Oral and Maxillofacial Pathology
supernumerary teeth followed by exposure and orthodontic extrusion of permanent teeth. The extractions may be conducted in stages (according to the extent of root development of the unerupted permanent dentition) or in a single procedure. If completed before adulthood, then such treatment may prevent short lower face height and mandibular prognathism. Orthognathic surgery also may be considered after growth completion. Additional treatment options include full-mouth extractions or autotransplantation of selected impacted teeth followed by fabrication of an appropriate prosthesis. In a few reported cases, dental implants have been placed successfully; however, further studies are needed to assess whether the altered bone might compromise osseointegration.

◆ FOCALOSTEOPOROTIC MARROW DEFECT

The focal osteoporotic marrow defect is an area of hematopoietic marrow that is sufficient in size to produce a radiolucency. This entity does not represent a pathologic process, but its radiographic features may be confused with an intraosseous neoplasm or other pathosis. The pathogenesis is unknown, although the following theories have been proposed:

• Aberrant bone regeneration after tooth extraction
• Persistence of fetal marrow
• Marrow hyperplasia in response to increased demand for erythrocytes

Clinical and Radiographic Features

Approximately 75% of cases occur in adult females, and about 70% involve the posterior mandible, most often in edentulous areas. The defect is typically asymptomatic and nonexpansile. Most cases are detected incidentally during radiographic examination, which shows a radiolucency ranging from several millimeters to several centimeters in diameter. The borders typically appear well-circumscribed on panoramic radiographs; however, more detailed periapical radiographs may exhibit ill-defined borders and fine central trabeculation (Fig. 14-8).

Histopathologic Features

Microscopically, the defect contains cellular hematopoietic and/or fatty marrow (Fig. 14-9). The associated bony trabeculae show no evidence of abnormal osteoblastic or osteoclastic activity.

Treatment and Prognosis

The radiographic findings are often suggestive of the diagnosis but are nonspecific. Incisional biopsy, therefore, often is necessary to establish the diagnosis. Once the diagnosis is made, no further treatment is needed. The prognosis is excellent, and there appears to be no significant association with anemia or other hematologic disorders.

◆ IDIOPATHICOSTEOSCLEROSIS

Idiopathic osteosclerosis represents focally increased bone density of unknown cause. It cannot be attributed to any inflammatory, dysplastic, neoplastic, or systemic disorder. Idiopathic osteosclerosis also has been termed dense bone island, bone eburnation, bone whorl, bone scar, enostosis, and focal periapical osteopetrosis. The following discussion focuses on jaw lesions, although similar sclerotic areas may occur in other bones.

In addition, similar radiopaque foci may develop in the periapical areas of teeth with nonvital or inflamed pulps; these lesions most likely represent a response to
Inflammation. Such reactive foci are termed **condensing osteitis** or **focal chronic sclerosing osteomyelitis** (see page 134) and should not be designated **idiopathic osteosclerosis**. Because past studies did not distinguish between idiopathic and inflammatory lesions, confusion in terminology has resulted.

**Clinical and Radiographic Features**

The estimated prevalence is 5%, with some investigators suggesting a slightly increased frequency in blacks and Asians. Most authors report no significant sex predilection. According to several long-term studies, most areas of idiopathic osteosclerosis arise in the late first or early second decade. The lesion may remain static or slowly increase in size. In almost all cases, once the patient reaches full maturity, the sclerotic area stabilizes. In a smaller percentage, the lesion diminishes or undergoes complete regression. The peak prevalence is in the third decade, with peak bone mass in the fourth decade.

Idiopathic osteosclerosis is invariably asymptomatic and nonexpansile. The condition typically is detected incidentally during routine radiographic examination. About 90% of cases occur in the mandible, most often in the first molar area. The second premolar and second molar areas also are common sites. In most patients, only one sclerotic focus is present, although some patients have two to four foci. For patients with multiple lesions, the possibility of multiple osteomas within the setting of Gardner syndrome (see page 606) should be excluded.

Radiographically, idiopathic osteosclerosis typically appears as a well-defined radiopacity, ranging from 0.2 cm to 2.0 cm in diameter. The radiopacity may be round, elliptical, or irregular and does not exhibit a radiolucent rim. Most lesions are uniformly radiopaque, although large lesions occasionally demonstrate a nonhomogeneous appearance. Most examples are associated with a root apex, but interradicular lesions and lesions unrelated to teeth also are possible (Fig. 14-10). Rarely, the sclerotic bone may surround an impacted tooth. Root resorption and tooth movement have been noted infrequently.

**Histopathologic Features**

Microscopic examination shows dense lamellar bone with scant fibrofatty marrow. Inflammatory cells are inconspicuous or absent.

