Advances in Anatomic Pathology
Vol. 8, No. 3, pp. 126–143

Benign Fibro-Osseous Lesions: A Review of Current Concepts

*Robert B. Brannon and †Craig B. Fowler

**Department of Oral and Maxillofacial Pathology, Louisiana State University Health Sciences Center, Dental School, New Orleans, Louisiana, U.S.A., and the †Department of Oral and Maxillofacial Pathology, 59th Dental Squadron, Wilford Hall Medical Center, Lackland Air Force Base, Texas, U.S.A.*

Summary: The benign fibro-osseous lesions (BFOL) represent a clinically diverse group of disorders of bone that share similar histopathologic features. As a group, they are relatively common in the craniofacial complex, especially the jaws. Although the general concept of BFOL is relatively well known, specific diagnostic interpretation of individual cases is often challenging. New concepts and controversies have arisen over the past 10 to 15 years regarding classification and diagnostic criteria. However, among the new theories and contentions, there is now essential agreement that the osseous dysplasias represent a single disease process, while the so-called "juvenile active ossifying fibroma" and other "aggressive," "active," "psammomatoid" ossifying/cementifying fibromas remain controversial. This review is presented to update the surgical pathologist on the various entities comprising the spectrum of BFOL and to examine the criteria for their diagnosis. **Key Words:** Benign fibro-osseous lesion—Ossifying fibroma—Cementifying fibroma—Cemento-osseous—Dysplasia—Fibrous

One of the most confusing areas of pathology involves the group of lesions generically termed benign fibro-osseous lesions (BFOL). The term fibro-osseous is descriptive, nosologically limited, and diagnostically nonspecific (1). Common to all BFOL is the replacement of normal bone with a tissue composed of collagen fibers and fibroblasts that contain varying amounts of mineralized substance, which may be bony or cementum-like in appearance (2). Many lesions contain an admixture of these calcifications (2). The concept of BFOL has recently evolved to include developmental lesions, reactive or dysplastic processes, and neoplasms (3–5). However, despite recent advances in the understanding of BFOL, distinguishing specific BFOL from one another may still pose significant problems (3,5,6). Moreover, the literature is confounding and contrary in regard to classification, diagnosis, and management of these lesions. Most agree that definitive diagnosis requires correlation of the histopathologic features with the patient's history, clinical findings, radiographic/imaging analysis, and operative findings because of the histologic similarities among this diverse group of lesions (3,5–8). Diagnosis is important because of the different treatments for these conditions. The objective of this paper is to clarify pertinent issues that have evolved over the past 10 to 15 years regarding BFOL of the jaws and sinonasal region. The intent is to approach the subject from a practical rather than a theoretical viewpoint and thereby provide the pathologist confronted with a fibro-osseous lesion a sensible and systematic approach to interpretation. To help accomplish this goal, at the beginning of the discussion for each lesion key features have been provided that are helpful in the diagnosis of the entity. This is intended to be only a general guideline for the surgical pathologist because many variables in the interpretation of BFOLs exist.

Address correspondence and reprint requests to Dr. Robert B. Brannon, Department of Oral and Maxillofacial Pathology, Louisiana State University School of Dentistry, 1100 Florida Avenue, New Orleans, LA 70119. E-mail: rbrann@lsusd.lsuhsc.edu

THE CEMENTUM-VERSUS-BONE CONTROVERSY

Many have debated whether dental cementum is a distinct tissue and whether or not it has any relevance to the

pathogenesis, diagnosis, and management of fibro-osseous lesions (5,8–13). Intrabony lesional tissue that is characterized by acellular to poorly cellular basophilic globular (spheroid) deposits of calcified extracellular matrix, has traditionally been designated "cementum" (8,10). This belief that lesional cementum exists stems from its resemblance to mineralized spherical particles (cementicles) found in the periodontal ligament (PDL) that connects the teeth with the alveolar bony socket (10). However, spherules identical to those observed in gnathic lesions have been well documented in extragnathic sites far from tooth-bearing areas, including the skull, facial skeleton, and long bones (5,10,12,14–17).

Researchers have used histochemical methods and polarized light to observe the direction and width of collagen fibers in an effort to distinguish between cementum and bone (9,18–21). These techniques yielded inconclusive results, and most pathologists continue to profess an inability to discriminate between bone and cementum by conventional histopathologic methods (5). However, some reports suggest evidence exists for distinguishing between the two via immunopathologic techniques utilizing bone-associated proteins and Type IX collagen (22,23). Cementum lacks the ultrastructural features indicative of osteogenic origin (5,22). Craig (11) has provided a detailed perspective on cementum versus bone and concluded that presently no biochemical markers that unequivocally distinguish cementum matrix or cells from bone exist. Final resolution will probably depend on molecular-biologic approaches (11). Several investigators have argued that to avoid confusion the term cementum should be reserved for a bonelike substance attached to the tooth root (5,8,10) and that considering this unattached cementumlike fibro-osseous tissue to be bone would alleviate arguments over confusing lesional nomenclature (5,8,10,13). Moreover, because the biologic activity of lesions containing primarily cementum-like calcifications does not differ from those containing primarily bone, the argument over nomenclature would appear to be merely academic.

CLASSIFICATION

Various investigators have attempted to classify BFOL. Some have included lesions originating from the PDL or medullary bone (18,24); others have included lesions containing giant cells and nongiant cells (pure fibro-osseous) (25). Many (7,9,26,27) other attempts at classification have been offered in the past, but in light of newly described entities (28–30) and changing concepts (22,27,31,32), Waldron's (3) classification appears to be the most workable and widely recognized. He divides BFOL by disease category into developmental (hamartomatous), reactive (dysplastic), which is presumably of PDL origin, and neoplastic (3). The lesions within these three aforementioned categories are fibrous dysplasia, the cemento-osseous dysplasias, and ossifying (cementifying) fibromas, respectively. In essential agreement with Waldron's classification, many investigators believe other entities are within the spectrum of BFOL, such as chronic diffuse sclerosing osteomyelitis (8), cherubism (25,26,33,34), aneurysmal bone cyst (25), and central giant cell granuloma (25). The list of "additional" entities seems almost endless and therefore will not be further pursued. Suffice it to say that lesions with no appreciable fibrous or osseous component do not fulfill the criteria for BFOL as defined by Waldron (2).

Waldron (3) reviewed the subject of BFOL in 1993 and suggested a modification of his earlier classification (2). More recently, Slater (8), Slootweg (10), Eversole (35), and Melrose (36) have made recommendations or modifications in classifying BFOL. Based on the aforementioned classifications (3,8,10,35,36) the following categorization is suggested:

Benign Fibro-Osseous Lesions (Modified)

I. Osseous dysplasia (OD)
   Nonhereditary
   - Periapical
   - Focal
   - Florid

   Hereditary
   - Familial gigantiform cementoma

II. Fibro-osseous neoplasms
   - Conventional ossifying fibroma (OF)
   - So-called "juvenile," "active," or "aggressive" forms of OF

III. Fibrous dysplasia (FD)
   - Polyostotic FD with endocrinopathy (McCune–Albright form)
   - Polyostotic FD
   - Craniofacial FD

This modified classification has merit, but further study and evaluation of BFOL are needed.

THE FIBRO-OSSEOUS LESIONS

Osseous Dysplasia (OD)(Cemento-Osseous Dysplasia)

The osseous dysplasias (periapical, focal, florid) represent a pathologic process in the tooth-bearing areas of the jaws, which all too often receives scant notice in the overall scheme of fibro-osseous lesions (7,9,12), yet

comprise a very important component of the fibro-osseous spectrum. In actuality, they probably represent the most common types of fibro-osseous lesions encountered in clinical practice (4,37). It is suspected that as a group they are one of the most frequently misinterpreted of the fibro-osseous lesions because of clinical and histologic similarities to other bone lesions including neoplasia.

In OD, the term dysplasia refers to the abnormal development and disordered production of bone and cementum-like tissue. Due to the insight of Robinson (38) and significant work by several other investigators (3,28–30,39–42), the concept of OD representing a spectrum of disease emerged. It is now generally accepted that the osseous dysplasias (periapical, focal, florid) represent variants of the same pathologic process and are separated on the basis of clinical and radiographic features (3,28). Controversy still surrounds their etiology and pathogenesis. Robinson (38) believed local injury was at play in the form of occlusal forces causing fibrous replacement of existing bony trabeculae and the subsequent formation of immature bone and cementum-like deposits. Melrose (36) has effectively questioned this theory pointing out that inflammation is not a feature of the uncomplicated disease, that pronounced gender and racial predilections exist, that existing lesions fail to resolve following elimination of presumed irritants, and that new lesions can develop in edentulous areas. Eversole (43) has pointed out that three major tissue compartments can contain progenitor cells for BFOL: the PDL, endosteum, and periosteum. The work of Cho et al. (44) supports the progenitor role of PDL fibroblasts for adjacent hard-tissue cells. Many have suspected a PDL origin for OD, a logical suspicion supported by the fact that it occurs only in tooth-bearing areas and histopathologically contains tissues similar to those that can form in the PDL (18,28,45). In addition, although some histologic overlap with extragnathic lesions of a fibro-osseous nature may exist, no clinical or radiographic counterpart to OD in orthopedic pathology exists (36). However, unanswered questions concerning the PDL origin of OD remain. Conventional radiographic and computed tomography findings, anatomic location, and histologic appearance do not readily answer these questions (46).

The histomorphology of periapical, focal, and florid OD is essentially indistinguishable and shows a spectrum of progressive features dependent upon the stage of development. In the initial stages, features consist of an unencapsulated proliferation of cellular fibrous connective tissue containing numerous small-caliber blood vessels (Figure 1). Inflammatory cells are virtually absent.

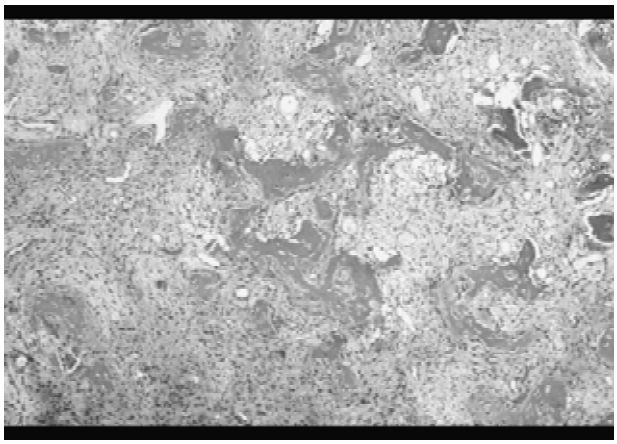

FIG. 1. Osseous dysplasia. Trabeculae of woven bone separated by a moderately cellular fibrous stroma with scattered vascular spaces.

Variable amounts of new (woven) bone trabeculae with osteoblastic rimming and/or spherules of cementum-like tissue are present (Figure 2). Lesional tissue often blends into the cortical bone especially in the focal type (Figure 3). Many cases display a morphology resembling "ginger roots," i.e., random anastomosing, thick, curvilinear, relatively acellular bony trabeculae (29) (Figure 3). In the more advanced stages, mineralized tissue consisting of woven and lamellar bone and cementum-like tissue may fuse together resulting in coalesced, acellular, poorly vascularized, sclerotic masses (Figure 4). These masses may appear pagetoid with prominent resting and reversal lines. Inflammation is scant at best. However, lesional contact with oral flora can lead to infection with a resulting superimposed osteomyelitis with sequestration of the sclerotic masses, a common sequela. This complication is most commonly associated with the florid type and without clinical and radiographic correlation can easily be misinterpreted as purely a primary inflammatory or infectious process. Simple (traumatic) bone cysts have been reported in association with florid OD and to a lesser degree with focal OD (39,47).

