandible may require an enbloc resection.[127,137,148]

No definitive histologic parameter exists that accurately predicts clinical behavior.

Recurrence rates for central giant cell lesions of the jaws are difficult to analyze because different series are not comparable [e.g., Austin, et al.[130] (3%), Seldin, et al.,[128] (8%), Waldron and Shafer[129] (15%), Horner[138] (23%), and Chuong, et al.[137] (35%)]. This is because many variables influence recurrence data and no one study has properly controlled for all of them. First, although some authors have included peripheral giant cell lesions in their series,[130] others separate central and peripheral lesions as distinct entities.[129] Second, treatment modalities are not standardized, both between studies and even within a particular study. Third, giant cell lesions present a spectrum of clinical behaviors and aggressiveness that can vary with the age of the patient and the location of the tumor. Only recently have certain investigators begun to stratify their data and control for this.[135,137,169] Finally, many older studies have included entities with inherently high recurrence rates (e.g., sarcomas and fibrous histiocytomas) within the giant cell lesion category, skewing the data. Given the inconsistencies in the literature, one should interpret any reported recurrence rates with some degree of caution. As more recent studies begin to stratify patients with regard to the above-mentioned variables recurrence data should become more reliable.

Although the treatment of central giant cell lesions is primarily surgical, other non-surgical modalities of treatment, including radiation therapy,[174] systemic calcitonin,[160] intralesional steroid therapy[175] and interferon therapy[153,154] have been reported. Radiation therapy is mentioned here only to be condemned. In those few cases of malignant transformation of a previously benign giant cell lesion, most had received radiation therapy.[176-178] In Hutter's large series of giant cell lesions of long bones 70% of all malignant giant cell tumors had received radiation prior to the diagnosis of cancer.[179] Consequently, this modality of treatment has been mostly abandoned. Currently radiation therapy is reserved for those large giant cell tumors involving the spine, pelvis and sacrum that cannot be adequately treated surgically.[180] Although a few reported cases of successfully radiated jaw lesions exist,[137,181,182] this modality has a very limited role in the treatment of central

giant cell lesions of the jaw. Chuong, et al.[137] reported four cases of large, highly aggressive lesions of the maxilla for which radiation therapy was used in conjunction with surgery.

The rationale for systemic calcitonin treatment is based on similarity of these lesions with the "brown tumor" of hyperparathyroidism. In addition, the discovery of calcitonin receptors on the multinucleated giant cells within these lesions suggests that calcitonin or some similar molecule might regulate these cells and subsequent bone resorption.[183-185] Calcitonin has also been shown to inhibit cortical bone resorption in cultures of human osteoclastoma cells.[186]

Harris,[160] in a small series of four patients with central giant cell lesions, was the first to report regression of these lesions utilizing systemic calcitonin therapy. Although two of the patients exhibited complete regression, the remaining two patients required additional surgery to eradicate the lesion. The largest series of patients treated with calcitonin was reported by Pogrel, where 8 of 10 patients had complete resolution of their lesions after an average of 20 months of calcitonin therapy.[187]

Intralesional steroid therapy is also described in the treatment giant cell lesions, based on the assumption that they are inflammatory in nature. Terry and Jacoway[175] describe the successful use of triamcinolone in three patients with giant cell lesions of the mandible, however, there are no references with regard to protocol and no controls. Carlos and Sedano reported a detailed protocol on four cases that were successfully treated with intralesional steroid injections.[188] They attributed the efficacy of steroid therapy to an inhibition of lysosomal protease production and induced apoptosis of osteoclast-like cells. Alternatively, Schlorf and Koop[189] reported that steroids were not useful and Body et al.[190] reported only a transient response in a single case. In light of these conflicting reports, it is clear that controlled studies with adequate follow-up comparing steroids and other modalities of treatment are indicated prior to recommending steroids as an efficacious nonsurgical treatment modality for central giant cell lesions of the jaw.

Radiation therapy is mentioned here only to be condemned.

The vascularity of these lesions has led some to hypothesize that giant cell lesions exist within a spectrum of mesenchymal angiogenic tumors. Based on the success of interferon alpha therapy in the treatment of aggressive hemangiomas and other proliferative vascular lesions, Kaban and others have proposed a similar therapeutic regimen for aggressive giant cell lesions.[153,154] According to their treatment protocol, aggressive giant cell lesions undergo a conservative surgical debulking procedure with preservation of surrounding teeth and nerves. Daily injections of interferon are initiated three days postoperatively and continued for approximately six months. Eight patients treated in accordance with this protocol had no recurrences over a follow-up period of one to six years. However, side effects from systemic interferon therapy were common and required frequent dosing adjustments and close monitoring. Wong's experience with eight patients treated with systemic interferon and no surgery was limited by significant systemic toxicity in a majority of patients.[191]

CONCLUSIONS

The locally aggressive benign processes of the oral and maxillofacial region discussed in this review are those most commonly encountered by oral and maxillofacial surgeons. Their biology and clinical expression can often be more deforming, destructive and ominous than some malignant tumors of the same anatomic area. The management of these benign neoplasms should involve a surgical approach with curative intent while preserving function. While many of these processes are slow growing in nature, they are nonetheless aggressive and warrant aggressive surgical management to optimize the patient's likelihood of cure. However, the vascular lesions are important exceptions to this general rule. For these benign processes, a medical approach to therapy may often provide cure or long-term palliation of the lesion. Under such circumstances, surgery may be avoided altoge-ther unless needed to salvage failed medical therapy.