**Diagnosis**

Usually a diagnosis of idiopathic osteosclerosis may be made with confidence, based on history, clinical features, and radiographic findings. Biopsy is warranted if there are symptoms or significant cortical expansion. Although idiopathic osteosclerosis demonstrates radiographic and histopathologic similarities with a compact osteoma (see page 605), lack of cortical expansion and failure of continued growth rule against a neoplastic process. Tooth vitality and the absence of a deep restoration or caries help to distinguish idiopathic osteosclerosis from condensing osteitis.

**Treatment and Prognosis**

If the lesion is discovered during adolescence, periodic radiographs appear prudent until the area stabilizes. After that point, no treatment is indicated, because there is little or no tendency for the lesions to progress or change in adulthood.
FIBRO-OSSEOUS LESIONS OF THE JAWS

Fibro-osseous lesions are a diverse group of processes that are characterized by replacement of normal bone by fibrous tissue containing a newly formed mineralized product. The term fibro-osseous lesion is descriptive and does not constitute a specific diagnosis. Lesions belonging to this category may be developmental (hamartomatous), reactive, dysplastic, or neoplastic.

Fibro-osseous lesions of the jaws include the following:
- Fibrous dysplasia
- Cemento-osseous dysplasia
- Focal cemento-osseous dysplasia
- Periapical cemento-osseous dysplasia
- Florid cemento-osseous dysplasia
- Ossifying fibroma

Although these conditions differ in etiology, they may exhibit very similar histopathologic features. Therefore, correlation of the histopathologic findings with the clinical and radiographic features typically is essential for establishing a specific diagnosis. (However, in some cases of cemento-osseous dysplasia, a presumptive diagnosis may be made based on the clinical and radiographic findings.) A specific diagnosis is critical because the treatment, biologic behavior, and prognosis of these pathoses vary greatly. Some fibro-osseous lesions only require monitoring, whereas others necessitate surgical recontouring or complete removal.

FIBROUS DYSPLASIA

Fibrous dysplasia is a developmental tumorlike condition, characterized by replacement of normal bone by proliferation of cellular fibrous connective tissue with irregular bony trabeculae. This sporadic condition results from postzygotic, activating mutations in the GNAS gene, which encodes the alpha subunit of a stimulatory G protein. Such mutations have not been detected in ossifying fibroma or cemento-osseous dysplasia.

Clinically, fibrous dysplasia may involve one bone or multiple bones; in some cases, involvement of multiple bones may occur in conjunction with cutaneous and endocrine abnormalities. The extent of disease depends on when the GNAS mutation occurs. During early embryonic development, mutation of a pluripotent stem cell can cause abnormalities in multiple cell types, including osteoblasts, melanocytes, and endocrine cells. In contrast, if the mutation occurs in a skeletal progenitor cell in a later stage of embryonic development, then only osteoblasts will be affected. Alternatively, if the mutation occurs during postnatal life, then osteoblasts in only a single bone will be affected. Furthermore, the parental origin of the mutated GNAS allele may affect the phenotype, because in certain cell types (such as pituitary somatotrophs) genomic imprinting results in expression of only the maternal allele.

Constitutive activation of G-protein signaling impairs osteoblastic differentiation in skeletal progenitor cells,
stimulates melanin production in melanocytes, and causes hyperplasia and hyperfunction of various endocrine cell types. In addition, mutated osteoblasts overexpress interleukin (IL)-6, which stimulates osteoclastic activity and may contribute to bone lesion expansion.

Clinical and Radiographic Features

Monostotic Fibrous Dysplasia

About 70% to 85% of patients with fibrous dysplasia have disease limited to a single bone (monostotic fibrous dysplasia). Monostotic fibrous dysplasia is diagnosed most often during the second and third decades of life. Males and females are affected with about equal frequency. Commonly involved sites include the craniofacial bones, ribs, femur, and tibia.

Among cases involving the jaws, the maxilla is affected more often than the mandible. There is a predilection for the posterior region. Although mandibular lesions are truly monostotic, maxillary lesions often extend to involve adjacent bones (e.g., zygoma, sphenoid, ethmoid, frontal bone, temporal bone, occiput) — in which case the term craniofacial fibrous dysplasia is appropriate. Painless, unilateral swelling is the most common clinical finding (Fig. 14-31). Growth is generally slow, and it is common for the patient to be aware of the condition for several years before seeking professional evaluation. Occasionally, however, the growth may be fairly rapid. Adjacent teeth may be displaced by the bony mass but usually remain firm.

The classic radiographic finding is a fine “ground-glass” opacification with poorly defined margins (Figs. 14-32 through 14-34). However, some lesions may appear radiolucent or mixed radiolucent-radiopaque. Mandibular lesions often exhibit buccolingual expansion and bulging of the inferior border. There may be superior displacement of the inferior alveolar canal. Periapical radiographs of the adjacent dentition may demonstrate narrowing of the periodontal ligament space and an ill-defined lamina dura that blends with the abnormal bone. Maxillary lesions often cause superior displacement of the sinus floor and obliteration of the antrum. In addition, extensive skull involvement may be evident (Fig. 14-35). Bone scintigraphy may aid in determining the extent of involvement and ruling out polyostotic disease.