Periapical osseous dysplasia (periapical cemento-osseous dysplasia, cementoma).

Keys to diagnosis.

Predilection for middle-aged black females
One or more (0.5cm or less) circumscribed lesions in periapical areas of vital teeth
Painless, nonexpansile, usual location in anterior mandible
Radiographic features can be radiolucent, mixed density (radiolucent with opacities), or opaque with lucent rim
Cellular fibrous stroma with woven and/or lamellar bone and/or oval calcifications

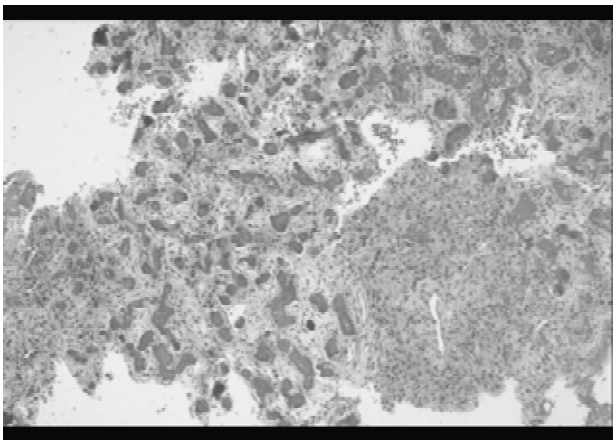

FIG. 2. Osseous dysplasia. Acellular spherules of cementum-like ossicles predominate in a variably cellular fibrous stroma.

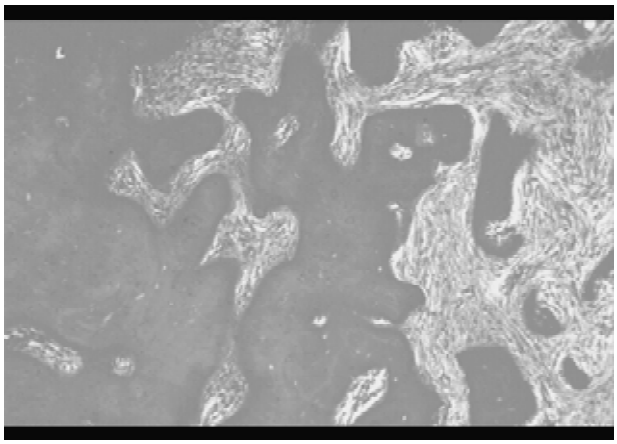

FIG. 4. Osseous dysplasia. Fused masses of bone and cementum-like tissue. The fibrous stroma is poorly vascularized.

Few studies have determined the incidence of periapical OD. Stafne (48) examined the radiographs of 10,000 consecutive adult patients and found a prevalence rate of .24%. Chaudry et al. (49) reviewed the radiographs of 10,500 patients and found 30 cases for a prevalence rate of .29%. Both of these studies may have had a predominantly Caucasian population. However, in a radiographic survey of 491 black women, Neville and Albenesius (50) determined a prevalence rate of 5.9% for periapical OD.

The clinical parameters of periapical OD are well established and remarkably constant. There is a marked predilection for females (14:1) and blacks (3). The lesions are most often detected in patients over the age of 30 and are rare before the age of 20. They are asymptomatic, nonexpansile, and typically at the apices of vital mandibular incisor teeth (Figure 5). Only one tooth may be involved, but multiple lesions are often the norm. Traditionally, the emphasis is that periapical OD initially presents radiographically as a circumscribed, seldom-corticated radiolucency that over an extended period of time (often years) shows increasing amounts of calcification resulting in a progressive pattern that successively evolves from radiolucent to mixed density to radiopaque (51,52). However, Zegarelli et al. (41) have shown that the progression of calcification is not always predictable and that, in fact, some lesions regress, some stay unchanged, and some resolve. Periapical OD usually does not exceed 0.5 cm in growth, but may reach a diameter of 1.0 to 1.5 cm on occasion. This apparent arrest in growth supports a nonneoplastic condition. Zegarelli et al. (41) have followed such lesions for as long as 25 years. Classically, the histologic features have three stages and are correlated with the radiograpic findings.

Stage 1: radiolucent (osteolytic stage), unencapsulated, cellular, fibrous connective tissue with numerous small-caliber blood vessels.

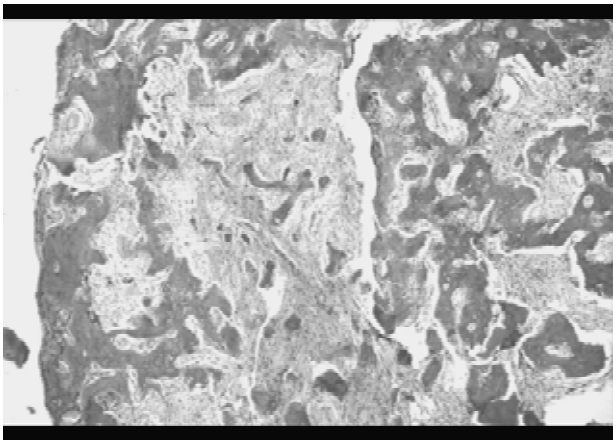

FIG. 3. Osseous dysplasia. Anastomosing, thick, bony trabeculae blending into cortical bone. Cellular fibrous stroma is free of inflammation.

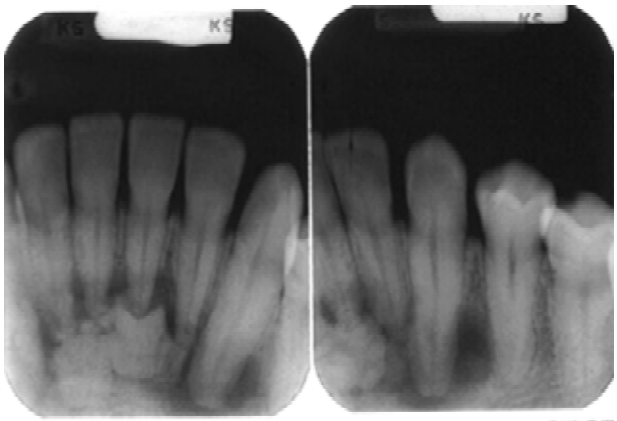

FIG. 5. Periapical OD. Mixed radiolucent/radiopaque lesions in apical region of anterior mandible.

Stage 2: radiolucent/radiopaque (cementoblastic stage), variable amounts of woven trabecular bone and/or spherules of cementumlike tissue (Figure 5).
Stage 3: radiopaque (mature stage), coalescence of the bone and/or cementumlike tissue.

Nevertheless, as emphasized previously, periapical OD is microscopically indistinguishable from the other forms of OD. Dentists seldom submit periapical OD to a histopathology service because they easily recognize the condition and know that treatment consists only of follow-up to ensure that the clinical impression is correct. Despite this fact, clinical misadventures do occur (53). Periapical OD in its early stages can mimic radiographically periapical inflammatory lesions associated with a nonvital pulp, such as the periapical (radicular) cyst or periapical granuloma (3,53). It may also be mistaken for a host of other neoplastic and nonneoplastic lesions (54).

Focal osseous dysplasia (focal cemento-osseous dysplasia).

Keys to diagnosis.

Predilection for middle-aged black females
Painless, nonexpansile, usual location in mandibular molar region, often in edentulous area
Most often demonstrates circumscribed radiolucency with opacities
Surgical findings reflect gross features: difficult to remove resulting in small hemorrhagic gritty fragments
Thick curvilinear trabeculae of woven and/or lamellar bone and/or oval calcifications in a more loosely arranged fibrous stroma than in OF
Sinusoid-like vascular spaces adjacent to bony trabeculae and free hemorrhage

For many years pathologists have been aware of solitary lesions that are histologically identical to periapical OD and occur in the tooth-bearing areas of the posterior jaws, often in sites of previous extractions. Though they were originally designated as "osseous dysplasia reaction of bone to injury" (38), Waldron (2) considered them to represent "localized fibro-osseous cemental lesions—presumably reactive in nature." In 1994, Summerlin and Tomich (28) introduced the term focal cemento-osseous dysplasia, which subsequently gained acceptance (3,29, 30). There is little doubt that focal OD has been confused and even misdiagnosed as the neoplastic OF, which is also known as conventional ossifying fibroma, because of shared similarities in their clinical, radiographic, and histologic features (28–30). Excellent clinicopathologic studies by Summerlin and Tomich (28) and Su et al. (29,30) have further defined the parameters of focal OD and its distinction from OF.

More common among blacks than whites, focal OD has a high female predilection, 8:1 female to male (28,30). The condition predominantly occurs in the 4th and 5th decades with an average age of 38 (28,30). Because the lesion is painless and frequently nonexpansile, it is usually discovered during routine radiographic examination. Cases occur in the tooth-bearing areas, especially in the posterior mandible, where Summerlin and Tomich (28) found 77% and Su et al. (30) 63%. Although many occur in edentulous areas where a tooth was previously extracted, they may also occur in the periapical area of an erupted tooth. Radiographically, they are usually well circumscribed with or without a sclerotic border and may be radiolucent or mixed radiolucent-radiopaque in appearance (Figure 6). The diameter seldom exceeds 2.0 cm (28,30,36).

The clinical, radiographic, and microscopic differential diagnosis of focal OD includes OF, a benign neoplasm. Collectively, Summerlin and Tomich (28) and Su et al. (29) have compared the features of 462 cases of focal OD with 120 cases of OF. Both are more common in the posterior mandible although a significant number of OFs occur in the maxilla. Both tend to be circumscribed and can be radiolucent, mixed, or radiopaque. Unlike focal OD, OFs grow in a centrifugal pattern,

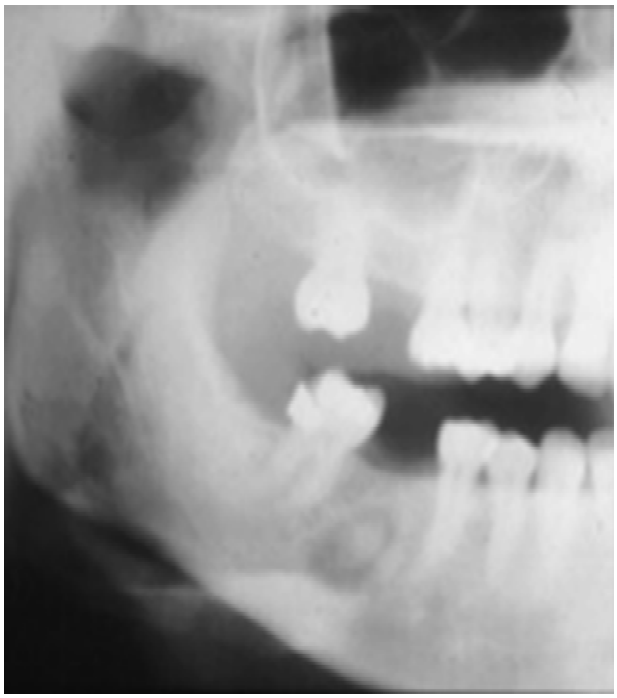

FIG. 6. Focal OD. A solitary, well-demarcated opacity with radiolucent rim in the edentulous mandibular first molar area.