One additional common denominator of the locally aggressive benign processes is their relatively controversial nature, including both their embryogenesis and recommendations for their treatment. With regard to the latter, the reader should follow an evidence-based approach to treatment, as has been discussed. This approach is likely to provide a high level of cure. While surgery is most commonly utilized to provide such a result, our understanding of cell cycle dynamics and pathogenetic mechanisms of these locally aggressive benign processes may, in the future, allow for biologic, non-surgical treatment by intervening at the level of the cell cycle.

Dr. Eric Carlson received his DMD from the University of Pennsylvania School of Dental Medicine. He then performed his oral and maxillofacial surgery residency at Allegheny General Hospital in Pittsburgh and a fellowship in Oral/ Head and Neck Surgery at the University of Miami/Jackson Memorial Medical Center. He received his MD from the University of Miami School of Medicine, and performed his General Surgery residency at the University of Tennessee. Dr. Carlson is currently Professor and Chairman of the Department of Oral and Maxillofacial Surgery and Director of the Oral and Maxillofacial Surgery Residency program at the University of Tennessee Graduate School of Medicine in Knoxville.

Dr. Meredith August received her DMD from Harvard School of Dental Medicine and performed her oral and maxillofacial surgery residency at Massachusetts General Hospital. She received her MD from Harvard Medical School and performed her general surgery residency at Massachusetts General Hospital. She is currently Associate Professor of Oral and Maxillofacial Surgery at Harvard School of Dental Medicine and Massachusetts General Hospital.

Dr. Salvatore Ruggiero received his DMD from Harvard School of Dental Medicine and performed his oral and maxillofacial surgery residency at Massachusetts General Hospital. He received his MD from Harvard Medical School, and performed his general surgery residency at Massachusetts General Hospital. He is currently Chief of Oral and Maxillofacial Surgery at Long Island Jewish Medical Center where he also serves as Associate Chairman of the Department of Dental Medicine.

REFERENCES

1. Marx RE and Stern D: Hyperplasias, hamartomas, and neoplasms: Their biology and its impact on treatment decisions. In: Marx RE and Stern D (eds.) ***Oral and Maxillofacial Pathology. A Rationale for Diagnosis and Treatment***, Chicago, Quintessence Publishing Co, Inc., Chapt. 5, pp. 255-259, 2003.

2. Carlson ER: Pathologic facial asymmetries. In: Lew D (ed): ***Management of Facial Asymmetry. Atlas of the Oral and Maxillofacial Surgery Clinics of North America.*** Philadelphia, WB Saunders, pp. 19-35, 1996.

3. Regezi JA, Sciubba JJ, Jordan RCK: Ulcerative Conditions In: Regezi JA, Sciubba JJ, Jordan RCK (eds): ***Oral Pathology. Clinical Pathologic Correlations.*** 4th Edition, St. Louis, Elsevier Science, Chapt. 2, pp. 54-55, 2003.

4. Lane DP: p53, guardian of the genome. Nature 358: 15, 1992.

5. Li FP, Fraumeni JF, Mulvihill JJ, et al: A cancer family syndrome in twenty-four kindreds. Cancer Res 48: 5358, 1988.

6. Malkin D, Li FP, Strong LC: Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 25: 1233, 1990.

7. Cotran RS, Kumar V, Collins T: Neoplasia. In: Cotran RS, Kumar V, Collins T (eds): ***Robbins Pathologic Basis of Disease***, 6th edition, Philadelphia, WB Saunders Co., Chapt. pp. 8260-327, 1999.

8. Jost CA, Marin MC, Kaelin WG: p73 is a human p53-related protein that can induce apoptosis. Nature 389: 191, 1997.

9. Oren M: Lonely no more: p53 finds its kin in a tumor suppressor haven. Cell 90: 829, 1997.

10. Carson DA and Ribeiro JM: Apoptosis and disease. Lancet 341: 1251, 1993.

11. Kumamoto H and Ooya K: Immunohistochemical analysis of bcl-2 family proteins in benign and malignant ameloblastomas. J Oral Pathol Med 28: 343, 1999.

12. Carvalhais JN, deAguiar MCF, deAraujo VC et al: p53 and MDM2 expression in odontogenic cysts and tumours. Oral Diseases 5: 218, 1999.

13. Ong'uti MN, Cruchley AT, Howells GL et al: Ki-67 antigen in ameloblastomas: correlation with clinical and histological parameters in 54 cases from Kenya. Int J Oral Maxillofac Surg 26: 376, 1997.

14. Gerdes J, Lemke H, Baisch H et al: Cell cycle analysis of a cell proliferation associated human antigen defined by the monoclonal antibody Ki-67. J Immunol 133: 1710, 1984.

REFERENCES

1. Marx RE and Stern D: Hyperplasias, hamartomas, and neoplasms: Their biology and its impact on treatment decisions. In: Marx RE and Stern D (eds.) ***Oral and Maxillofacial Pathology. A Rationale for Diagnosis and Treatment***, Chicago, Quintessence Publishing Co, Inc., Chapt. 5, pp. 255-259, 2003.