Polyostotic Fibrous Dysplasia; Jaffe-Lichtenstein Syndrome; McCune-Albright Syndrome

A minority of patients with fibrous dysplasia exhibits involvement of two or more bones (polyostotic fibrous dysplasia). Most patients with polyostotic disease are diagnosed before 10 years of age, and there is a female predilection. The number of involved bones varies from a few to 75% of the entire skeleton.

Presenting signs and symptoms typically are related to long bone involvement and include pain, pathologic fracture, limping, leg length discrepancy, and bowing deformity. Radiographic examination may reveal malformation...
of the proximal femur (known as coxa vara, shepherd’s crook deformity, or hockey stick deformity). Involvement of the skull and jaws may result in facial asymmetry (Fig. 14-36). Craniofacial involvement may cause vision changes, hearing impairment, sinonasal congestion, and airway obstruction. Hypophosphatemia caused by renal phosphate wasting is a fairly common finding, which appears to be related to the release of fibroblast growth factor 23 (FGF23) by the affected bones.

A small subset of patients may exhibit polyostotic fibrous dysplasia in association with the following syndromes:

- **Jaffe-Lichtenstein syndrome**, characterized by polyostotic fibrous dysplasia and café au lait (coffee with milk) pigmentation
- **McCune-Albright syndrome**, characterized by polyostotic fibrous dysplasia, café au lait pigmentation, and multiple endocrinopathies
- **Mazabraud syndrome**, characterized by fibrous dysplasia and intramuscular myxomas

The café au lait pigmentation may be congenital and consists of well-defined, tan macules. The macules are generally unilateral and most commonly affect the skin, although oral mucosal involvement also is possible. The margins of the café au lait spots are typically very irregular, resembling a map of the coastline of Maine (Fig. 14-37). In contrast, the café au lait spots of neurofibromatosis (see page 495) tend to exhibit smooth borders (like the coast of California).

In McCune-Albright syndrome, the most common endocrine abnormality is sexual precocity, particularly in females. Menstrual bleeding, breast development, and pubic hair may be apparent within the first few months or years of life. Other possible endocrinopathies include hyperthyroidism, hyperparathyroidism, hypercortisolism, and excess growth hormone. In addition, in one study of craniofacial fibrous dysplasia mainly occurring in McCune-Albright syndrome, investigators have reported various dental anomalies, including tooth displacement, oligodontia, enamel hypoplasia, enamel hypomineralization, taurodontism, and retained deciduous teeth.

**Histopathologic Features**

Microscopic examination shows irregularly shaped trabeculae of immature (woven) bone in a cellular fibrous stroma (Fig. 14-38). At the periphery, the lesional bone fuses with normal bone, without a capsule or line of demarcation. The abnormal bony trabeculae tend to be thin and disconnected, with curvilinear shapes likened to Chinese characters. Osteoblastic rimming is usually absent or minimal, and peritrabecular clefting (artifactual retraction of the stroma from the bony trabeculae) is common. In addition, tiny calcified spherules rarely may be seen but are never numerous. In later stages, the woven bone is replaced by lamellar bone with roughly parallel trabeculae (Fig. 14-39). The rather monotonous pattern of calcification in fibrous dysplasia differs from the more haphazard mixture of woven
• Fig. 14-36 Polyostotic Fibrous Dysplasia. Jaffe-Lichtenstein syndrome. A, Young man exhibiting enlargement of the right maxilla and mandible. B, Intraoral photograph showing unilateral maxillary expansion. C, Panoramic radiograph showing ill-defined lesions of the right side of both jaws.

Fig. 14-37 Polyostotic Fibrous Dysplasia. Jaffe-Lichtenstein syndrome. Café au lait pigmentation of the abdomen. This is the same patient as shown in Fig. 14-36.

Bone, lamellar bone, and spheroid particles characteristic of ossifying fibroma and cemento-osseous dysplasia.

Fibrous dysplasia may appear more sclerotic in the jaw and skull than other sites. Microscopic variations include a pagetoid pattern (characterized by thick, interconnected bone trabeculae) and a hypercellular pattern (characterized by parallel bone trabeculae with numerous osteocytes and polarized osteoblastic rimming). Secondary aneurysmal bone cyst formation has been reported as well.

Genetic testing for GNAS mutations can be performed on lesional tissue or, possibly, peripheral blood samples. Such testing may be helpful when there is diagnostic uncertainty, but it exhibits low sensitivity and is not performed routinely.

Treatment and Prognosis

Fibrous dysplasia tends to stabilize upon skeletal maturation, and spontaneous regression even has been reported in a few cases. Therefore, conservative management is preferred. Some lesions, nevertheless, exhibit continued growth into adulthood. The risk for severe deformity and complications is particularly elevated among patients with widespread polyostotic fibrous dysplasia—especially in the setting of McCune-Albright syndrome with uncontrolled growth hormone excess.