when large cause cortical expansion, and characteristically expand the inferior border of the mandible (Figure 7). Teeth may be displaced and/or show root resorption. A notable difference between focal OD and OF are the intraoperative findings. Ossifying fibromas tend to shell or enucleate out intact as a solid mass (29) (Figure 8), whereas focal ODs are tenaciously adherent to surrounding bone, and as a consequence, are removed in gritty, hemorrhagic tissue fragments. Reasons for these intraoperative and gross findings are supported by the histopathologic findings. As stated previously, the focal OD lesional tissue tends to blend with the cortex and medullary bone (36,37), in contrast to the demarcation (sometimes encapsulation) seen in OF that separates it from adjacent bone (55) (Figure 9). Although there is considerable histologic overlap between focal OD and OF, there are features that are statistically significant between them (29). Focal OD connective-tissue stroma is composed of loose collagen fibers with sinusoidal-like vascularity adjacent to thick curvilinear bony trabeculae and/or irregular-shaped cementoid calcifications (29). Free hemorrhage is interspersed throughout the lesion (29). Simple bone cysts have been encountered in several cases (3,28,47). Ossifying fibromas have a hypovascular,

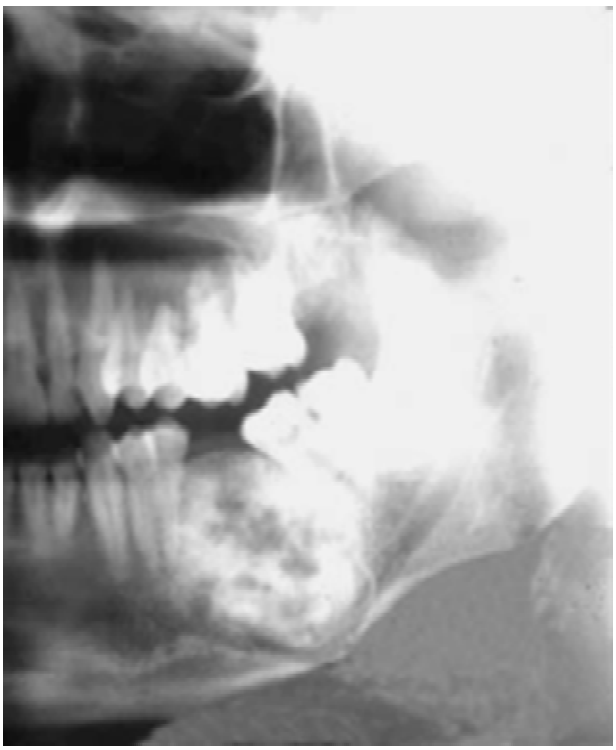

FIG. 7. Ossifying fibroma. A solitary, expansile, demarcated, mixed, radiolucent/radiopaque lesion in the edentulous mandibular first-molar area. Note displacement of adjacent teeth with mild expansion of the crest of the alveolar ridge and inferior border of the mandible.

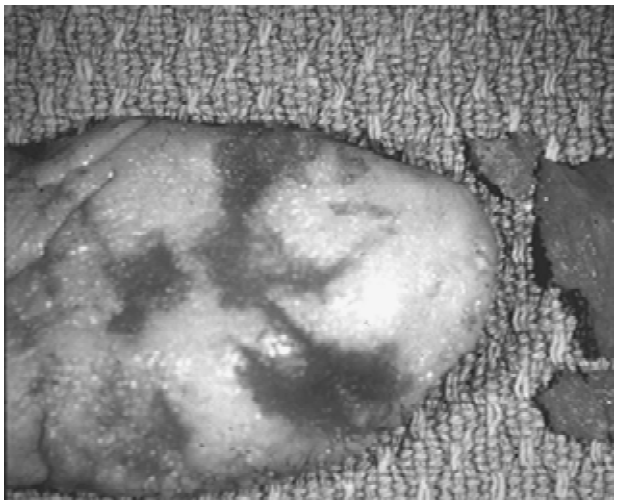

FIG. 8. Ossifying fibroma. Gross appearance of solid mass.

uniform cellular, often storiform stroma with intermixed dense collagen (28,29). The calcified components are thin, separate, bony trabeculae often with osteoblastic rimming and/or ovoid cementoid deposits, sometimes with "brush borders" (29) (Figure 10).

Focal OD requires no treatment once the diagnosis has been established. The lesions typically persist without remarkable change although in the Summerlin and Tomich (28) series two patients subsequently developed florid OD. This progression from a solitary to multiple-site involvement supports focal OD as being part of a spectrum of a unified disease process. In the Summerlin and Tomich (28) series of 221 cases, initial treatment consisted of incomplete curettage. Follow-up revealed all but two patients with asymptomatic residual disease. Further surgical intervention was deemed unnecessary (28).

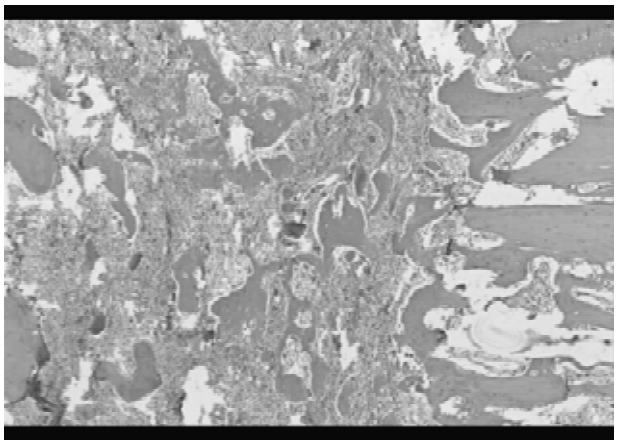

FIG. 9. Ossifying fibroma. There is a clear demarcation between the tumor and surrounding bone.

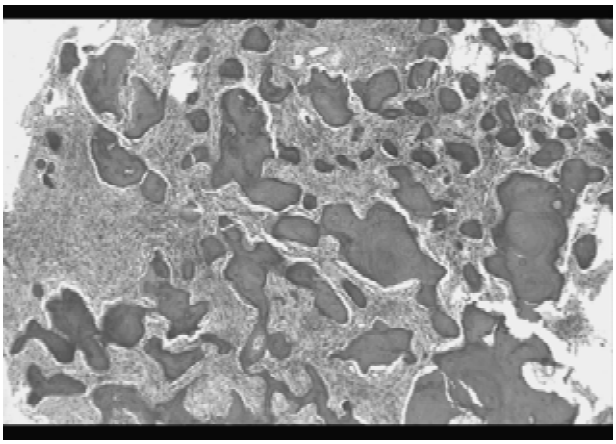

FIG. 10. Ossifying fibroma. Admixture of bony trabeculae and cementum-like deposits in a cellular, dense, collagenous stroma.

Florid osseous dysplasia (florid cemento-osseous dysplasia).

Keys to diagnosis.

Predilection for middle-aged black females
Painless, nonexpansile; involvement of two or more jaw quadrants
Radiographic features are multiple confluent lobular sclerotic masses in tooth-bearing areas
Initially unencapsulated proliferation of cellular fibrous tissue with trabeculae of woven bone and/or oval calcifications without inflammation
Late-stage lesions show acellular, avascular, coalesced sclerotic bony masses
May be associated with superimposed infection and osteomyelitis
Sometimes associated with simple bone cysts (idiopathic bone cavities)

Over the years a confounding number of terms have been applied to florid OD. The terminology that evolved for this diffuse form of OD reflects the disagreements regarding the calcified product as well as the pathologic process involved. Terms proposed have included multiple enostosis, chronic diffuse sclerosing osteomyelitis (CDSO), gigantiform cementoma, and sclerotic cemental masses. However, Melrose et al. (39) eliminated this confusion in their description of 34 cases of a condition they reported as florid OD.

As with the other variants of OD, black females in the fourth and fifth decades, with a mean age of 42 years, have a high predisposition for florid OD (39). Although more common in blacks, florid OD can occur in Caucasians (56) and has been reported in Asians of Chinese (57,58), Japanese (46,59,60), and Singaporean (36) origin. Florid OD has a penchant for bilateral, symmetrical involvement, most often in the mandible, but it is not uncommon for all four quadrants of the jaws to be affected. Many patients are partially or totally edentulous when the condition is first discovered (3). Cortical expansion is usually lacking; if it is present, it is usually of a limited degree. The most common radiographic presentation is multiple confluent sclerotic lobular masses admixed with less well-defined areas of a mixed radiolucent/radiopaque pattern involving edentulous and/or dentulous areas (3) (Figure 11). Only the alveolar processes are involved with the mandibular inferior border and vertical rami spared (39). Well-defined radiolucent areas representing simple bone cysts are a frequent finding in florid OD (39,46,60–62). Large, simple bone cysts may result in cortical expansion. Concomitant periapical OD is found in a significant proportion of patients with florid OD, reinforcing the concept that they are manifestations of the same basic disease process.

Florid OD is a clinical and radiographic diagnosis, especially in those cases without accompanying simple bone cysts. According to Melrose (36), the typical changes of florid OD must be manifest in at least two jaw quadrants to make the clinical diagnosis. In the asymptomatic patient, surgical intervention for diagnostic purposes is not recommended, but follow-up is advocated (3,36). The altered osseous tissue is very susceptible to infection. In fact, inflammation introduced by periodontal disease, periapical pathosis, trauma from removable prosthetic appliances, and surgical procedures can result in the development of acute osteomyelitis with bony sequestration and fistula formation (63). Antibiotic therapy with removal of necrotic bone and debridement may be required. Waldron (3) has warned that even antibiotics and/or surgical excision of the sclerotic bone is not always successful in controlling the complications of infection. The simple bone cysts associated with florid OD do not always respond to the usual recommended treatment of inducing hemorrhage via curettage (36,39).

As alluded to previously, it is important to avoid misinterpreting a secondary osteomyelitis developing in

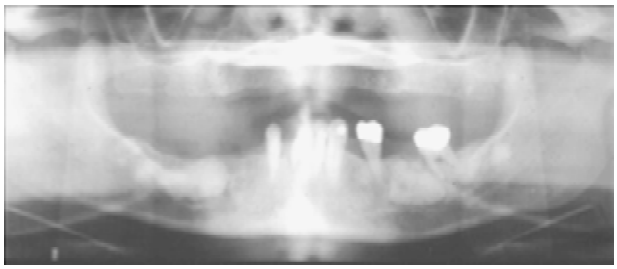

FIG. 11. Florid OD. Diffuse sclerotic masses involving the right and left mandible.

florid OD from an inflammatory condition, such as CDSO. Florid OD and the distinct entity CDSO are frequently confused with each other in part because of the bewildering array of terms that have been used synonymously for both in the past. The differences between the two have been relevantly discussed by Slater (8), Schneider and Mesa (64), and Groot et al. (65). Chronic diffuse sclerosing osteomyelitis is a primary inflammatory condition primarily in the mandible. It is characterized by cyclic episodes of swelling and pain and radiographically exhibits a unilateral, diffuse opacity with poorly defined borders that involve the alveolus to the inferior border and may extend into the ramus (64). Women are affected more often, and a bias for blacks is lacking (64,65). Microscopically, acute inflammation and necrotic bone typically present in osteomyelitis are absent. Slater (8) has enumerated the histologic findings for CDSO:

1. slender osseous trabeculae with osteoblastic rimming,
2. pagetoid coarse trabeculae (evidence of bone turnover),
3. rare small foci of chronic inflammation.

Marx et al. (66), Jacobsson (67), and Jacobsson et al. (68) have discussed the elusive role of bacteria in the etiology of the condition. A variety of treatment modalities have been employed with variable success including antibiotics, corticosteroids, and surgical decortication (8).

Familial gigantiform cementoma (familial florid osseous dysplasia).

Keys to diagnosis.