2. Carlson ER: Pathologic facial asymmetries. In: Lew D (ed): ***Management of Facial Asymmetry. Atlas of the Oral and Maxillofacial Surgery Clinics of North America.*** Philadelphia, WB Saunders, pp. 19-35, 1996.

3. Regezi JA, Sciubba JJ, Jordan RCK: Ulcerative Conditions In: Regezi JA, Sciubba JJ, Jordan RCK (eds): ***Oral Pathology. Clinical Pathologic Correlations.*** 4th Edition, St. Louis, Elsevier Science, Chapt. 2, pp. 54-55, 2003.

4. Lane DP: p53, guardian of the genome. Nature 358: 15, 1992.

5. Li FP, Fraumeni JF, Mulvihill JJ, et al: A cancer family syndrome in twenty-four kindreds. Cancer Res 48: 5358, 1988.

6. Malkin D, Li FP, Strong LC: Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. Science 25: 1233, 1990.

7. Cotran RS, Kumar V, Collins T: Neoplasia. In: Cotran RS, Kumar V, Collins T (eds): ***Robbins Pathologic Basis of Disease***, 6th edition, Philadelphia, WB Saunders Co., Chapt. pp. 8260-327, 1999.

8. Jost CA, Marin MC, Kaelin WG: p73 is a human p53-related protein that can induce apoptosis. Nature 389: 191, 1997.

9. Oren M: Lonely no more: p53 finds its kin in a tumor suppressor haven. Cell 90: 829, 1997.

10. Carson DA and Ribeiro JM: Apoptosis and disease. Lancet 341: 1251, 1993.

11. Kumamoto H and Ooya K: Immunohistochemical analysis of bcl-2 family proteins in benign and malignant ameloblastomas. J Oral Pathol Med 28: 343, 1999.

12. Carvalhais JN, deAguiar MCF, deAraujo VC et al: p53 and MDM2 expression in odontogenic cysts and tumours. Oral Diseases 5: 218, 1999.

13. Ong'uti MN, Cruchley AT, Howells GL et al: Ki-67 antigen in ameloblastomas: correlation with clinical and histological parameters in 54 cases from Kenya. Int J Oral Maxillofac Surg 26: 376, 1997.

14. Gerdes J, Lemke H, Baisch H et al: Cell cycle analysis of a cell proliferation associated human antigen defined by the monoclonal antibody Ki-67. J Immunol 133: 1710, 1984.

31. Muller H and Slootweg PJ: The ameloblastoma, the controversial approach to therapy. J Max Fac Surg 13: 79, 1985.

32. Gardner D: A pathologist's approach to the treatment of ameloblastoma. J Oral Maxillofac Surg 42: 161, 1984.

33. Atkinson CH, Harwood AR and Cummings BJ: Ameloblastoma of the jaw. A reappraisal of the role of megavoltage irradiation. Cancer 53: 869, 1984.

34. Gardner DG: Radiotherapy in the treatment of ameloblastoma. Int J Oral Maxillofac Surg 17: 201, 1988.

35. Robinson L and Martinez MG: Unicystic ameloblastoma. A prognostically distinct entity. Cancer 40: 2278, 1977.

36. Vickers RA and Gorlin RJ: Ameloblastoma: delineation or early histopathologic features of neoplasia. Cancer 26: 699, 1970.

37. Gardner DG and Corio RL: The relationship of plexiform unicystic ameloblastoma to conventional ameloblastoma. Oral Surg Oral Med Oral Pathol 56: 54, 1983.

38. Regezi JA, Sciubba JJ, Jordan RCK: Odontogenic Tumors. In: Regezi JA, Sciubba JJ, Jordan RCK (eds): ***Oral Pathology Clinical Pathologic Correlations***. 4th Edition, St. Louis, Elsevier, Chapt. 11, pp. 267-288, 2003.

39. Gardner DG and Corio RL: Plexiform unicystic ameloblastoma. A variant of ameloblastoma with a low recurrence rate after enucleation. Cancer 53: 1730, 1984.

40. Carlson ER: Odontogenic cysts and tumors. In: Miloro (ed): ***Peterson's Principles of Oral and Maxillofacial Surgery***, Chapter 30, Hamilton, BC Decker, 2004.

41. Gardner DG: Plexiform unicystic ameloblastoma: A diagnostic problem in dentigerous cysts. Cancer 47: 1358, 1981.

42. Eversole LR, Leider AS and Strub D: Radiographic characteristics of cystogenic ameloblastoma. Oral Surg 57: 572, 1984.

43. Barker BF: Odontogenic myxoma. Sem Diag Pathol 16: 297, 1999.

44. Fenton S, Slootweg PJ, Dunnebier EA et al: Odontogenic myxoma in a 17-month old child: A case report. J Oral Maxillofac Surg 61: 734, 2003.

45. Bast BT, Pogrel MA and Regezi JA: The expression of apoptotic proteins and matrix metalloproteinases in odontogenic myxomas. J Oral Maxillofac Surg 61: 1463, 2003.

46. Franklin CD and Pindborg JJ: The calcifying epithelial odontogenic tumor. A review and analysis of 113 cases. Oral Surg 42: 753, 1976.

47. Schmitz L and Favara BE: Nosology and pathology of Langerhans cell histiocytosis. Hematology/Oncology Clinics of North America 12: 221, 1998.

