

Oral pathology

Lecture 8

د. بشار

Metabolic and Genetic diseases of bone

Osteogenesis imperfecta

Osteogenesis imperfecta comprises a heterogeneous group of heritable disorders characterized by impairment of collagen maturation. Except on rare occasions, the disorder arises from heterozygosity for mutations in one of two genes that guide the formation of type I collagen: the COL1A1 gene on chromosome 17 and the COL1A2 gene on chromosome 7. Collagen forms a major portion of bone, dentin, sclerae, ligaments, and skin: osteogenesis imperfecta demonstrates a variety of changes that involve these sites. Several different forms of osteogenesis imperfecta are seen, and they represent the most common type of inherited bone disease. Abnormal collagenous maturation results in bone with a thin cortex, fine trabeculation, and diffuse osteoporosis. Upon fracture healing will occur but may be associated with exuberant callus formation.

Clinical and Radiographic Features

Osteogenesis imperfecta is a rare disorder that affects one in 8000 individuals, with many being stillborn or dying shortly after birth. Both autosomal dominant and recessive hereditary patterns occur, and many cases are sporadic. The severity of the disease varies widely, even in affected members of a single family. In addition to bone fragility, some affected individuals also have blue sclera, altered teeth, hypoacusis (hearing loss), long bone and spine deformities, and joint hyper extensibility. The radiographic hallmarks of osteogenesis imperfecta include osteopenia, angulation or deformity of the long bones, multiple fractures, and wormian bones in the skull. Wormian bones consist of ten or more sutural bones that are 6X 4 mm in diameter or

larger and arranged in a mosaic pattern. Wormian bones are not specific and can be seen in other processes, such as cleidocranial dysplasia.

Several distinctive findings are noted in the oral cavity. Dental alterations that appear clinically and radiographically identical to dentinogenesis imperfecta are occasionally noted. In affected patients; both dentitions are involved and demonstrate blue to brown translucence. Radiographs typically reveal premature pulpal obliteration, although shell teeth rarely may be seen. Although the altered teeth closely resemble dentinogenesis imperfecta, the two diseases are the result of different mutations and should be considered as separate processes. Such dental defects in association with the systemic bone disease should be termed opalescent teeth, reserving the diagnosis of dentinogenesis imperfecta for those patients with alterations isolated to the teeth. In addition, patients with osteogenesis imperfecta demonstrate an increased prevalence of class III malocclusion that is caused by maxillary hypoplasia, with or without mandibular hyperplasia. On rare occasions, panoramic radiographs may reveal multifocal radiolucencies, mixed radiolucencies, or radiopacities that resemble those seen in florid cemento-osseous dysplasia. When predominantly radiopaque, these areas are sensitive to inflammation and undergo sequestration easily. In these patients, marked coarseness also is noted in the remainder of the skeleton. **Four major types of osteogenesis imperfecta are recognized, each having several subtypes.**

1-Type I osteogenesis imperfecta. Type I is the most common and mildest form. Affected patients have mild to moderately severe bone fragility. Fractures are present at birth in about 10% of cases, but there is great variability in frequency and age of onset of fractures, with 10% of patients not demonstrating fractures. Most fractures occur during the preschool years and are less common after puberty. Hearing loss commonly develops before age 30 and most older patients have hearing deficits. Hypermobile joints and easy bruising because of capillary fragility are not rare. Some affected patients have normal teeth, but others show opalescent dentin. The sclera are

distinctly blue at all ages and aid in classification. Osteogenesis imperfecta type I is inherited as an autosomal dominant trait.

2-Type II osteogenesis imperfect: Osteogenesis imperfect type II is the most severe form and exhibits extreme bone fragility and frequent fractures, which may occur during delivery. Many patients are stillborn and 90% die before 4 weeks of age. Blue sclera are present, opalescent teeth may be present both autosomal recessive and dominant patterns may occur, and many cases appear to be sporadic.

3-Type III osteogenesis imperfecta, Type III is the most severe form noted in individuals beyond the perinatal period and demonstrates moderately severe to severe bone fragility. The sclerae are normal or pale blue or gray at birth; if discoloration is present, it fades as the child grows older. Ligamentous laxity and hearing loss are common. Fractures may be present at birth, but there is a low mortality in infancy. Although one third survives into adulthood, the majority of affected individuals die during childhood, usually from cardiopulmonary complications caused by kyphoscoliosis. Some patients have opalescent dentin whereas others have normal teeth, both autosomal dominant and recessive hereditary patterns are noted.