Patients with minimal cosmetic and functional disturbances may not require surgical treatment. For young patients with significant problems due to large or extensive lesions, surgical contouring, shaving, or other debulking
CHAPTER 14
Bone Pathology

Fig. 14-38 Fibrous Dysplasia. A, Irregularly shaped trabeculae of woven bone in a fibrous stroma. B, Medium-power view showing peripheral osteoid without osteoblastic rimming.

Fig. 14-39 Mature Fibrous Dysplasia. A, This long-standing lesion shows separate, broad trabeculae of bone within fibrous connective tissue. B, Note the lamellar maturation of the bone.

procedures may be performed. However, subsequent regrowth may require additional surgery. Approximately 20% to 50% of patients show some regrowth after surgical debulking, and the risk for regrowth is greater among younger than older patients. Therefore, if possible, many authorities prefer to delay surgery until the disease is quiescent. Some investigators have proposed that serum alkaline phosphatase levels after incomplete surgical removal may be predictive of disease progression, although validation studies are needed.

Alternatively, complete surgical removal may be considered in some cases, such as monostotic lesions, very aggressive lesions, or lesions refractory to repeated debulking. Combined orthodontic treatment and orthognathic surgery may be performed to correct malocclusion. Successful placement of dental implants has been reported in a few cases, but additional studies are needed. Several reports suggest that bisphosphonates (e.g., IV pamidronate, oral alendronate) may help to relieve bone pain in fibrous dysplasia. However, well-designed studies are needed to confirm these findings, to assess the potential for inducing disease stabilization, and to evaluate the long-term safety of such treatment in young patients. Radiation therapy is contraindicated because of the risk for postirradiation bone sarcoma.

Transformation into malignancy, usually an osteosarcoma, is estimated to occur in less than 1% of patients with fibrous dysplasia. The risk for sarcomatous transformation is greatest among those with a history of radiation therapy, McCune-Albright syndrome, or Mazabraud syndrome. Rapid lesion growth, sudden onset of pain, neurosensory changes, or marked changes in radiographic appearance should alert the clinician to rule out malignant transformation.

CEMENTO-OSSEOUS DYSPLASIAS (OSSEOUS DYSPLASIA)

Cemento-osseous dysplasia occurs in the tooth-bearing areas of the jaws and is probably the most common fibro-osseous lesion encountered in clinical practice. Because the histopathologic features share many similarities with fibrous dysplasia and ossifying fibroma, correct diagnosis can be problematic but is critical for appropriate management.

Some investigators have suggested that cemento-osseous dysplasia originates from the periodontal ligament, because of microscopic similarity and lesion proximity to this structure. Others believe this condition represents a defect in extrafolimentary bone remodeling that may be triggered by local injury or, possibly, an underlying hormonal imbalance.
Clinical and Radiographic Features

Based on clinical and radiographic features, cemento-osseous dysplasia includes the following variants: (1) focal, (2) periapical, and (3) florid.

Focal Cemento-Osseous Dysplasia

Focal cemento-osseous dysplasia involves a single site. Before the concept of focal cemento-osseous dysplasia was clarified in the mid-1990s, most cases were misdiagnosed as a variant of ossifying fibroma.

About 90% of cases of focal cemento-osseous dysplasia occur in females, with an approximate mean age of 41 years and a predilection for the third to sixth decades. The lesion has been reported across ethnic groups—most often American blacks followed by East Asians and whites. In contrast to the periapical and florid variants, the focal variant seems to affect a greater proportion of whites, although this finding may be due to study population bias.

Focal cemento-osseous dysplasia most commonly involves the posterior mandible. The disease typically is asymptomatic and is detected incidentally by radiographic examination. Most lesions are smaller than 1.5 cm in diameter.

Radiographically, the lesion varies from completely radiolucent to densely radiopaque with a thin peripheral radiolucent rim. Most commonly, however, there is a mixed radiolucent and radiopaque pattern (Fig. 14-40). The borders tend to be well defined but slightly irregular. The lesions typically occur around tooth apices or in extraction sites. A focal lesion occasionally may represent an early stage in the transition to multifocal involvement, especially in black females.

Periapical Cemento-Osseous Dysplasia (Osseous Dysplasia; Periapical Cemental Dysplasia; Periapical Cementoma)

Periapical cemento-osseous dysplasia predominantly involves the periapical region of the anterior mandible. Solitary lesions may occur, but multiple foci typically are present. There is a marked female predilection (female-to-male ratio ranging from 10:1 to 14:1), and approximately 70% of cases affect blacks. Most patients are diagnosed initially between 30 and 50 years of age, with the diagnosis almost never made in individuals younger than 20 years. The associated teeth are usually vital and seldom have restorations.