Autosomal dominant inheritance with variable expressivity
Multiple quadrant involvement of radiopaque lesions similar to florid OD
Variable presence of rapidly expansile lesions, especially in anterior mandible
Onset at young age
No racial predilection
Similar histopathologic features to other osseous dysplasias

A rare hereditary condition with radiographic and histologic features of florid OD has been reported as familial gigantiform cementoma (69–71). It has also been recorded as familial florid cemento-osseous dysplasia (72) and familial florid osseous dysplasia (73). Family pedigrees manifesting the disease include Caucasian (69–71,73), African (72), and Japanese (74). Familial gigantiform cementoma differs from florid OD in several ways:

the lesions evolve during childhood,
no gender or racial predilection exists,
some patients experience relatively rapid-growing expansile lesions resulting in facial deformity while others do not,
a hereditary basis (autosomal dominant with variable phenotypic expression) exists (70,72).

Fibro-Osseous Neoplasms

Conventional ossifying fibroma (cementifying fibroma, cemento-ossifying fibroma).

Keys to diagnosis.

Well demarcated radiographically with smooth, often sclerotic borders
Usually a solitary lesion; majority in mandible
Centrifugal growth pattern (maintains round/oval shape with enlargement)
"Shells out" from surrounding bone intact or in large pieces
Relatively avascular cellular fibrous stroma, often with storiform pattern
Retiform bone trabeculae, some with osteoblastic rimming and/or cementumlike spherules

It is now well accepted that OF is a distinct entity separate from both focal OD (28–30) and FD (3,21,55) although skeptics remain regarding the latter (77). Chromosomal abnormalities have been identified in an ossifying fibroma (75) and a cementifying fibroma (76). Differentiation of OF from focal OD and FD is important because of differences in treatment and prognosis. The OF is a true neoplasm that demonstrates a demarcated or, rarely, an encapsulated proliferation of cellular fibrous connective tissue with varying amounts of osseous products, which include bone and/or spherical calcifications (35,55). Ossifying fibroma is the preferred term regardless of the product, be it bone, spherical (cementum-like) calcifications, or a mixture of both. Attempts to establish criteria for distinguishing between OF, cementifying fibroma, and cemento-ossifying fibroma only add to the confusion (78). Ossifying fibroma is confined to the jaws and craniofacial complex. However, there have been similar cases reported in long bones (14–17). Summerlin and Tomich (28) and Su et al. (29, 30) have presented collectively an excellent detailed analysis of 120 OFs of the jaws. Collective demographics from four studies involving 202 jaw OFs found presentation most commonly in the 2nd through 4th decades with a mean age of 32

(13,28,30,79). Over 70% of the patients were female. The racial distribution was decidedly white (58%), followed by blacks (23%). A minimum of 12% were Hispanic. Lesions were most frequently in the mandible (77%), specifically the molar region, followed by the premolar region. Radiologic features are that of a well-circumscribed lesion with smooth, often sclerotic borders. It is usually unilocular although multilocularity has been reported (79,80). Appearance is dependent on the maturity of the lesion, i.e., purely radiolucent, mixed (radiopaque foci admixed with radiolucent areas), or radiopaque (81). Centrifugal growth will commonly cause bowing of the inferior border of the mandible (28,80). Resorption and/or divergence of tooth roots can occur with continued growth of the neoplasm.

As stated previously, the studies of Summerlin and Tomich and Su et al. (29,30) have been instrumental in expanding one's knowledge of ossifying fibroma and, in particular, one's ability to discern it from focal OD. At surgery, the OF tends to shell away from the surrounding bone intact or in large pieces. This feature, along with the microscopic evidence of demarcation, serves to characterize it from focal OD and FD. Accordingly, biopsies preserving the cortical-lesional relationship are invaluable in the histologic interpretation of OF, focal OD, and FD. Ossifying fibroma consists of dense fibrous connective tissue with varying degrees of cellularity. It is frequently hypercellular with numerous spindle-shaped fibroblasts which often have a storiform pattern (3,28,29) (Figure 12). An occasional multinucleated giant cell may be seen. The stroma is relatively avascular, but the blood vessels are ovoid and regular in shape and are not closely associated with the bony elements (28,29) (Figure 12). The calcified components consist of thin separate trabeculae of woven bone that may be rimmed by osteoblasts (Figure 12). The bony trabeculae may present in a retiform pattern (29,45). Lamellar bone can be present but is not a constant finding (45). Cementum-like deposits of cellular or acellular spherules may also be present, either alone or in combination with the bony trabecular component (3,29). Nevertheless, despite these seemingly straightforward criteria for OF, significant histologic overlap with focal OD and FD exists (3,12,21,29). Clinical and radiographic features as well as surgical and gross findings must be correlated with the histologic findings.

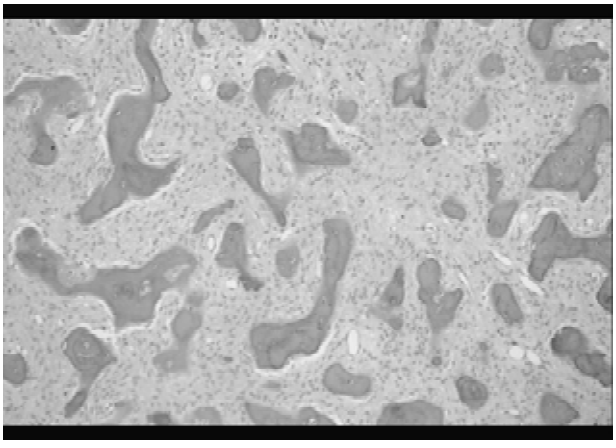

FIG. 12. Ossifying fibroma. Cellular fibrous stroma with isolated blood vessels and an occasional giant cell. Thin trabeculae of woven bone are interspersed throughout.

There are numerous case reports on OF with adequate follow-up data documenting its uncertain behavior. Growth rate is unpredictable and may be slow and steady or rapid (82–87). Cases with multiple recurrences have been recorded (13,88,89), and, though there are no clinical or histologic features to predict behavior, a few series provide detailed information regarding recurrent lesions. Recurrence rates have varied from less than 1% (18,45, 79,90) to 13% (91), 25% (92), 28% (13), 30% (93), and 63% (88). Some of these aforementioned series considered only mandibular and maxillary lesions, some of which included antral involvement (13,18,45,79,88,90, 92), while others considered sinonasal, craniofacial, and jaw sites (91,93). Adding to the problem is the likelihood that focal OD has been included in previous studies of OF involving the jaws, thereby distorting the data for the behavior and recurrence rate of the latter (28).

Complete surgical excision is recommended for OF. Circumscription of the neoplasm allows surgical removal with relative ease (94). Therefore, simple enucleation/curettage is the initial treatment of choice in uncomplicated jaw cases (13,63). On the other hand, lesions demonstrating aggressive features require a more extensive surgical resection (13,63). The anatomic site of the tumor can play a role in the aggressiveness and propensity for recurrence as it can in craniofacial bones and may dictate a more radical surgical approach (95).

Other clinical variations of OF have been reported, including multiple ossifying fibromas (96–99) and familial ossifying fibromas (100), but these are rare. The idea of a purported giant ossifying fibroma as a form of OF has been put forth although no exact definition has been offered (98,101). van Heerden et al. (101) reported eight cases that were all greater than 8 cm in diameter. Distinguishing features are pronounced fibroblastic activity at the expense of osteoblastic activity resulting in a radiographic picture of relatively fewer calcifications than one would expect in a smaller OF.

So-called "juvenile," "active," or "aggressive" forms of ossifying fibroma. Within the confusing ar-

ray of fibro-osseous lesions, the so-called juvenile active ossifying fibroma (JAOF) is perhaps the most enigmatic. Pathologists considering such a diagnosis are faced with a plethora of subjective and arbitrary criteria and will find little consolation in the literature. Occupying a subset within the spectrum of OF, JAOF is considered by many to be a unique lesion because of its reported tendency to occur in children and adolescents, its more complex histologic features, and its purported tendency for locally aggressive growth. However, the literature on this entity indicates that

1. not all JAOFs are diagnosed in children and adolescents,
2. not all JAOFs exhibit locally aggressive behavior,
3. not all lesions reported as JAOF have the same histopathologic features.

At this time, there is no general agreement among pathologists with regard to the proper terminology, histopathologic features, or criteria for separating these lesions from conventional ossifying (cemento-ossifying) fibromas (2,3,37,102).

Lent C. Johnson of the Armed Forces Institute of Pathology formally introduced the term JAOF at a College of American Pathologists Seminar in 1952 (103). At that time, Johnson was apparently using the term to describe locally aggressive lesions that occur most often in the maxilla during the first two decades of life and contain trabeculae of so-called "paint brush" osteoid in a cellular fibrous stroma. He stated that the osteoid in these tumors resembled the osteoid seen in osteosarcomas (104). However, in the definitive 1991 paper, Johnson et al. (31) reserved the term JAOF for lesions containing "spherical ossicles of uniform size, an intensely cellular stroma, and myxomatous material, which may degenerate to form cysts."

To add to the confusion, the World Health Organization (WHO) (55) has recently set forth histologic criteria for JAOF that does not include spherical ossicles at all. The WHO definition states that JAOF is "an actively growing lesion mainly affecting individuals below the age of 15 years, which is composed of a cell-rich fibrous tissue containing bands of cellular osteoid without osteoblastic rimming together with trabeculae of more typical woven bone. Small foci of giant cells may be present, and in some parts, there may be abundant osteoclasts related to the woven bone. Usually no fibrous capsule can be demonstrated, but the lesion is well demarcated from the surrounding bone." This definition seems to correspond more closely with the original description by Johnson (103,104). Therefore, two different histologic patterns have been described for lesions designated as JAOF. Whether these two patterns are variants of a single lesion or represent separate entities is undecided at this time (37). Makek (27) considers them to be two variants of the same lesion and prefers the designations trabecular desmo-osteoblastoma and psammous desmo-osteoblastoma, reflecting his belief that these are lesions of osteoblastic origin that arise in the desmal preformed (intramembranous) bones of the jaws and skull. Slootweg et al. (105) consider them separate entities and prefer to restrict the term juvenile ossifying fibroma to lesions that correspond to the WHO definition. They consider lesions containing spherical (psammomatoid) ossicles to be variants of cemento-ossifying fibroma (105,106); Margo et al. (107) and Wenig et al. (32) prefer to call such lesions psammomatoid ossifying fibromas. Eversole (35) also discusses this nosologic dilemma pointing out that lesions containing rounded ossicles are often called cementifying fibromas or cemento-ossifying fibromas when they are in the jaws and psammomatoid ossifying fibromas when they are in the parasinonasal facial bones or cranial bones. In our opinion, the clinical and radiographic characteristics of trabecular and psammomatoid lesions show enough similarity and sufficient overlap in histopathologic features to warrant their consideration as variants of the same tumor. However, the reliable separation of these variants from conventional OF on histologic grounds often remains an exercise in futility. Therefore, strictly for the purposes of discussion and case retrieval from the literature, lesions reported as JAOF, aggressive OF, or other related terms are hereby divided into two groups:

1. JAOF, trabecular variant, are those that correspond to the WHO definition,
2. JAOF, psammomatoid variant, are those that correspond to the 1991 definition of Johnson et al. (31) and contain spherical ossicles.

JAOF, trabecular variant.

Keys to diagnosis.