4-Type IV osteogenesis imperfecta. Type IV is associated with mild to moderately severe bone fragility. The sclera may be pale blue in early childhood, but the blue color fades later in life. Fractures are present at birth in about 50% of these patients. The frequency of fractures decreases after puberty and some individuals never experience bone fracture at any time. Some of the patients have opalescent dentin; others have normal teeth. This variant appears to be inherited as an autosomal dominant trait.

Histopathologic Features

Upon histopathologic examination, cortical bone appears attenuated. Osteoblasts are present, but bone matrix production is reduced markedly. The bone architecture

remains immature throughout life and there is a failure of woven bone to become transformed to lamellar bone.

Treatment and Prognosis

There is no treatment for osteogenesis imperfecta, Management of the fractures may be a major problem. Patients with opalescent dentin usually show severe attrition of their teeth, leading to tooth loss. Treatment of the dentition is similar to that employed for dentinogenesis imperfecta, but use of implants is questionable because of the deficient quality of the supporting bone.

In patients with significant malocclusion, orthognathic surgery may be performed but associated medical problems make presurgical planning paramount. Although highly variable occasional patients have associated bleeding disorders. Cardiac malformations, and an increased risk of hyperthermia. The prognosis varies from relatively good to very poor. Some patients have little to no disability, whereas others have severe crippling as a result of the fractures. In severe forms, death occurs *in utero*, during delivery or early in childhood .

Osteopetrosis (albers-schonbergdisease; marble bone disease)

Osteopetrosis is a group of rare hereditary skeletal disorders characterized by a marked increase in bone density resulting from a defect in remodeling caused by failure of normal osteoclast function. The number of osteoclasts present is often increased; however, because of their failure to function normally, bone is not resorbed. Defective osteoclastic bone resorption , combined with continued bone formation and endochondral ossification, results in thickening of cortical bone and sclerosis of the cancellous bone. **Although a number or types have been identified, these pathoses group into two major clinical patterns :(1) infantile and (2) adult osteopetrosis. Although the exact prevalence has not been determined, it is estimated to be 1 in**

100,000 to 1 in 500,000. The clinical severity of the disease varies widely, even within the same pattern of osteopetrosis.

Clinical and Radiographic Features

Infantile osteopetrosis: Patients discovered with osteopetrosis at birth or in early infancy usually have severe disease that is termed malignant osteopetrosis. In most cases, infantile osteopetrosis is inherited as an autosomal recessive trait and leads to a diffusely sclerotic skeleton, marrow failure, frequent fractures, and evidence of cranial nerve compression are common. The initial signs of infantile osteopetrosis often are normocytic anemia with hepatosplenomegaly resulting from compensatory extramedullary hematopoiesis. Increased susceptibility to infection is common as a result of granulocytopenia. Facial deformity develops in many of the children, manifesting as a broad face, hypertelorism, snub nose, and frontal bossing. Tooth eruption almost always is delayed. Failure of resorption and remodeling of the skull bones produces narrowing of the skull foramina that press on the various cranial nerves and result in optic nerve atrophy and blindness, deafness, and facial paralysis. In spite of the dense bone, pathologic fractures are common. Osteomyelitis of the jaws is a common complication of tooth extraction.

Radiographically

There is a widespread increase in skeletal density with defects in metaphyseal remodeling. The radiographic distinction between cortical and cancellous bone is lost. In dental radiographs, the roots of the teeth often are difficult to visualize because of the density of the surrounding bone. Less severe variants of infantile osteopetrosis exist and have been termed intermediate osteopetrosis. Affected patients often are asymptomatic at birth but frequently exhibit fractures by the end of the first decade.

Adult osteopetrosis: Adult osteopetrosis is usually discovered later in life and exhibits less severe manifestations. In most patients, this pattern is inherited as an autosomal dominant trait and has been termed benign osteopetrosis. The axial skeleton usually

reveals significant sclerosis whereas the long bones demonstrate little or no defects. Approximately 40% are asymptomatic, and marrow failure is rare. Occasionally; the diagnosis is discovered initially on review of dental radiographs that reveal a diffuse increased radiopacity of the medullary portions of the bone. In symptomatic patients, bone pain is frequent. Two major variants of adult osteopetrosis are seen. In one form, cranial nerve compression is common, although fractures occur rarely. In contrast, the second pattern demonstrates frequent fractures, but nerve compression is uncommon. When the mandible is involved, fracture and osteomyelitis after tooth extraction are significant complications.

Histopathologic Features

Several patterns of abnormal endosteal bone formation have been described. These include the following:

- Tortuous lamellar trabeculae replacing the cancellous portion of the bone
- Globular amorphous bone deposition in the marrow spaces
- Osteophytic bone formation.
- Numerous osteoclasts may be seen, but there is no evidence that they function because Howship's lacunae are not visible.