48. Eckardt A and Schultze A: Maxillofacial manifestations of Langerhans cell histiocytosis: A clinical and therapeutic analysis of 10 patients. Oral Oncology 39: 687, 2003.

49. Regezi J, Sciubba J, Jordan RCK: Inflammatory jaw lesions. In: Regezi J, Sciubba J, Jordan RCK (eds): ***Oral Pathology-Clinical Pathologic Correlations***, 4th Edition, Philadelphia, WB Saunders Co., Chapt. 13, p 303, 2003.

50. Neville BW, Damm DD, Allen CM, Bouquot JE: Hematologic Disorders. In: Neville BW, Damm DD, Allen CM, Bouquot JE (eds): ***Oral and Maxillofacial Pathology***, 2nd edition, , Philadelphia, WB Saunders Co., Chapt. 13, pp. 497- 531, 2002.

51. Waldron CA: Fibro-osseous lesions of the jaws. J Oral Maxillofac Surg 51:823, 1993.

52. Waldron CA and Giansanti JS: Benign fibro-osseous lesions of the jaws: a clinico-radiographic-histologic review of sixty five cases. Oral Surg Oral Med Oral Pathol 35:340, 1973.

53. Voytek TM, Ro JY, Edeikel J, et al: Fibrous dysplasia and cemento-ossifying fibroma. A histologic spectrum. Am J Surg Pathol 19:775, 1995.

54. Eversole LR, Merrell PW and Strub D: Radiographic characteristics of central ossifying fibroma. Oral Surg Oral Med Oral Pathol 59:522, 1985.

55. Fechner RE: Problematic lesions of the craniofacial bones. Am J Surg Pathol 13(Suppl 1):17, 1989.

56. Boysen ME, Olving JH, Vatne K, et al: Fibro-osseous lesions of the cranio-facial bones. J Laryngol Otol 93:793, 1979.

57. Margo CE, Ragsdale BD, Perman KI, et al: Psammomatoid (juvenile) ossifying fibroma of the orbit. Ophthalmology 92:150, 1985.

58. Slootweg PJ: Maxillofacial fibro-osseous lesions: classification and differential diagnosis. Semin Diagn Pathol 13:102, 1966.

59. Brannon RB and Fowler CB:Benign fibro-osseous lesions: a review of current concepts. Adv Anat Pathol 8:126, 2001.

60. Su L, Weathers DR and Waldron CA: Distinguishing features of focal cemento-osseous dysplasias and cemento-ossifying fibromas. A pathologic spectrum of 316 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 84:301, 1997.

61. Craig RG: Cementum vs. bone. Oral Maxillofac Surg Clin North Am 9:581, 1997.

62. Mirra JM, Bernard GW, Bullough PG, et al: Cementum-like production in solitary bone cysts (so-called "cementoma" of long bones). Clin Orthop 135:295, 1978.

63. Warnakulasuriya S, Markwell BD and Williams DM: Familial hyperparathyroidism associated with cementifying fibromas of the jaws in two siblings. Oral Surg Oral Med Oral Pathol 59:269, 1985.

64. Bertolini F, Caradonna L, Binachi B, et al: Multiple ossifying fibromas of the jaws. J Oral Maxillofac Surg 60:225, 2002.

65. Eversole LR, Leider AS and Nelson K: Ossifying fibroma: a clinico-pathologic study of sixty four cases. Oral Surg Oral Med Oral Pathol 60:505, 1985.

66. Slootweg PJ and Muller H. Juvenile ossifying fibroma. Report of four cases. J Craniomaxillofac Surg 18:125, 1990.

67. Johnson LC, Youseff M and Vinh TN: Juvenile active ossifying fibroma. Its nature, dynamics and origin. Acta Otolaryngol Suppl 488:1, 1991.

68. Lawton MT, Heiserman JE, Coons SW, et al: Juvenile active ossifying fibroma. Report of four cases. J Neurosurg 86:279, 1997.

69. Janecka IP and Housepian E: Craniofacial approach to ossifying fibromas. Laryngoscope 93:305, 1985.

70. Noffke CEE: Juvenile ossifying fibroma of the mandible. An 8-year radiologic follow-up. Dentomaxillofac Radiol 27:363, 1998.

71. Som PM and Lidor M: The benign fibro-osseous lesion: its association with paranasal sinus mucoceles and its MR appearance. J Comput Assist Tomogr 16:871:1992.

72. Slootweg PJ, Panders AK, Koopmans R, et al: Juvenile ossifying fibroma. An analysis of 33 cases with emphasis on histopathological aspects. J Oral Pathol Med 23:385, 1994.

73. Dehner LP: Tumors of the mandible and maxilla in children. Clinicopathologic study of 46 histologically benign lesions. Cancer 31:364, 1973.

74. Sciubba JJ and Younai F: Ossifying fibroma of the mandible and maxilla: review of 18 cases. J Oral Pathol Med 18:315, 1989.

75. El-Mofty S: Psammomatoid and trabecular juvenile ossifying fibroma of

the craniofacial skeleton: two distinct clinicopathologic entities. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 93:296, 2002.

76. Alawi F: Benign fibro-osseous diseases of the maxillofacial bones. A review and differential diagnosis. Am J Clin Pathol 188 (suppl):50, 2002.