Periapical cemento-osseous dysplasia is an asymptomatic condition that often is discovered when radiographs are taken for other purposes. Early lesions appear as circumscribed periapical radiolucencies, similar to periapical granulomas or periapical cysts (Fig. 14-41). Adjacent lesions may fuse to form a linear radiolucency that envelops the

![Fig. 14-40 Focal Cemento-Osseous Dysplasia.](image)

A, A radiolucent area involves the edentulous first molar area and the apical area of the second molar. B, Radiograph of the same patient taken 9 years later showing a mixed radiolucent and radiopaque pattern.

![Fig. 14-41 Periapical Cemento-Osseous Dysplasia.](image)

Periapical radiograph showing multiple radiolucent lesions at the apices of the anterior mandibular teeth. (Courtesy of Dr. Aaron Carner.)
apices of several teeth (Fig. 14-42). Over time, the lesions tend to “mature” and become mixed radiolucent-radiopaque (Fig. 14-43). In the end stage, the lesions appear as circumscribed, dense radiopacities surrounded by narrow radiolucent rims. The periodontal ligament space usually appears intact, and fusion to the tooth is rare. Most lesions are nonexpansile with self-limiting growth; individual lesions seldom exceed 1.0 cm in diameter.

**Florid Cemento-Osseous Dysplasia**

Florid cemento-osseous dysplasia exhibits multifocal involvement not limited to the anterior mandible. Although many cases affect only the posterior portions of the jaws, synchronous involvement of the anterior mandible may be observed as well (Fig. 14-44). Like the periapical pattern, this form predominantly affects black females (in some series, more than 90% of patients), with a marked
cemento-osseous dysplasia. Initially, the lesions are predominantly radiolucent but with time become mixed, then predominantly radiopaque with only a thin radiolucent rim (Fig. 14-46). On occasion, a lesion can become almost totally radiopaque and blend with the adjacent normal-appearing bone. Typically, the radiopacities remain separated from adjacent teeth with an intervening, intact periodontal ligament space. However, in some end-stage lesions, the cemento-osseous material may fuse with the tooth root surface to produce thickened root apices surrounded by radiolucency (or a “hypercementosis-like” appearance).

Both dentulous and edentulous areas may be affected, and involvement appears to be unrelated to the presence or absence of teeth. Sharply defined radiolucent areas, which on surgical exploration prove to be simple bone cysts (see page 589), may be intermixed with the other lesional elements. Investigators have suggested that these simple bone cysts may result from interstitial fluid obstruction by the fibro-osseous proliferation.

**Histopathologic Features**

All three patterns of cemento-osseous dysplasia demonstrate similar histopathologic features. There are typically fragments of cellular fibrovascular connective tissue with scattered hemorrhage and a variable mixture of woven bone, lamellar bone, and cementum-like particles (Figs. 14-47 and 14-48). As the lesions mature, the ratio of fibrous connective tissue to mineralized material decreases. Over time, the bony trabeculae become thick and curvilinear, with shapes likened to ginger roots. In the final radiopaque stage,
the individual trabeculae fuse to form sheetlike or globular masses of sclerotic, disorganized cemento-osseous material (Fig. 14-49).

**Diagnosis**

In most instances of periapical or florid cemento-osseous dysplasia, the distinctive clinical and radiographic findings (e.g., a black female patient with multiquadrant involvement or multiple lesions involving vital lower incisor teeth) allow a strong presumptive diagnosis. In contrast, the features of focal cemento-osseous dysplasia tend to be less specific, and biopsy often is needed for diagnosis.

In particular, distinguishing focal cemento-osseous dysplasia from ossifying fibroma can be difficult. However, the findings at surgery may be helpful in discriminating between these two lesions. Before the final sclerotic stage, cemento-osseous dysplasia consists of gritty tissue that the surgeon typically curettes into small fragments during biopsy. In contrast, ossifying fibromas tend to separate cleanly and are removed in one or several large masses. Microscopically, both lesion types demonstrate a mixture of bone and cementum-like particles, although subtle histopathologic differences may be appreciated. The bony trabeculae in ossifying fibroma tend to be more delicate and show more prominent osteoblastic rimming compared to those in cemento-osseous dysplasia. Also, the cementum-like particles in cemento-osseous dysplasia are irregularly shaped and often exhibit retraction from the adjacent stroma, whereas those in ossifying fibroma are more ovoid and often demonstrate brush borders in intimate association with the adjacent stroma. Although ossifying fibroma can exhibit peripheral hemorrhage, cemento-osseous dysplasia typically reveals hemorrhage throughout the lesion and sinusoidal vascularity in close association with the bony trabeculae.

**Treatment and Prognosis**

Cemento-osseous dysplasia does not appear to be neoplastic and, therefore, generally does not require removal. During the predominantly radiolucent phase, the lesions cause few problems. However, in the sclerotic phase, the lesions tend to be hypovascular and prone to necrosis and secondary infection with minimal provocation. For the asymptomatic patient, the best management consists of regular recall examinations with prophylaxis and oral hygiene reinforcement to control periodontal disease and prevent tooth loss.