Usual onset in childhood or adolescence
Usual location in jaws with slight maxillary predominance
Well demarcated radiographically; radiolucent with small opacities or ground glass
Highly cellular fibrous stroma with "garlandlike" strands of cellular osteoid
Variable presence of clustered multinucleated giant cells
Variable presence of myxoid areas with cystic degeneration

A selected literature review yielded 92 cases of the trabecular variant of JAOF (6,27,105,108,109). Patient ages range from 2–25 years with the majority of cases being diagnosed before 15 years of age. There is a slight male predominance with 57% of the cases occurring in males and a male-to-female ratio of 1.3/1. The maxilla is the most common site (54%), followed by the mandible (35%), and the fronto-ethmoid complex (9%). The lesions typically present as a swelling or mass. Symptoms are related to the site of involvement and include epistaxis, proptosis, exophthalmos, and diplopia. Pain is only rarely described. The growth rate is variable with some cases progressing slowly but others, particularly those in young children, often progressing very rapidly. Radiographic studies usually show a well-defined unilocular or multilocular radiolucent lesion that may contain fine specks of radiopacity. Some lesions may demonstrate a "ground-glass" appearance. Microscopically, the tumor is composed of a highly cellular stroma with little tendency to form collagen. The tumor has thin garland-like strands of cellular osteoid, which may bear some resemblance to the osteoid in an osteosarcoma (Figure 13). The osteoid strands are surrounded by osteoblasts, some of which may be incorporated into the osteoid. Incipient trabecular formation, clusters of multinucleated giant cells (Figure 14), and myxoid areas with cystic degeneration may also be observed. Small foci of concentrically lamellated particles may rarely be seen (105). Mitoses may be observed, but are not numerous. These tumors have a tendency for local recurrence with reported rates ranging from 25% to 58%. However, radical surgery does not appear to be appropriate because recurrences may be managed by local excision and sarcomatous transformation has not been reported.

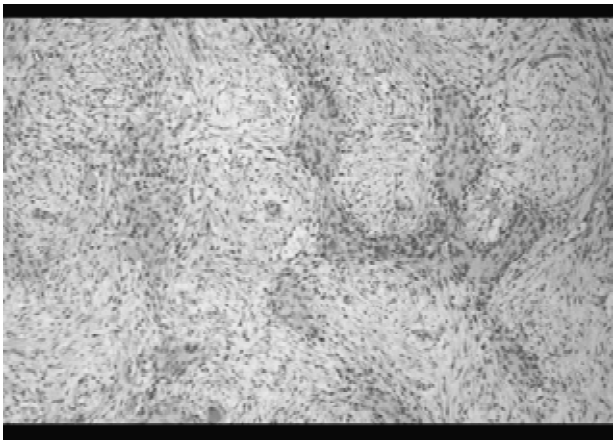

FIG. 13. Juvenile active ossifying fibroma, trabecular variant. Anastomosing garland-like strands of osteoid trabeculae in a hypercellular stroma.

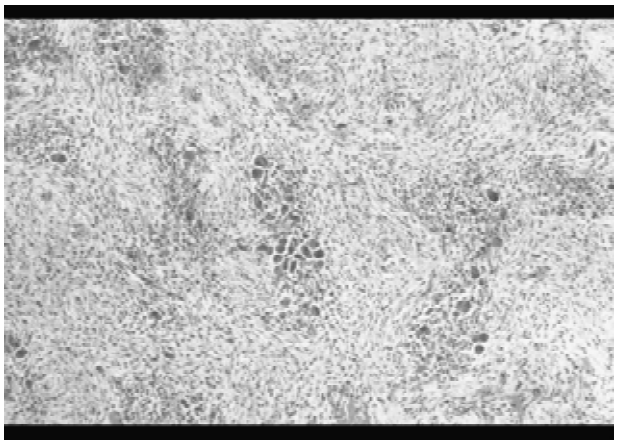

FIG. 14. Juvenile active ossifying fibroma, trabecular variant. Foci of multinucleated giant cells in a cellular stroma.

JAOF, psammomatoid variant.

Keys to diagnosis.

Majority of cases with onset in childhood or adolescence; however, some in adults
Usual location in orbit or paranasal sinuses
Well demarcated radiographically; mixed density with loculated radiolucent areas or clouding of sinus
Highly cellular fibrous stroma often with whorled pattern containing closely packed spherical ossicles resembling psammoma bodies
Definite myxoid component with variable presence of threadlike or thorn-shaped calcifications
Aneurysmal-bone cystlike areas (blood-filled cysts and multinucleated giant cells)

A selected review of the literature yielded 239 cases of the psammomatoid variant of JAOF (27,31,32,105–107,110,111). The majority of cases are diagnosed in patients 5–15 years of age; however, the age range is much wider than for the trabecular variant. In several series, the upper range of patient ages was in the 5th or 6th decade. Johnson et al. (31) reported an age range of 3 months to 72 years with a mean of 21 years. Males outnumbered females by a ratio of 1.2:1. The orbit and paranasal sinuses are the most common sites, accounting for over 72% of reported cases, followed by the calvarium (11%), maxilla (10%), and mandible (7%). Symptoms may include exophthalmos, bulbar displacement, proptosis, impaired vision, facial swelling, nasal obstruction, periorbital pain, headache, and sinusitis. The lesions most often display a steady progressive growth with more rapid expansion sometimes noted, usually in cases arising in infancy. Radiographically, the lesions are usually well delineated at the periphery with varying

degrees of radiolucency and radiopacity. Mixed-density lesions with areas of polycyclic (loculated) radiolucency are typical in cases involving the cranial vault. Clouding of the sinuses resembling sinusitis may also be seen. Microscopically, the lesions are composed of a cell-rich fibrous stroma, which may display a whorled appearance. Variable numbers of relatively acellular rounded calcifications resembling psammoma bodies are embedded in the stroma (Figure 15). In some tumors, these rounded ossicles (cementicles) may be very closely packed with little intervening stroma. An eosinophilic rim is present at the periphery of most of the ossicles. In areas, the ossicles may connect to form trabecular structures. Some lesions may also contain acellular mineralized deposits with bizarre shapes described as threadlike or thorn-shaped (27,31). These unusual calcified structures are seen most often in the myxoid portion of the tumor. The myxoid component is usually separate from the more cellular stroma (Figure 16). Johnson et al. (31) considers this myxoid tissue to be an integral part of the tumor and not merely a reactive or degenerative phenomenon. In fact, he believes that sinus lesions arise from the myxoid mucoperiosteum and that mandibular lesions arise from the myxoid dental papilla. These myxoid areas may undergo cystic change with edema, hemorrhage, and clusters of multinucleated giant cells; these areas, therefore, bear some resemblance to aneurysmal bone cyst. Mitotic figures may be seen, but are never prominent. Some lesions may be difficult to separate from conventional ossifying (cemento-ossifying) fibroma on histologic grounds; however, the extremely cellular stroma with closely packed ossicles and the myxoid areas with hemorrhage, multinucleated giant cells, and cystic degeneration are not typically seen in conventional ossifying (cemento-ossifying) fibroma. The psammomatoid JAOF appears to be best managed by conservative excision although lesions that involve the orbit or cranial vault may necessitate rather extensive surgery to assure complete removal. Recurrence rates of 20% to 56% have been reported. In Johnson's series (31), 90% of recurrent lesions occurred in patients under 10 years of age.

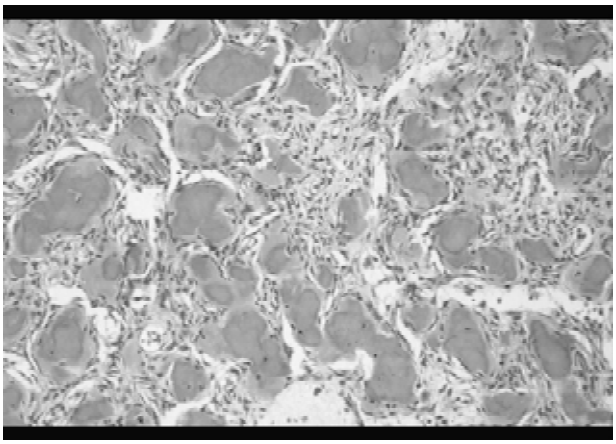

FIG. 15. Juvenile active ossifying fibroma, psammomatoid variant composed of acellular ossicles or psammomatoid bodies.

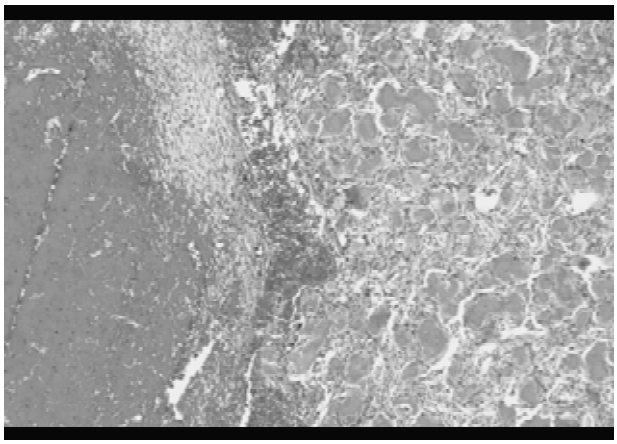

FIG. 16. Juvenile active ossifying fibroma, psammomatoid variant. Myxoid tissue with cystic degeneration and hemorrhage in area of ossicles.

In summary, both variants of JAOF, trabecular and psammomatoid, tend to occur at an earlier age than conventional OF. Both variants involve the craniofacial bones with the trabecular variant being more common in the jaws and the psammomatoid variant being more common in the paranasal sinuses and periorbital bones. Psammomatoid JAOF appears to be the more common tumor based on reported cases. No definitive predictor variables with regard to histopathologic features of JAOF have been uncovered to aid in determining the potential for aggressive behavior or propensity for recurrence (13). Although significant recurrence rates have been reported, assured conservative excision is the treatment of choice. Surgical approach is dictated more by anatomic location and tumor size than histologic subtype. Local re-excision can usually manage recurrence. Malignant transformation has not been reported.

For the surgical pathologist, the dilemma of how to reliably distinguish these lesions from conventional OF still exists. Such an exercise is often difficult, arbitrary, and may not be of added value to the surgeon. It is well known that OFs may sometimes attain a very large size, but may not differ histologically from lesions displaying limited growth (101,112). Furthermore, the histologic features that supposedly set JAOF apart, such as the extremely cellular stroma, spherical ossicles, and garland-like strands of cellular osteoid, may be quite variable from one tumor to another, from field to field within the

same tumor, and may even be observed focally in conventional OFs (13). Moreover, the myxoid tissue, cystic degeneration, and aneurysmal-bone cystlike areas characteristic of some JAOFs may simply be reactive changes and may not be specific for JAOF (10). As with all lesions involving bone, the clinical and radiographic characteristics must be taken into account when rendering the microscopic diagnosis. Although the histopathologic characteristics, when combined with the clinical and radiographic features, may sometimes be sufficient to permit distinction of JAOF from conventional OF, there are many cases that defy such pigeonholing. The literature indicates that the diagnosis of JAOF is sometimes more dependent on age, location, and behavior than histomorphology. Until more clarification is attained and agreement reached on the histologic criteria for JAOF, perhaps the most prudent way to handle these tumors would simply be to assign them the diagnosis of "ossifying fibroma" with an accompanying comment that certain histologic features (i.e., hypercellular stroma, psammomatoid ossicles, garland-like strands of cellular osteoid, and myxoid tissue) are sometimes associated with locally aggressive or destructive behavior. Because the initial treatment for ***all*** OFs is assured complete surgical excision and because follow-up is recommended for all, the necessity of the diagnosis "JAOF" may be unwarranted.