77. Rinaggio J, Land M and Cleveland DB: Juvenile ossifying fibroma of the mandible. J Pediatr Surg 38:648, 2003.

78. Kwon PH, Horswell BB and Gatto DJ: Desmoplastic fibroma of the jaws: surgical management and review of the literature. Head Neck 11:67, 1989.

79. Green MF and Sirikumara M: Desmoplastic fibroma of the mandible. Ann Plastic Surg 19:284, 1987.

80. Batsakis JG: ***Tumors of the Head and Neck: Clinical and Pathological Considerations.*** 2nd edition Baltimore, MD, Williams and Wilkins, 1984, p.410

81. Williams HK, Mangham C and Speight PM: Juvenile ossifying fibroma. An analysis of eight cases and a comparison with other fibro-osseous lesions. J Oral Pathol Med 29:13, 2000.

82. MacIntosh RB: Juvenile ossifying fibroma. Oral Maxillofac Surg Clin North Am 9:713, 1997.

83. Alvarez-Mendoza A, Lourdes TS, Ridaura-Sanz C, et al: Histopathology of vascular lesions found in Kassabach-Merritt syndrome: review based on 13 cases. Pediatr Dev Pathol 3:556, 2000.

84. Inwards CY, Unni KK, Beabout JW, et al: Desmoplastic fibroma of the bone. Cancer 68:1978, 1991.

85. Fowler CB, Hartman KS and Brannon RB: Fibromatosis of the oral and paroral region. Oral Surg Oral Med Oral Pathol 77:373, 1994.

86. Jaffe HL. ***Tumors and Tumorous Conditions of the Bones and Joints.*** Philadelphia, PA, Lea and Febiger, 1958, p.298.

87. Hopkins KM, Huttula CS, Kahn MA, et al: Desmoplastic fibroma of the mandible: review and report of two cases. J Oral Maxillofac Surg 54:1249, 1996.

88. Vally IM and Altini M: Fibromatosis of the oral and paroral soft tissues and jaws. Review of the literature and report of 12 new cases. Oral Surg Oral Med Oral Pathol 69:191, 1990.

89. Glowacki J and Mulliken JB: Mast cells in hemangiomas and vascular malformations. Pediatrics 70:48, 1982.

90. Mulliken JB and Young AE: Classification of vascular birthmarks. In: ***Vascular Birthmarks: hemangiomas and malformations.*** Philadelphia PA, W.B. Saunders Co, 1988, p.30.

91. Mulliken JB and Glowacki J: Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg 69:412, 1982.

92. Persky MS, Yoo HJ and Berenstein A: Management of vascular malformations of the mandible and maxilla. Laryngoscope 113:1885, 2003.

93. Powell J: Update on hemangiomas and vascular malformations. Curr Opin Pediatr 11:457, 1999.

94. Ceisler EJ, Santos L and Blei F: Periocular hemangiomas: what every physician should know. Pediatr Dermatol 21:1, 2004.

95. Howell DM, Gumbiner CH and Martin GE: Congestive heart failure due to giant cutaneous cavernous hemangioma. Clin Pediatr 23:504, 1984.

96. Gangopadhyay AN, Sinha CK, Gopal SC, et al: Role of steroids in childhood hemangioma: a 10 year review. Int Surg 82: 49, 1992.

97. Hosono S, Ohno T, Kimoto H, et al: Successful transcutaneous arterial embolization of a giant hemangioma associated with high-output cardiac failure and Kassabach-Merritt syndrome in a neonate: a case report. J Perinat Med 27:399, 1999.

98. Fledelius HC, Illum N, Jensen H, et al: Interferon-alfa treatment of facial infantile hemangiomas with emphasis on the sight-threatening varieties. A clinical series. Acta Ophthalmol Scand 79:370, 2001.

99. Chang E, Boyd A, Nelson CC, et al: Successful treatment of infantile hemangiomas with interferon-alpha-2b. J Pediatr Hematol Oncol 19:237, 1997.

100. Padwa BL. Hayward PG, Ferraro NF, et al: Cervicofacial lymphatic malformation: clinical course, surgical intervention, and pathogenesis of skeletal hypertrophy. Plast Reconstr Surg 95:951, 1995.

101. Hamoir M, Plouin-Gaudon I, Rombaux P, et al: Lymphatic malformations of the head and neck: a retrospective review and support for staging. Head Neck 23:326, 2001.

102. Smith RJH, Burke DK, Sato Y, et al: OK-432 therapy for lymphangiomatosis. Arch Otolaryngol Head Neck Surg 122:1195, 1996.

103. de Serres LM, Sie KC and Richardson MA: Lymphatic malformations of the head and neck. A proposal for staging. Arch Otolaryngol Head Neck Surg 121:577, 1995.

104. Van Aslst JA, Bhuller A and Sadove AM: Pediatric vascular lesions. J Craniofac Surg 14:566, 2003.

105. Law PJ and Hall CM: Clavicular overgrowth in association with cystic hygroma. Skeletal Radiol 20:597, 1991.

106. Nosan DK, Martin DS and Stith JA: Lymphangioma presenting as a delayed posttraumatic expanding neck mass. Am J Otolaryngol 16:186, 1995.

107. Herbreteau D, Riche MC, Enjolras O, et al: Percutaneous embolization with Ethibloc of lymphatic cystic malformations with a review of the experience in 70 patients. Int Angiol 12:34, 1993.