Because the onset of symptoms usually is associated with exposure of the sclerotic masses to the oral cavity, surgical procedures (e.g., biopsy, elective tooth extraction) should be avoided. In some instances, symptoms begin after lesion exposure resulting from progressive alveolar atrophy under a denture. Therefore, affected patients should be encouraged to retain their teeth. Dental implant placement in an area of cemento-osseous generally is not recommended. Management of the symptomatic patient who has developed secondary osteomyelitis is more difficult. Antibiotics may be indicated but often are not effective. Sequestration of the sclerotic cementum-like masses occurs slowly and is followed by healing. Saucerization of dead bone may speed healing. When simple bone cysts arise within foci of
cemento-osseous dysplasia, surgical exploration is necessary to establish the diagnosis. These simple bone cysts often do not heal as rapidly as those noted in younger patients without cemento-osseous dysplasia. In some cases the cysts persist or enlarge after surgical intervention; when they fill in, the bone retains an abnormal radiographic appearance. Thorough curettage of the cyst and the surrounding fibrous proliferation may assist healing.

Some investigators have noted a rare subset of cases (termed expansive osseous dysplasia) that exhibit progressive growth but otherwise typical clinicopathologic features of cemento-osseous dysplasia. Such lesions have been reported most often in the anterior mandible of African black females and typically require surgical removal.

Overall, the prognosis is good. Development of a sarcoma within an area of cemento-osseous dysplasia has been reported but is extremely rare.

**FAMILIAL GIGANTIFORM CEMENTOMA**

Although the term gigantiform cementoma has been used in the past as a synonym for florid cemento-osseous dysplasia, most authorities now restrict use of this term to a rare hereditary disorder known as familial gigantiform cementoma. This disorder exhibits an autosomal dominant pattern of transmission with high penetrance and variable expressivity. It is characterized by a cemento-osseous proliferation involving multiple quadrants of the jaws and often resulting in massive expansion.

Based on microscopic similarities, some authors consider familial gigantiform cementoma to be a variant of cemento-osseous dysplasia. However, a tendency for progressive lesion growth suggests a truly neoplastic process; thus, many authors prefer to regard familial gigantiform cementoma as a distinct neoplasm or a subtype of ossifying fibroma.

Sporadic cases with clinical and radiographic features similar to those of familial gigantiform cementoma also have been reported using various terms, including nonfamilial gigantiform cementoma, multiple (cemento-) ossifying fibromas, bilateral ossifying fibromas, and expansive osseous dysplasia. Whether such cases represent spontaneous mutations, multiple ossifying fibromas, or unusual progressive forms of cemento-osseous dysplasia remains unclear. Molecular genetic studies are needed to improve the understanding and appropriate classification of this problematic disease spectrum.

**Clinical and Radiographic Findings**

Unlike florid cemento-osseous dysplasia, familial gigantiform cementoma exhibits neither a predilection for blacks nor a significant gender predilection. Although blacks may be affected, most reported families are white or Asian. Radiographic alterations may begin to develop during the first decade of life. By adolescence, most patients exhibit clinically obvious expansion of the jaws (Fig. 14-50). The lesions affect multiple quadrants, often with simultaneous involvement of the maxilla and mandible. Lesion growth may be rapid or slow. In a few reported cases, especially rapid growth has been noted during pregnancy. Although the course is variable, many patients develop significant facial deformity,
Fig. 14-72 Desmoplastic Fibroma. Ill-defined, destructive radiolucency of the left mandible.

Fig. 14-73 Desmoplastic Fibroma. The tumor consists of a cellular proliferation of fibroblasts arranged in interfascicular fibers.

may be present at the interface between the tumor and adjacent bone but are never an integral part of the lesion. This reactive bone at the periphery may be mistaken for osteoid production, which may lead to a misdiagnosis of a benign fibro-osseous lesion or osteosarcoma. Therefore, diagnostic biopsies should be sampled generously from the center rather than the periphery of the lesion.

Treatment and Prognosis

Although the desmoplastic fibroma is a benign tumor, it often behaves in a locally aggressive fashion, with extensive bone destruction and soft tissue extension; thus, radical surgery may be required to control the disease. Most cases are treated by resection, although curettage may be adequate for localized lesions without cortical perforation or soft tissue extension. The recurrence rate is approximately 30% for lesions treated by curettage or enucleation, compared with about 5% for those treated by resection. Given the potential for recurrence, patients should be monitored postoperatively for at least 3 years. The long-term prognosis is good, but there may be considerable morbidity. Malignant transformation is rare.

It may be very difficult to distinguish desmoplastic fibroma of bone from well-differentiated fibrosarcoma. Some authorities suggest that all desmoplastic fibromas of bone be considered potentially malignant.