Fibrous Dysplasia

Fibrous dysplasia is considered to be a developmental, tumorlike (hamartomatous), fibro-osseous disease of unknown etiology (3). However, Cohen and Howell (113) have recently advanced the theory that somatic mutations in the GNAS1 gene cause monostotic FD, polyostotic FD, and McCune–Albright syndrome. Mertens et al. (114) found clonal structural chromosomal aberrations in a case of monostotic FD suggesting a neoplastic process. There are four main clinical subtypes of FD: monostotic FD, which affects one bone; polyostotic, which affects multiple bones; McCune–Albright syndrome in which multiple disseminated lesions of bone are accompanied by skin hyperpigmentation and endocrine disturbances, which present as precocious puberty and/or hyperthyroidism; and a craniofacial form that is confined to bones of the craniofacial complex (115). The remainder of the discussion concerns the craniofacial form of FD.

Craniofacial fibrous dysplasia.

Keys to diagnosis.

Onset during 1st and 2nd decades, painless swelling of involved bone

Typically contiguous involvement of maxillofacial and cranial bones

Radiographic appearance reflects histologic features, ground-glass opacity without defined borders

Curvilinear woven bone trabeculae with minimal-to-no osteoblastic rimming in cellular fibrous stroma blending into surrounding cancellous and cortical bone

Some lamellar bone formation is acceptable; ovoid calcifications are rare

The jaws and skull are commonly affected in monostotic FD. Though mandibular lesions may be purely monostotic, the classification of the more commonly involved lesions of the maxilla is not as clear-cut. When the maxilla is affected, adjacent bones, such as the zygoma and sphenoid, may also be involved, precluding a strict monostotic interpretation (3,116). Other common patterns of contiguous involvement include maxilla-zygoma-sphenoid-frontal-nasal bones and frontal-sphenoid-temporal-zygoma bones (117). Fibrous dysplasia may also affect base-of-the-skull and orbital bones (117). Because lesional distribution is restricted to contiguous bones within a defined anatomical area, the pattern is not typically associated with polyostotic disease (116). Therefore, the term craniofacial FD is appropriate for these lesions (3,116).

Clinically, craniofacial FD presents as a painless enlargement of the affected bone, most often during the first and second decades of life. There is a maxillary predominance when craniofacial FD occurs in the jaws and the maxillary sinus is commonly involved. Although early lesions may be radiolucent, more typically the lesion is a ground-glass opacification with indistinct borders that blend into the surrounding uninvolved bone (Figure 17). This blending is in contrast to the radiographically well-defined OF and is an important distinguishing feature. As Waldron (3) maintained, the most characteristic radiographic feature of craniofacial FD of the skull is increased radiodensity of the skull base involving occiput, sella tursica, orbital roof, and frontal bones.

Eversole (35) defines craniofacial FD histologically as a benign, nonneoplastic, intramedullary, cellular proliferation of fibroblasts, with formation of irregular trabeculae of bone or ovoid calcifications that show indistinct, nonencapsulated borders (Figure 18). Others have described craniofacial FD as demonstrating irregular-shaped woven-bone trabeculae, often with curvilinear shapes resembling Chinese characters (3,8) (Figure 19). Residing in a cellular, fibrous connective-tissue stroma, these delicate trabeculae are without osteoid rims and have minimal to no osteoblastic rimming (3,10). Patholo-

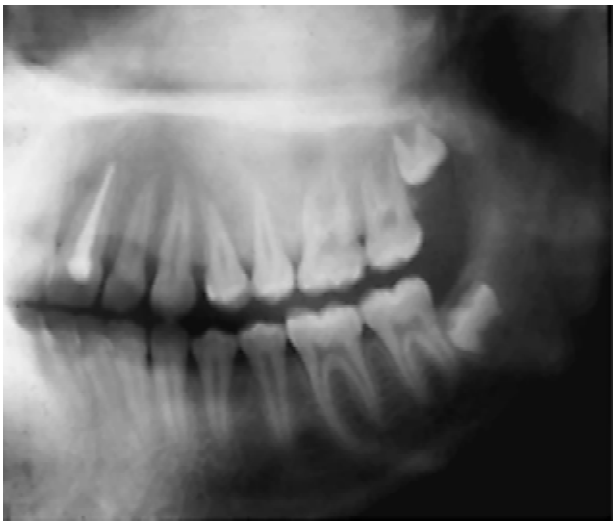

FIG. 17. Craniofacial FD. A cropped panograph showing a diffuse ground-glass radiopaque lesion of the posterior maxilla and antrum.

gists have not yet agreed on whether or not the bone in FD can exhibit a retiform pattern (3,35). Small ovoid calcifications may be present but are never numerous (10). In contrast to long-bone FD, craniofacial FD may undergo progressive lamellar-bone maturation with trabeculae often arranged in parallel fashion in moderately cellular fibrous connective tissue (3). Most helpful in the microscopic interpretation of FD is that lesional bone fuses with adjacent uninvolved cancellous and cortical bone (10) (Figure 20). This histologic feature is reflected in the radiographic appearance. Both findings are essential in ruling out OF. We are in agreement with Slootweg (10): small incisional biopsy specimens and curettings that do not demonstrate this interface between lesion and normal bone, can preclude definitive diagnosis for

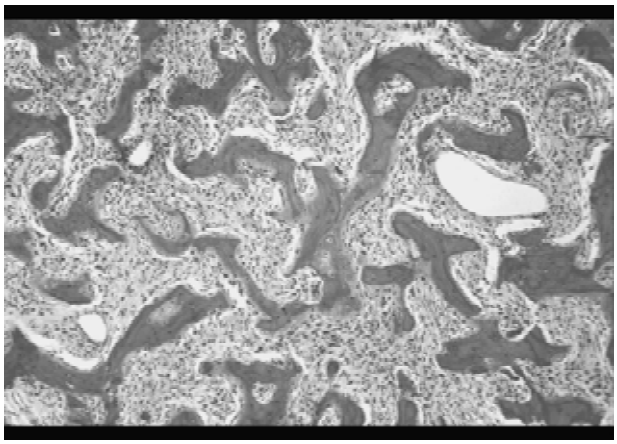

FIG. 19. Craniofacial FD. Irregular-shaped woven-bone trabeculae sans osteoblastic rimming. Bone resembles Chinese characters.

both craniofacial FD and OF. Granted, the separation of craniofacial FD from OF has become easier in most cases because other fibro-osseous lesions with their own defining features have been identified (3,10,35). Nevertheless, more often than not, distinguishing craniofacial FD from OF solely on histopathologic grounds has limitations (2,12,93). In addition to OF, a primary consideration in the histologic differential diagnosis of craniofacial FD is the low-grade intraosseous well-differentiated osteosarcoma. Kurt et al. (118) have discussed the subtleties in distinguishing this rare variant of osteosarcoma from FD. Correlation of the histopathology with the clinical, surgical, and radiographic findings is the standard for diagnosis.

Enlargement of craniofacial FD occurs during active skeletal growth and ceases with skeletal maturation; however, periods of regrowth may be experienced in adulthood for unknown reasons. With the exception of

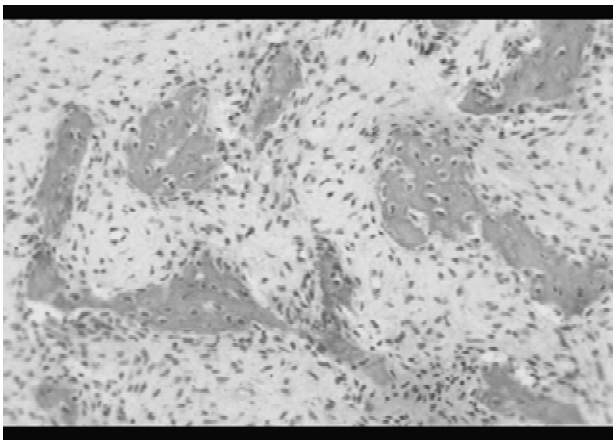

FIG. 18. Craniofacial FD. Cellular fibrous element and irregular trabeculae-containing lacunae.

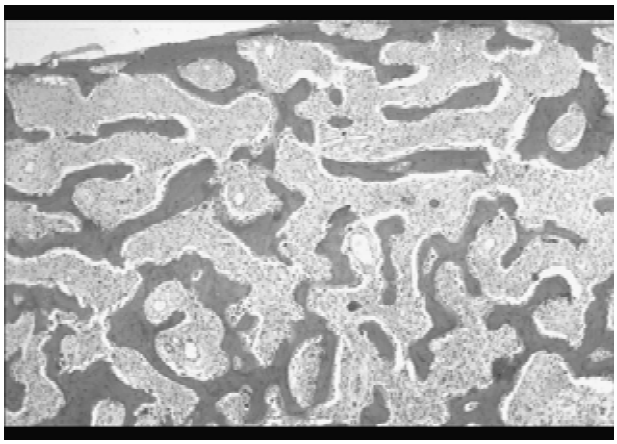

FIG. 20. Craniofacial FD. Lesional tissue fusing with bony cortex in upper left corner.

small mandibular lesions amenable to surgical resection, the treatment goal has been one of conservatism because of the large size and diffuse nature of the lesion, especially in the maxillary complex (3). Treatment for those lesions that have caused functional and/or cosmetic disfigurement necessitate surgical contouring without complete removal, especially in the young patient with related psychological disturbances. Regrowth can be expected in the 25%–50% range following contouring procedures (3). Several investigators have presented more aggressive surgical procedures and their indications (8,119-121).

Although rare, sarcomas can arise in craniofacial FD, usually osteosarcomas or fibrosarcomas (122–126). Most have occurred in patients who had received radiation therapy (127), but spontaneous sarcomatous transformation can occur (123). There is no conclusive evidence that FD is a premalignant disease. Unexplained, progressive, and often rapid enlargement resulting in grotesque features occasionally occur in otherwise histologically benign craniofacial FD (128–130). Aggressive, juvenile aggressive, and progressive are terms that have been applied to these clinically persistent, often relentless cases of craniofacial FD (35).

CONCLUSIONS

Nomenclature for the bone lesions collectively known as BFOL has historically been inconsistent, confusing, and downright aggravating. Significant progress has been achieved in recent years in understanding the histogenetic and pathogenetic similarities and differences of the various fibro-osseous lesions, thereby enhancing one's ability to diagnose accurately and to manage many specific conditions, including craniofacial FD, OF, focal OD, and florid OD. There is still a need for clarification of many aspects of this perplexing group of lesions. Elimination of confusing clinical terminology, such as "juvenile" and "aggressive," in histologic diagnoses, and questionable terms, such as "cemento-" and "cementifying," for bone-forming neoplasms, would be a start in clearing the air.

Investigators should accept and utilize only scientifically-documented data. Unfortunately, the perpetuation of an "entity"—the JAOF—that remained unpublished by Johnson for 39 years has resulted in the JAOF being attributed with many proposed and subjective characteristics. The efforts of some to jump on the bandwagon and publish cases on this ill-defined "entity" and to use a bewildering array of descriptive adjectives or modifiers have resulted in a rush to general acceptance, which has only furthered its ambiguity and controversy.

Last, the surgical pathologist must demand and correlate all relevant data (clinical information, radiographs/images, surgical/gross findings, histology) in order to avoid misinterpretation of this group of histologically similar, but clinically distinct, bone lesions.

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

The authors wish to acknowledge Michael Higgins, editorial consultant, and Maureen Raymond, computer services software supporter, for their assistance in the preparation of this manuscript. Both are with the Louisiana State University School of Dentistry, New Orleans, LA.