108. Castanon M, Margarit J, Carrasco R, et al: Long-term follow-up of nineteen cystic lymphangiomas treated with fibrin sealant. J Pediatr Surg 34:1276, 1999.

109. Rowley H, Perez-Atayde AR, Burrows PE, et al: Management of giant lymphatic malformation of the tongue. Arch Otolaryngol Head Neck Surg 128:190, 2002.

110. Giguere CM, Bauman NM and Smith RJH. New treatment options for lymphangioma in infants and children. Ann Oto Rhinol Laryngol 111:1066, 2002.

111. Emery PJ, Bailey CM and Evans JN: Cystic hygroma of the head and neck. A review of 37 cases. J Laryngol Otol 98:613, 1984.

112. Green AK, Rogers GF and Mulliken JB: Management of parotid hemangiomas in 100 children. Plast Reconstr Surg 113:53, 2004.

113. Low DW: Management of adult facial vascular anomalies. Facial Plast Surg 19:113, 2003.

114. Hein KD, Mulliken JB, Kozakewich HP, et al: Venous malformations of skeletal muscle. Plast Reconstr Surg 110:1625, 2002.

115. Vargel I, Cil BE, Kiratli P, et al: Hereditary intraosseous vascular malformation of the craniofacial region: imaging findings. Br J Radiol 77:197, 2004.

116. Burrows PE and Mason KP: Percutaneous treatment of low flow vascular malformations. J Vasc Interv Radiol 15:431, 2004.

117. Mazoyer E, Enjolras O, Laurian C, et al: Coagulation abnormalities associated with extensive venous malformations of the limbs: differentiation from Kassabach-Merritt syndrome. Clin Lab Haematol 24:243, 2002.

118. Puig S, Aref H, Chigot V, et al: Classification of venous malformations in children and implications for sclerotherapy. Pediatr Radiol 33:99, 2003.

119. Babin RW, Osborn DB and Khansure MS: Arteriovenous malformations of the mandible. Otolaryngol Head Neck Surg 91:366, 1983.

120. Perrott DH, Schmidt B, Dowd CF, et al: Treatment of a high-flow arteriovenous malformation by direct puncture and coil embolization. J Oral Maxillofac Surg 52:1083, 1994.

121. Riche MC, Hadjean C, Tricot JF, et al: Risks of ligation of the external carotid artery in the treatment of cervicofacial angiodysplasia. Ann Oto-Laryngol 97:3, 1980.

122. Azzolini A, Bertani A and Riberti C: Superselective embolization and immediate surgical treatment: our present approach to treatment of large vascular hemangiomas of the face. Ann Plast Surg 9:42, 1982.

123. Giaoui L, Princ G, Chiras J, et al: Treatment of vascular malformations of the mandible: a description of 12 cases. Int J Oral Maxillofac Surg 32:132, 2003.

124. Larson PE and Peterson LJ. A systemic approach to management of high-flow vascular malformations of the mandible. J Oral Maxillofac Surg 51:62, 1993.

125. Behnia H and Motamedi MHK: Treatment of central arteriovenous malformation of the mandible via resection and immediate replantation of the segment: a case report. J Oral Maxillofac Surg 55:79, 1997.

126. Jaffe H: Giant cell reparative granuloma, traumatic bone cyst and fibrous (fibro-osseous) dysplasia of the jaw bones. Oral Surg 6:159, 1952.

127. Shklar G and Meyer I: Giant cell tumors of the mandible and maxilla. Oral Surg 7:809, 1961.

128. Seldin HM, Seldin SD, Rakower W, et al: Giant cell tumor of the jaws. J Amer Dent Assoc 55:210, 1957.

129. Waldron C and Shafer W: The central giant cell reparative granuloma of the jaws; an analysis of 38 cases. Amer J Clin Path 45:437, 1966.

130. Austin LT, Dahlin D and Royer RQ: Giant cell reparative granuloma and related conditions affecting the jawbones. Oral Surg 12:1285, 1959.

131. Khanna S and Khanna N: Giant cell lesions of the jaw. Ear, Nose & Throat J 58:198, 1979.

132. Andersen L, Fejerskov O and Philipsen HP: Oral giant cell granulomas. Acta Path Microbiol Scand 5:606, 1973.

133. Scully R, Mark E, McNeely W, et al: Case records of the Mass. Gen. Hospital, Case 20-1993. N Engl J Med 328:1478, 1993.

134. Eisenbud L, Stern M, Rothberg M, et al: Central giant cell granuloma of the jaws: experiences in the management of thirty seven cases. J Oral Maxillofac Surg 46:376, 1988.

135. Ficarra G, Kaban LB and Hansen LS: Central giant cell lesions of the mandible

and maxilla: a clinicopathologic and cytometric study. J Oral Surg 64:44, 1987.

136. Whitaker SB and Waldron C: Central giant cell lesions of the jaws. Oral Surg 75:199, 1993.

137. Chuong R, Kaban L, Kozakewich H, et al: Central giant cell lesions of the jaws: a clinicopathologic study. J Oral Maxillofac Surg 44:708, 1986.

138. Horner K: Central giant cell granuloma of the jaws: A clinico-radiological study. Clinical Radiology 40:62, 1989.

139. Cohen MM and Gorlin RJ: Noonan-like/ multiple giant cell lesion syndrome. Am J Medical Genet. 40:159, 1991.

140. Bertola DR, Kim CA, Pereira AC, et al: Are Noonan syndrome and Noonan-like /multiple giant cell lesion syndrome distinct entities? Am J Med Genet. 98:230, 2001.