OSTEOSARCOMA

Osteosarcoma is a malignancy of mesenchymal cells that have the ability to produce osteoid or immature bone. Excluding hematopoietic neoplasms, osteosarcoma is the most common malignancy to originate within bone. In the United States, the age-adjusted annual incidence is approximately 3 cases per million population.

The etiology of osteosarcoma is largely unknown. A strong association with the adolescent growth spurt and the metaphyses of long bones suggests that rapid bone growth and hormonal factors may play a role. Additional risk factors include radiation exposure, alkylating agents, Paget disease of bone, Li-Fraumeni syndrome, hereditary retinoblastoma, and Rothmund-Thompson syndrome. Studies have demonstrated a complex genetic profile among osteosarcomas, with alterations frequently detected in p53, RB1, and chromosome 21q.

Osteosarcomas may be classified as central (arising within the medullary cavity), surface (arising in the juxtacortical region), or, vary rarely, extraskeletal (arising within soft tissue) (Table 14-4). The vast majority of cases are central. Surface osteosarcomas are discussed in the next section (see page 617). In addition, some authors regard gnathic osteosarcomas as a separate entity, because these lesions exhibit somewhat distinctive clinical features and biologic behavior.

Clinical and Radiographic Features

Extragnathic osteosarcoma demonstrates a bimodal age distribution, with a major peak during adolescence and a lesser peak among adults older than 60 years. The initial peak occurs during the period of greatest bone growth; accordingly, most of these osteosarcomas arise in the distal femoral and proximal tibial metaphyses. In older patients, osteosarcoma often is attributed to Paget disease of bone or previous irradiation, and the axial skeleton and flat bones are involved most frequently.

About 6% of all osteosarcomas arise in the jaws. Jaw lesions occur over a broad age range, with a peak in the third through fifth decades of life. The mean age is approximately 33 to 39 years, which is about 1 to 2 decades older than the mean age for osteosarcomas of the long bones. Both gnathic and extragnathic osteosarcomas exhibit a slight male predilection.
Most studies report either a fairly even distribution between the mandible and maxilla or a slight mandibular predilection. Mandibular tumors arise most frequently in the body, followed by the angle, symphysis, and ramus. Maxillary lesions develop more often in the inferior portion (alveolar ridge, sinus floor, and/or palate) than the superior aspect (zygoma and orbital rim).

Swelling and pain are the most common clinical findings (Figs. 14-74 and 14-75). Tooth mobility, paresthesia, and nasal obstruction (in the case of maxillary tumors) also may be noted. Some patients report symptoms for relatively long periods before diagnosis, which suggests that some osteosarcomas of the jaws grow rather slowly.

Radiographic examination may show a radiopaque, mixed radiolucent-radiopaque, or entirely radiolucent lesion with ill-defined borders (Figs. 14-74, B, 14-75, B, and 14-76). Cortical destruction, cortical expansion, and a periosteal reaction also may be evident. The latter may appear as a “classic” sunburst pattern (present in about 25% of jaw osteosarcomas) or a triangular elevation of the periosteum (Codman triangle). Occasionally, the adjacent teeth exhibit “spiking” root resorption (with tapered narrowing of the root). Symmetrical widening of the periodontal ligament space (Fig. 14-77) may be an important clue for diagnosis of early osteosarcoma, although this feature also may be seen in other malignancies. At times an extensive osteosarcoma may show only subtle variation in the trabecular pattern. Plain radiography often is used for initial evaluation. However, MRI is superior for assessment of primary tumor extent, and CT is important for detection of pulmonary metastasis.

**Histopathologic Features**

Although osteosarcomas exhibit considerable histopathologic variation, the essential microscopic criterion is direct production of osteoid by malignant mesenchymal cells (Fig. 14-78). In addition to osteoid, the tumor cells may produce chondroid and fibrous connective tissue. The tumor cells may vary from relatively uniform, round or spindle-shaped
**Fig. 14-75 Osteosarcoma.** A, This massive tumor had been present for many months before the patient sought treatment. B, Intraoral photograph of the tumor mass. C, The panoramic radiograph shows a “sunburst” pattern of trabeculation.

**Fig. 14-76 Osteosarcoma.** Computed tomography (CT) scan showing a mottled radiopacity of the mandible with cortical destruction and a focal “sunburst” periosteal reaction. (Courtesy of Dr. Steve Anderson.)

**Fig. 14-77 Osteosarcoma.** This 26-year-old woman had a 6-cm painful tumor of the anterior mandible. The periapical radiograph shows widening of the periodontal ligament spaces and a mottled radiopacity superimposed on the teeth. (Courtesy of Dr. Charles Ferguson.)
study has shown that chondroblastic osteosarcomas lack IDH1 mutations, whereas such mutations are frequent among chondrosarcomas. Low-grade osteosarcomas show minimal cellular atypia and abundant bone formation. On microscopic examination, these lesions may be difficult to differentiate from benign bone lesions, such as fibrous dysplasia or ossifying fibroma. Correlation with imaging studies is essential for accurate diagnosis. Immunohistochemical expression of MDM2 and CDK4 also may help to distinguish low-grade osteosarcoma from benign fibro-osseous lesions and other benign bone tumors.