REFERENCES

1. Eisenberg E, Eisenbud L. Benign fibro-osseous disease. Current concepts in historical perspective. *Oral Maxillofac Surg Clin North Am* 1997;9:551–62.
2. Waldron CA. Fibro-osseous lesions of the jaws. *J Oral Maxillofac Surg* 1985;43:249–62.
3. Waldron CA. Fibro-osseous lesions of the jaws. *J Oral Maxillofac Surg* 1993;51:828–35.
4. Waldron CA. Bone pathology. In: Neville BW, Damm DD, Allen CM, Bouquot JE, eds. *Oral & maxillofacial pathology*. Philadelphia: WB Saunders, 1995:443–92.
5. Margo CE, Ragsdale BD, Perman KI, et al. Psammomatoid (juvenile) ossifying fibroma of the orbit. *Ophthalmology* 1985;92: 150–9.
6. Slootweg PJ, Muller H. Differential diagnosis of fibro-osseous lesions. A histological investigation on 30 cases. *J Craniomaxillofac Surg* 1990;18:210–4.
7. Pecaro BC. Fibro-osseous lesions of the head and neck. *Otolaryngol Clin North Am* 1986;19:489–96.
8. Slater LJ. Fibro-osseous lesions. *Oral and Maxillofacial Surgery Knowledge Update,* 1995;1(Part II):33–47.
9. Yoon JH, Kim J, Lee CK, et al. Clinical and histopathological study of fibro-osseous lesions of the jaws. *Yonsei Med J* 1989; 30:133–43.
10. Slootweg PJ. Maxillofacial fibro-osseous lesions: classification and differential diagnosis. *Semin Diagn Pathol* 1996;13:102–12.
11. Craig RG. Cementum versus bone. *Oral Maxillofacial Surg Clin North Am* 1997;9:581–95.
12. Fechner RE. Problematic lesions of the craniofacial bones. *Am J Surg Pathol* 1989;13(Suppl 1):17–30.
13. Eversole LR, Leider AS, Nelson K. Ossifying fibroma: a clinicopathologic study of sixty-four cases. *Oral Surg Oral Med Oral Pathol* 1985;60:505–11.
14. Friedman NB, Goldman RL. Cementoma of long bones-an extragnathic odontogenic tumor. *Clin Orthop* 1969;67:243–8.
15. Sissons HA, Kancherla PL, Lehman WB. Ossifying fibroma of bone: report of two cases. *Bull Hosp Joint Dis* 1983;43:1–13.
16. Sissons HA, Steiner GC, Dorfman HD. Calcified spherules in fibro-osseous lesions of bone. *Arch Pathol Lab Med* 1993;117: 284–90.
17. Povysil C, Matejovsky Z. Fibro-osseous lesion with calcified spherules (cementifying fibromalike lesion) of the tibia. *Ultrastruct Pathol* 1993;17:25–34.
18. Hamner JE, Scofield HH, Cornyn J. Benign fibro-osseous jaw lesions of periodontal membrane origin: an analysis of 249 cases. *Cancer* 1968;22:861–78.
19. Giansanti JS. The pattern and width of the collagen bundles in

bone and cementum. *Oral Surg Oral Med Oral Pathol* 1970;30: 508–14.
20. Giansanti JS. The effects of acids upon the pathologic interpretation of the widths of the collagen bundles in bone. *Oral Surg Oral Med Oral Pathol* 1970;30:151–7.
21. Eversole LR, Sabes WR, Rovin S. Fibrous dysplasia: a nosologic problem in the diagnosis of fibro-osseous lesions of the jaws. *J Oral Pathol* 1972;1:189–220.
22. Storkel S, Wagner W, Makek MS. Psammous desmo-osteoblastoma: ultrastructural and immunohistochemical evidence for an osteogenic histogenesis. *Virchows Arch A* 1987;411: 561–8.
23. Landesberg R, Takeuchi E, Zaslow M, et al. Immunolocalization of bone associated proteins in fibrous dysplasia, ossifying fibroma and cementifying fibroma [abstract]. *J Oral Maxillofac Surg* 1995;53(Suppl 4):85.
24. Edwards PA, Corio RL. Benign fibro-osseous lesions of the jaws. *Ear Nose Throat J* 1984:383–92.
25. Eversole LR. *Clinical outline of oral pathology: diagnosis and treatment.* 3rd ed. Philadelphia: Lea & Febiger, 1992: 436.
26. Sapp JP, Eversole, LR, Wysocki GP. Contemporary oral and maxillofacial pathology. St. Louis: Mosby, 1997: 88–125.
27. Makek MS. So called "fibro-osseous lesions" of tumorous origin: biology confronts terminology. *J Craniomaxillofac Surg* 1987; 15:154–68.
28. Summerlin DJ, Tomich CE. Focal cemento-osseous dysplasia: a clinicopathologic study of 221 cases. *Oral Surg Oral Med Oral Pathol* 1994;78:611–20.
29. Su L, Weathers DR, Waldron CA. Distinguishing features of focal cemento-osseous dysplasias and cemento-ossifying fibromas I. A pathologic spectrum of 316 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997;84:301–9.
30. Su L, Weathers DR, Waldron CA. Distinguishing features of focal cemento-osseous dysplasia and cemento-ossifying fibromas II. A clinical and radiologic spectrum of 316 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997;84:540–9.
31. Johnson LC, Yousefi M, Vinh TN, et al. Juvenile active ossifying fibroma: its nature, dynamics and origin. *Acta Otolaryngol (Stockh)* 1991;488(suppl):3–40.
32. Wenig BM, Vinh TN, Smirniotopoulos JG, et al. Aggressive psammomatoid ossifying fibromas of the sinonasal region. *Cancer* 1995;76:1155–65.
33. Cawson RA, Binnie WH, Speight PM, et al. *Lucas's pathology of tumors of the oral tissues.* 5th ed. London: Churchill Livingstone, 1998:89–93.
34. Pindborg JJ, Kramer IRH, Torloni H. Histological typing of odontogenic tumours, jaw cysts, and allied lesions. In: *WHO International Histological Classification of Tumours*. Geneva: Roto-Sadg S.A., 1971: 37–8.
35. Eversole LR. Craniofacial fibrous dysplasia and ossifying fibroma. *Oral Maxillofac Surg Clin North Am* 1997;9:625–42.
36. Melrose RJ. The clinico-pathologic spectrum of cemento-osseous dyspalsia. *Oral Maxillofacial Surg Clin North Am* 1997;9: 643–53.
37. Odell EW, Morgan PR. *Biopsy Pathology of the Oral Tissues. Biopsy Pathology Series 22*. London: Chapman & Hall Medical, 1998: 271–88.
38. Robinson HBG. Osseous dysplasia-a reaction of bone to injury. *J Oral Surg* 1956;14:3–14.
39. Melrose RJ, Abrams AM, Mills BG. Florid osseous dysplasia. *Oral Surg Oral Med Oral Pathol* 1976;41:62–82.
40. Zegarelli EV, Kutscher AH, Naploi N, et al. The cementoma-a study of 230 patients with 435 cementomas. *Oral Surg Oral Med Oral Pathol* 1964;17:219–24.
41. Zegarelli EV, Kutscher AH, Budowsky J, et al. The progressive calcification of the cementoma-a roentgenographic study. *Oral Surg Oral Med Oral Pathol* 1964;18:180–3.
42. Ackerman GL, Altini M. The cementomas-a clinicopathologic study re-appraisal. *J Dent Assoc S Africa* 1992;47:187–94.
43. Eversole LR. Benign fibro-osseos lesions of the jaws: nosology revisited [abstract]. *Oral Surg Oral Med Oral Pathol* 1989;68: 598.
44. Cho M-I, Garant PR, Lee YL. Periodontal ligament fibroblasts, preosteoblasts, and prechondrocytes express receptors for epidermal growth factor in vivo: a comparative radioautographic study. *J Periodontal Res* 1988;23:287–94.
45. Waldron CA, Giansanti JS. Benign fibro-osseous lesions of the jaws: a clinical-radiologic-histologic review of sixty-five cases. Part II. Benign fibro-osseous lesions of periodontal ligament origin. *Oral Surg Oral Med Oral Pathol* 1973;35:340–50.
46. Ariji Y, Ariji E, Higuchi Y, et al. Florid cemento-osseous dysplasia. Radiographic study with special emphasis on computed tomography. *Oral Surg Oral Med Oral Pathol* 1994;78:391–6.
47. Higuchi Y, Nakamura N, Tashiro H. Clinicopathologic study of cemento-osseous dysplasia producing cysts of the mandible-report of four cases. *Oral Surg Oral Med Oral Pathol* 1988;65: 339–42.
48. Stafne EC. Periapical osteofibrosis with formation of cementum. *J Am Dent Assoc* 1934;21:1822–9.
49. Chaudry AP, Spink JH, Gorlin RJ. Periapical fibrous dysplasia (cementoma). *J Oral Surg* 1958;16:483–8.
50. Neville BW, Albenesius RJ. The prevalence of benign fibro-osseous lesions of periodontal ligament origin in black women: a radiographic survey. *Oral Surg Oral Med Oral Pathol* 1986;62: 340–4.
51. Shafer WG, Hine MK, Levy BM. A textbook of oral pathology. 4th ed. Philadelphia: WB Saunders, 1983:297–8.
52. Manne MS. Cementoma: periapical cemental dysplasia. *Mo Dent J*, September-October 1987;67:28–9.
53. Smith S, Patel K, Hoskinson AE. Periapical cemental dysplasia: a case of misdiagnosis. *Br Dent J* 1998;185:122–3.
54. Ward RM. Periapical cemental dysplasia: a case report. *N Z Dent J* 1993;89:53–4.
55. Kramer IRH, Pindborg JJ, Shear M, eds. Histological typing of odontogenic tumours. In: *WHO International Histological Classification of Tumors*. 2nd ed. Berlin: Springer-Verlag, 1992: 27–9.
56. Wolf J, Hietanen J, Sane J. Florid cemento-osseous dysplasia (gigantiform cementoma) in a Caucasian woman. *Br J Oral Maxillofac Surg* 1989;27:46–52.
57. Fun-chee L, Jinn-fei Y. Florid osseous dysplasia in Orientals. *Oral Surg Oral Med Oral Pathol* 1989;68:748–53.
58. MacDonald-Jankowski DS. Florid osseous dysplasia in Hong Kong Chinese. *Dentomaxillofac Radiol* 1996;25:39–41.
59. Tanaka H, Yoshimoto A, Toyama Y, et al. Periapical cemental dysplasia with multiple lesions. *Int J Oral Maxillofac Surg* 1987; 16:757–63.
60. Miyauchi M, Ogawa I, Takata T, et al. Florid cemento-osseous dysplasia with concomitant simple bone cysts: a case in a Japanese woman. *J Oral Pathol Med* 1995;24:285–87.
61. Horner K, Forman GH. Atypical bone cysts of the jaws. II: a possible association with benign fibro-osseous (cemental) lesions of the jaws. *Clin Radiol* 1988;39:59–63.
62. Saito Y, Hoshina Y, Nagamine T, et al. *Oral Surg Oral Med Oral Pathol* 1992;74:487–91.
63. Said-Al-Naief N, Surwillo E. Florid osseous dysplasia of the mandible: report of a case. *Compendium* 1999;20:1017–30.
64. Schneider LC, Mesa LM. Differences between florid osseous dysplasia and chronic diffuse sclerosing osteomyelitis, *Oral Surg Oral Med Oral Pathol* 1990;70:308–12.
65. Groot RH, van Merkesteyn JPR, Bras J. Diffuse sclerosing osteomyelitis and florid osseous dysplasia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996;81:333–42.
66. Marx RE, Carlson ER, Smith BR, et al. Isolation of Actiniomyces species and Eikenella corrodens from patients with chronic diffuse sclerosing osteomyelitis. *J Oral Maxillofac Surg* 1994;52: 26–33.
67. Jacobsson S. In discussion of: Marx RE, Carlson ER, Smith BR,