141. Levine B, Skope L and Parker R: Cherubism in a patient with Noonan's syndrome: report of a case. J Oral Maxillofac Surg. 49:1018, 1991.

142. Dunlap C, Neville B, Vickers RA, et al: The Noonan syndrome/cherubism association. Oral Surg Oral Path Oral Path. 67:698, 1989.

143. Ruggieri M, Pavone V, Polizzi A, et al: Unusual form of recurrent giant cell granuloma of the mandible and lower extremities in a patient with neurofibromatosis type 1. Oral Surg Oral Path Oral Path Oral Radiol Endod. 87:67, 1999.

144. Ardekian L, Manor R, Peled M et al: Bilateral central giant cell granulomas in a patient with neurofibromatosis: Report of a case and review of the literature. J Oral Maxillofac Surg. 57:869, 1999.

145. Regezi JA and Sciubba J: ***Oral Pathology. Clincal-pathologic Correlations***. 2nd ed. Philadelphia: W.B. Saunders, 1993.

146. Khalifa MC and Ibrahim RA: Cherubism. J Laryng Otol 102:568, 1988.

147. Shafer WG, Hine MK and Levy BM: ***A Textbook of Oral Pathology.*** 4th ed. Philadelphia: W.B. Saunders Company, 1983.

148. Neville BW, Damm DD, Allen CM, et al: ***Oral and Maxillofacial Pathology.*** 1st ed. Philadelphia: W.B Saunders Company, 1995.

149. Schneider RE and Schneider LC: Central giant cell lesions. ***Oral & Maxillofacial Surgery Knowledge Update 1: Part II:*** 25-33 1995.

150. O'Malley M, Pogrel MA, Stewart JCB, et al: Central giant cell granulomas of the jaws: phenotype and proliferation-associated markers. J Oral Pathol Med. 26:159, 1997.

151. El-Mofty SK and Osdoby P: Growth behavior and lineage of isolated and cultured cells derived from giant cell granuloma of the mandible. J Oral Path 14:539, 1985.

152. Andersen L, Fejerskow O and Theilade J: Oral giant cell granulomas. Acta Path Microbiol Scand 83:69, 1975.

153. Kaban LB, Mulliken JB, Ezekowitz RA, et al: Antiangiogenic therapy of a recurrent giant cell tumor of the mandible with interferon alpha-2a. Pediatrics. 103:1145, 1999

154. Kaban LB, Troulis MJ, Ebb D, et al: Antiangiogenic therapy with interferon alpha for giant cell lesions of the jaws. J Oral Maxillofac Surg. 60:1103, 2002.

155. El-Labban NG and Lee KW: Myofibroblasts in central giant cell granuloma of the jaws: an ultrastructural study. Histopathology 7:907, 1983.

156. Lim L and Gibbins JR. Immunohistochemical and ultrastructural evidence of a modified microvasculature in the giant cell granuloma of the jaws. Oral Surg 79:190, 1995.

157. Doussis I, Pubble B and Athanasou N: Immunophenotype of multinucleated and mononuclear cells in giant cell lesions of bone and soft tissue. J Clin Pathol 45:398, 1992.

158. Regezi J, Zarbo R and Lloyd R: Muramidase, 1 antichymotrypsin and S-100 protein immunoreactivity in giant cell lesions. Br J Cancer 59:64, 1987.

159. Flanagan AM, Tinkler MB, Horton MA, et al: The multinucleate cells in giant cell granulomas of the jaw are osteoclasts. Br J Cancer 62:1139, 1988.

160. Harris M: Central giant cell granulomas of the jaws regress with calcitonin therapy. Br J Oral Maxillofac Surg 31:89, 1992.

161. Mori M, Fukuda M, Tsukamoto S, et al: Enzyme histochemistry of osteogenic sarcoma, chondrosarcoma and giant cell lesions in jawbones. Oral Surg 26 :103, 1968.

162. Souza PEA, Paim JFO, Carvalhais JN, et al: Immunohistochemical expression of p53, MDM2, Ki-67 and PCNA in central giant cell granuloma and giant cell tumor. J Oral Pathol Med. 28:54, 1999.

163. Pammer J, Weninger W, Hulla H, et al: Expression of regulatory apoptotic proteins in peripheral giant cell granulomas and lesions containing osteoclasts-like giant cells. J Oral Pathol Med. 27:267, 1998.

164. Rao VH, Singh RK, Delimont DC, et al: Transcriptional regulation of MMP-9 expression in stromal cells of human giant cell tumor of bone by tumor necrosis factor-a. Inter J Oncol. 14:291, 1999.

165. Liotta LA and Stettler-Stevenson WG: Tumor invasion and metastasis: an imbalance of positive and negative regulation. Cancer Res. 51(Suppl.):5054S, 1991.

166. Sapp JP: Ultrastructure and histogenesis of peripheral giant cell reparative granuloma of the jaws. Br J Cancer 30:1119, 1972.

167. Mintz G, Abrams A, Carlsen G, et al: Primary malignant giant cell tumor of the mandible. J Oral Surg 51:164, 1981.

168. Hjorting-Hansen E and Worsoe-Petersen J: Recurrent benign giant cell lesions of the jaws with metastasis. Laryngol Otolog 81:1033, 1967.