**Treatment and Prognosis**

The treatment of choice for osteosarcoma of the jaws is wide surgical resection. The additional use of chemotherapy and/or radiotherapy for gnathic osteosarcomas is controversial but may be considered in some cases (e.g., tumors of questionable resectability, surgical margins positive for tumor, and recurrent tumors). For high-grade osteosarcomas of the long bones, management usually consists of neoadjuvant (preoperative) chemotherapy followed by radical surgery and adjuvant (postoperative) chemotherapy. Among patients with localized disease at diagnosis, such treatment has resulted in 5-year survival rates of approximately 60% to 80%, compared to only about 20% with surgery alone. However, for patients with gnathic osteosarcomas, such protocols have yielded variable outcomes, and further studies are needed.

The most important prognostic factor is the ability to achieve initial complete surgical removal. Compared to mandibular lesions, maxillary lesions often are more difficult to resect and exhibit a worse prognosis. Additional adverse factors include prior radiation exposure and underlying Paget disease of bone. Interestingly, some investigators have reported a better prognosis for osteosarcoma of the jaws than osteosarcoma of the long bones. This observation may be related to a tendency for gnathic osteosarcomas to exhibit a low rate of metastasis despite often high-grade histopathologic features. However, other studies have shown no significant survival advantage among patients with gnathic osteosarcoma.

For patients with osteosarcoma of the jaws, death results more often from uncontrolled local disease than from distant metastases. Most deaths from uncontrolled local disease occur within 2 years of initial treatment. Metastases most often affect the lungs. In recent years, most large series of jaw tumors have reported 5-year overall survival rates of approximately 60% to 70%, and some centers have reported greater than 80% survival.

**SURFACE (JUXTACORTICAL) OSTEOSARCOMAS**

Although most osteosarcomas arise within the medullary cavity of bone, some cases originate in the periosteal or
therapy of choice. Periosteal osteosarcoma is an intermediate-grade tumor, with a prognosis better than conventional intramedullary osteosarcoma but worse than parosteal osteosarcoma.

**High-grade surface osteosarcoma** is extremely rare. This variant is similar to conventional intramedullary osteosarcoma in terms of microscopic features and biologic behavior.

**POSTIRRADIATION BONE SARCOMA**

Sarcoma arising in bone previously subjected to radiation therapy is an uncommon but well-recognized phenomenon. The jaws and craniofacial bones are among the more common sites for such tumors. Bone sarcomas have been reported to develop 3 to 55 years after radiation exposure, with a mean latency period of about 4 to 17 years. Studies estimate that 0.03% to 0.2% of irradiated patients develop postirradiation bone or soft tissue sarcomas. The risk appears to increase with increasing radiation dose. Reported mean and median radiation doses for postirradiation bone sarcomas vary from 43 to 64 Gy. Some investigators have suggested that the risk is negligible with a dose less than 10 Gy; however, a recent prospective study of atomic bomb survivors in Japan suggests an increased risk for bone sarcoma with a radiation dose as low as 0.85 Gy. **Osteosarcoma** is the most common postirradiation bone sarcoma type, accounting for 49% to 85% of cases. Other reported types include undifferentiated pleomorphic sarcoma (malignant fibrous histiocytoma), fibrosarcoma, and chondrosarcoma. The lesions tend to be poorly differentiated, and the prognosis is generally poor.

**CHONDROSARCOMA**

**Chondrosarcoma** is a malignant neoplasm in which the tumor cells form cartilage but not bone. Chondrosarcoma is about half as common as osteosarcoma and twice as common as Ewing sarcoma. Chondrosarcomas comprise about 11% of all primary malignant bone tumors but involve the jaws only rarely. Approximately 1% to 12% of all chondrosarcomas arise in the head and neck, and such lesions comprise only 0.1% of all head and neck malignancies.

Chondrosarcoma may develop de novo (primary chondrosarcoma) or from a preexisting benign cartilaginous tumor (secondary chondrosarcoma). The histogenesis is controversial; investigators have hypothesized that the tumor may originate from chondrocytes, embryonal chondroid, or pluripotential mesenchymal stem cells. Interestingly, there is an increased risk for chondrosarcoma among patients with Ollier disease and Maffucci syndrome (see page 611). These forms of chondromatosis are associated with somatic mutations in isocitrate dehydrogenase 1 (IDH1) gene and isocitrate dehydrogenase 2 (IDH2) gene; likewise, chondromas and chondrosarcomas of bone frequently exhibit IDH1 mutations.