et al. Isolation of Actinomyces species and Eikenella corrodens from patients with chronic diffuse sclerosing osteomyelitis. *J Oral Maxillofac Surg* 1994;52:33–4.
68. Jacobsson S, Dahlen G, Moller AJR. Bacteriologic and serologic investigation in diffuse sclerosing osteomyelitis (DSO) of the mandible. *Oral Surg Oral Med Oral Pathol* 1982;54:506–12.
69. Cannon JS, Keller EE, Dahlin DC. Gigantiform cementoma: report of two cases (mother and son). *J Oral Surg* 1980;38:65–70.
70. Young SK, Markowitz NR, Sullivan S, et al. Familial gigantiform cementoma: classification and presentation of a large pedigree. *Oral Surg Oral Med Oral Pathol* 1989;68:740–7.
71. Oikarinen K, Altonen M, Happonen R-P. Gigantiform cementoma affecting a Caucasian family. *Br J Oral Maxillofac Surg* 1991;29:194–7.
72. Coleman H, Altini M, Kieser J, et al. Familial florid cemento-osseous dysplasia-a case report and review of the literature. *J Dental Assoc S Africa* 1996;56:766–70.
73. Musella AE, Slater LJ. Familial florid osseous dysplasia: a case report. *J Oral Maxillofac Surg* 1989;47:636–40.
74. Miyake M, Nagahata S. Florid cemento-osseous dysplasia-report of a case. *Int J Oral Maxillofac Surg* 1999;28:56–7.
75. Gollin SM, Storto PD, Malone PS, et al. Cytogenetic abnormalities in an ossifying fibroma from a patient with bilateral retinoblastoma. *Genes Chromosomes Cancer* 1992;4:146–52.
76. Cin PD, Sciot R, Fossion E, et al. Chromosome abnormalities in cementifying fibroma. *Cancer Genet Cytogenet* 1993;71:170–2.
77. Voytek TM, Ro JY, Edeiken J, et al. Fibrous dysplasia and cemento-ossifying fibroma. A histologic spectrum. *Am J Surg Pathol* 1995;19:775–81.
78. Abrams AM, Melrose RJ. Fibro-osseous lesion. *J Oral Pathol* 1975;4:158–65.
79. Sciubba JJ, Younai F. Ossifying fibroma of the mandible and maxilla: review of 18 cases. *J Oral Pathol Med* 1989;18:315–21.
80. Eversole LR, Merrell PW, Strub D. Radiographic characteristics of central ossifying fibroma. *Oral Surg Oral Med Oral Pathol* 1985;59:522–7.
81. Wenig BM. *Atlas of head and neck pathology*. Philadelphia: WB Saunders, 1993: 45.
82. Hamner JE, Ketcham AS, Swerdlow H. Cemento-ossifying fibroma of the maxilla. *Oral Surg Oral Med Oral Pathol* 1968; 26:579–87.
83. Pedersen GW. Fibro-osseous lesion of the mandible: cementifying fibroma: report of case. *J Oral Surg* 1971;29:280–4.
84. Azaz B, Shteyer A, Soskolne WA. Fibro-osseous lesions of the jaws-a report of two uncommon cases. *J Oral Med* 1976;31: 19–23.
85. Sugimura M, Okunaga T, Yoneda T, et al. Cementifying fibroma of the maxilla-report of a case. *Int J Oral Surg* 1981;10:298–303.
86. Wenig BL, Sciubba JJ, Goldstein MN, et al. A destructive maxillary cemento-ossifying fibroma following maxillofacial trauma. *Laryngoscope* 1984;94:810–5.
87. Ong AHM, Siar CH. Cemento-ossifying fibroma with mandibular fracture. Case report in a young patient. *Aust Dent J* 1998;43: 229–33.
88. Dehner LP. Tumors of the mandible and maxilla in children. I. Clinicopathologic study of 46 histologically benign lesions. *Cancer* 1973;31:354–84.
89. Mayo K, Scott RF. Persistent cemento-ossifying fibroma of the mandible: report of a case and review of the literature. *J Oral Maxillofac Surg* 1988;46:58–63.
90. Zachariades N, Vairaktaris E, Papanicolaou S, et al. Ossifying fibroma of the jaws-review of the literature and report of 16 cases. *Int J Oral Surg* 1984;13:1–6.
91. Smith AG, Zavaleta A. Osteoma, ossifying fibroma, and fibrous dysplasia of facial and cranial bones. *AMA Arch Pathol* 1952;54: 507–27.
92. Swett RM, Bryarly RC, Konblut AD, et al. Recurrent cementifying fibroma of the jaws. *Laryngoscope* 1981;91:1137–44.
93. Boysen ME, Olving JH, Vatne K, et al. Fibro-osseous lesions of the cranio-facial bones. *J Laryngol Otol* 1979;93:793–807.
94. Hyams VJ, Batsakis JG, Michaels L. Tumors of the upper respiratory tract and ear. In: Hartmann WH, Sobin LH, eds. *Atlas of tumor pathology; series 2, fascicle 25*. Washington, DC: Armed Forces Institute of Pathology, 1986: 179–82.
95. Commins DJ, Tolley NS, Milford CA. Fibrous dysplasia and ossifying fibroma of the paranasal sinuses. *J Laryngol Otol* 1998; 112:964–8.
96. Bradley ES, Leake D. Ossifying fibroma involving the maxilla and mandible. *Oral Surg Oral Med Oral Pathol* 1968;26:605–14.
97. Hauser MS, Freije S, Payne RW, et al. Bilateral ossifying fibroma of the maxillary sinus. *Oral Surg Oral Med Oral Pathol* 1989; 68:759–63.
98. Khanna JN, Andrade NN. Giant ossifying fibroma-case report on a bimaxillary presentation. *Int J Oral Maxillofac Surg* 1992;21: 233–5.
99. Sakuma T, Kawasaki T, Watanabe K. Concurrent cementifying and ossifying fibromas of the mandible: report of a case. *J Oral Maxillofac Surg* 1998;56:778–82.
100. Yih W-Y, Pederson GT, Bartley MH. Multiple familial ossifying fibromas: relationship to other osseous lesions of the jaws. *Oral Surg Oral Med Oral Pathol* 1989;68:754–8.
101. van Heerden WFP, Raubenheimer EJ, Weir RG, Kreidler J. Giant ossifying fibroma: a clinicopathologic study of 8 tumors. *J Oral Pathol Med* 1989;18:506–9.
102. Mills SE, Fechner RE. Tumors and tumorlike lesions of the craniofacial bones and cervical vertebrae. In: Gnepp DR, ed. *Pathology of the head and neck. Contemporary issues in surgical pathology.* New York: Churchhill Livingstone, 1988: 382–91.
103. Johnson LC. Proceedings of the Seminar of the Southwestern and South-central regions. College of American Pathologists, Miami, FL, Discussion of case 1, November 12–13, 1952.
104. Hoffman S, Jacoway JR, Krolls SO. Intraosseous and parosteal tumors of the jaws. In: Hartmann WH, Sobin LH, eds. *Atlas of tumor pathology; 2nd series, fascicle 24*. Washington, DC: Armed Forces Institute of Pathology, 1987: 208–10.
105. Slootweg PJ, Panders AK, Koopmans R, et al. Juvenile ossifying fibroma. An analysis of 33 cases with emphasis on histopathologic aspects. *J Oral Pathol Med* 1994;23:385–8.
106. Slootweg PJ, Panders AK, Nikkels PGJ. Psammomatoid ossifying fibroma of the paranasal sinuses. An extragnathic variant of cemento-ossifying fibroma. Report of three cases. *J Craniomaxillofac Surg* 1993;21:294–7.
107. Margo CE. Psammomatoid ossifying fibroma. *Arch Ophthalmol* 1986;104:1347–51.
108. Slootweg PJ, Muller H. Juvenile ossifying fibroma. Report of four cases. *J Craniomaxillofac Surg* 1990;18:125–9.
109. Halkias LE, Larsen PE, Allen CM, et al. Rapidly growing expansile mass of the mandible in a 6-year old boy. *J Oral Maxillofac Surg* 1998;56:866–71.
110. Lawton MT, Heiserman JE, Coons SW, et al. Juvenile active ossifying fibroma. Report of four cases. *J Neurosurg* 1997;86: 279–85.
111. Bertrand B, Eloy P, Cornelis JP, et al. Juvenile aggressive cemento-ossifying fibroma: case report and review of the literature. *Laryngoscope* 1993;103:1385–90.
112. Sekorarith C, Dharamadhach A, Thitadilok V, et al. Gigantiform ossifying fibroma of maxillary bone. *J Med Assoc Thai* 1977;60: 330–4.
113. Cohen MM, Howell RE. Etiology of fibrous dysplasia and McCune–Albright syndrome. *Int J Oral Maxillofac Surg* 1999: 28:366–71.
114. Mertens F, Albert A, Heim S, et al. Clonal structural chromosome aberrations in fibrous dysplasia. *Genes Chromosomes Cancer* 1994;11:271–2.

115. Pierce AM, Wilson DF, Goss AN. Inherited craniofacial fibrous dysplasia. *Oral Surg Oral Med Oral Pathol* 1985;60:403–9.
116. Soames JV, Southam JC. *Oral pathology*. Oxford: Oxford University Press, 1998: 292–4.
117. Posnick JC. Fibrous dysplasia of the craniomaxillofacial region: current clinical perspectives. *Br J Oral Maxillofac Surg* 1998;36: 264–73.
118. Kurt A-M, Unni KK, McLeod RA, et al. Low-grade intraosseous osteosarcoma. *Cancer* 1990;65:1418–28.
119. Edgerton MT, Persing JA, Jane JA. The surgical treatment of fibrous dysplasia. *Ann Surg* 1985;202:459–78.
120. Chen Y-R, Noordhoff MS. Treatment of craniomaxillofacial fibrous dysplasia: how early and how extensive? *Plast Reconstr Surg* 1990;86:835–42.
121. Munro IR. In discussion of: Chen Y-R, Noordhoff MS. Treatment of craniomaxillofacial fibrous dysplasia: how early and how extensive? *Plast Reconstr Surg* 1990;86:843–4.
122. Gross CW, Montgomery WW. Fibrous dysplasia and malignant degeneration. *Arch Otolaryngol* 1967;85:97–101.
123. Slow IN, Stern D, Friedman EW. Osteogenic sarcoma arising in a preexisting fibrous dysplasia: report of case. *J Oral Surgery* 1971;29:126–9.
124. Bazar-Malik G, Mukerjee S. Fibrosarcomatous change in fibrous dysplasia of mandible. *Indian J Cancer* 1980;17:67–9.
125. Mock D, Rosen IB. Osteosarcoma in irradiated fibrous dysplasia. *J Oral Pathol* 1986;15:1–4.
126. Chetty R, Kalan MR, Kranold DH. Malignant transformation in fibrous dysplasia – a report of 3 cases. *S Afr J Surg* 1990;28:80–2.
127. Tanner HC, Dahlin DC, Childs DS. Sarcoma complicating fibrous dysplasia. Probable role of radiation therapy. *Oral Surg Oral Med Oral Pathol* 1961;14:837–46.
128. Ramsey HE, Strong EW, Frazell EL. Progressive fibrous dysplasia of the maxilla. *J Am Dent Assoc* 1970;81:1388–91.
129. Daramola JO, Ajagbe HA, Obisesan AA, et al. Fibrous dysplasia of the jaws in Nigerians. *Oral Surg Oral Med Oral Pathol* 1976; 42:290–300.
130. Adekeye EO, Edwards MB, Goubran GF. Fibro-osseous lesions of the skull, face and jaws in Kaduna, Nigeria. *Br J Oral Surg* 1980;18:57–72.