169. Hayward JR: Malignant giant cell tumor of the mandible: report of case. J Oral 17:75, 1959.

170. Whitaker SB, Vigneswaran N, Budnick SD, et al: Giant cell lesions of the jaws: evaluation of nucleolar organizer regions in lesions of varying behavior. J Oral Pathol Med 22:402, 1993.

171. Eckardt A, Pogrel M, Kaban L, et al: Central giant cell granulomas of the jaws. Int J Oral Maxillofac Surg 18: 3, 1989.

172. Auclair PL, Cuenin P, Kratochvil FJ, et al: A clinical and histomorphologic comparison of the central giant cell granuloma and the giant cell tumor. Oral Surg Oral Med Oral Path 66:197, 1988.

173. High AS and Mathews A: The importance of radiography in assessing the behaviour of an aggressive giant cell lesion of the jaws. Dentomaxillofac Radiol 18:36, 1989.

174. Herendeen RE: The roentgen ray in the treatment of giant cell tumors. Amer J Radiol 12:117, 1925.

175. Terry BC and Jacoway JR: Management of central giant cell lesions. An alternative to surgical therapy. In: Gold L (ed.) ***Oral and Maxillofacial Surgery Clinics of North America. Surgical pathology: Considerations in diagnosis and management***. Vol. 6. Philadelphia: W.B. Saunders Company: pp. 579-600, 1994.

176. Dahlin D and Unni K: ***Bone Tumors (General aspects and data on 8,542 cases).*** 4th ed. Springfield, Ill: Charles C. Thomas, 1986.

177. Sanerkin N: Malignancy, aggressiveness, and recurrence in giant cell tumor of bone. Br J Cancer 46:1641, 1980.

178. Mnaymneh WA, Dudley R and Mnaymneh LG: Giant cell tumor of bone. J Bone and Joint Surg 46A:63, 1964.

179. Hutter VP, Worcester JN, Francis KC, et al: Benign and malignant giant cell tumors of bone. Br J Cancer 15:653, 1962.

180. Schajowicz F: Current trends in the diagnosis and treatment of malignant bone tumors. Clinical Orthopaedics and Related Research 180:220, 1983.

181. Mcgowan DA: Central giant cell tumor of the mandible occurring in pregnancy. Br J Oral Surg 131, 1969.

182. Berger A: Solitary central giant cell tumor of the jaw bones. J Oral Surg 5:154, 1947.

183. Goldring SR, Schiller AL, Mankin HJ, et al: Characterization of cells from human giant cell tumors of bone. Clin Orthop 204:59, 1986.

184. Nicholson GC, Horton MA and Sexton PM: Calcitonin receptors of human osteoclastoma. Hormone and Metabolic Research 19:585, 1987.

185. Gorn AH, Rudolph SM, Flannery MR, et al. Expression of two human skeletal calcitonin receptor isoforms cloned from giant cell tumor of bone. The first intracellular domain modulates ligand binding and signal transduction. J Clin Invest 95:2680, 1995.

186. Chamers TJ, Fuller K, Mcsheehy PMJ, et al: The effects of calcium regulating hormones on bone resorption by isolated human osteoclastoma cells. J Pathol 145:297, 1985.

187. Pogrel MA: Calcitonin therapy for central giant cell granuloma. J Oral Maxillofac Surg. 61:649, 2003.

188. Carlos R and Sedano HO: Intralesional corticosteroids as an alternative treatment for central giant cell granuloma. Oral Surg Oral Med Oral Path Oral Radiol Endod. 93:161, 2002.

189. Schlorf RA and Koop SH: Maxillary giant cell granuloma. Laryngoscope 87:10, 1977.

190. Body JJ, Jortay AM, deJager R, et al: Treatment with steroids of a giant cell granuloma of the maxilla. J Surg Oncol 16:7, 1981.

191. Wong M: Personal communication. University of Texas at Houston Medical Center. February, 2004.

RELATED ARTICLES FROM *SELECTED READINGS IN ORAL AND MAXILLOFACIAL SURGERY.*

The Ameloblastoma: A Review of the Literature. Tom Williams, DDS. Selected Readings in Oral and Maxillofacial Surgery, Vol. 2, #2, 1992.

Fibro-osseous Lesions of the Facial Bones: A Review of the Literature. Martin Stern, DMD; Salvatore L. Ruggiero, DMD, MD. Selected Readings in Oral and Maxillofacial Surgery, Vol. 3, #1, 1994.

The Odontogenic Keratocyst. Thomas P. Williams, DDS. Selected Readings in Oral and Maxillofacial Surgery, Vol. 3, #2, 1994.

Laser Technology in Oral and Maxillofacial Surgery. Part II: Applications. Guy Catone, DMD. Selected Readings in Oral and Maxillofacial Surgery, Vol. 3, #5, 1994.

Head and Neck Vascular Anomalies. Leonard B. Kaban, DMD, MD, FACS; Bart Blaeser, DMD; David H. Perrott, DDS, MD, FACS. Selected Readings in Oral and Maxillofacial Surgery Vol. 5, #3, 1996.

Giant Cell Lesions of the Jaws. Salvatore L. Ruggiero, DMD, MD. Selected Readings in Oral and Maxillofacial Surgery Vol. 5, #5, 1996.