Treatment and Prognosis

Because of the mild severity of the disease, adult osteopetrosis is usually associated with long-term survival.

1-Bone marrow transplantation is the only hope for permanent cure.

2-Interferon gamma-1 b, often in combination with calcitriol, has been shown to reduce bone mass, decrease the prevalence of infections, and lower the frequency of nerve compression.

3-administration of corticosteroids to increase circulating red blood cells and platelets, parathormone, macrophage colony stimulating factor, and erythropoietin.

4-The antibiotics most frequently selected include penicillin, clindamycin, cephalexin, cefotaxime, tobramycin, and gentamicin.

Cleidocranial dysplasia

Best known for its dental and clavicular abnormalities, cleidocranial dysplasia is a disorder of bone caused by a defect in the CBFAI gene of chromosome 6p21. This gene normally guides osteoblastic differentiation and appropriate bone formation. The process was initially thought to involve only membranous bones (e.g., clavicles, skull, flat bones) but now is known also to affect endochondral ossification and to represent a generalized disorder of skeletal structures. The disease shows an autosomal dominant inheritance pattern, but as many as 40% of cases appear to represent spontaneous mutations. This condition formerly was known as *cleidocranial dysostosis*.

Clinical and Radiographic Features

The bone defects in patients with cleidocranial dysplasia chiefly involve the clavicles and skull, although a wide variety of anomalies may be found in other bones. The clavicles are absent, either unilaterally or bilaterally, in about 10% of all cases. More commonly, the clavicles show varying degrees of hypoplasia and malformation. The muscles associated with the abnormal clavicles are under developed. The patient's neck appears long: the shoulders are narrow and show marked drooping. The absence or hypoplasia of the clavicles leads to an unusual mobility of the patient's shoulders. In some instances, the patient can approximate the shoulders in front of the chest. Although the clavicular defects result in variations of the associated muscles, function is remarkably good. The appearance of the patient affected by cleidocranial dysplasia often is diagnostic. The patients tend to be of short stature and have large heads with pronounced frontal and parietal bossing. Ocular hypertelorism and a broad base of the nose with a depressed nasal bridge often are noted. On skull radiographs, the sutures and fontanelles show delayed closure or may remain open throughout the patient's life. Secondary centers of ossification appear in the suture lines, and many wormian bones

may be seen. The gnathic and dental manifestations are distinctive and may lead to the initial diagnosis. The patients often have a narrow, high-arched palate, and there is an increased prevalence of cleft palate. Prolonged retention of deciduous teeth and delay or complete failure of eruption of permanent teeth are characteristic features. Upon review of dental radiographs, the most dramatic finding is the presence of numerous unerupted permanent and supernumerary teeth, many of which frequently exhibit distorted crown and root shapes. The number of supernumerary teeth can be impressive, with reports of some patients demonstrating greater than 60 such teeth. In addition to the dental alterations, review of panoramic radiographs also reveals an increased prevalence of a number of additional osseous malformations. The mandible often demonstrates coarse trabeculation with areas of increased density, narrow ascending rami, and slender, pointed coronoid processes. The maxilla often is associated with a thin zygomatic arch and small or absent maxillary sinuses. Although young patients typically exhibit a relatively normal jaw relationship, as the individuals age, a short lower face height, acute gonial angle, anterior inclination of the mandible, and mandibular prognathism. Clinicians believe that these changes may be from inadequate vertical growth of the maxilla and hypoplastic alveolar ridge development caused by delay or lack of eruption of the permanent teeth.

Histopathologic Features

The reason for failure of permanent tooth eruption in patients with cleidocranial dysplasia is not understood well. Microscopic study of unerupted permanent teeth shows that these teeth lack secondary cementum.

Treatment and Prognosis

No treatment exists for the skull, clavicular, and other bone anomalies associated with cleidocranial dysplasia. Most patients function well without any significant problems. It is not unusual for an affected individual to be unaware of the disease until some professional calls it to his or her attention.

Treatment of the dental problems associated with the disease, however, may be a major problem. Therapeutic options include full-mouth extractions with denture construction, autotransplantation of selected impacted teeth followed by prosthetic restoration, or removal of primary and supernumerary teeth followed by exposure of permanent teeth that are subsequently extruded orthodontically. The latter mode of therapy appears to be the treatment of choice; if performed before adulthood, it can prevent the short lower face height and mandibular prognathism.

Focal osteoporotic marrow defect

The focal osteoporotic marrow defect is an area of hematopoietic marrow that is sufficient in size to produce an area of radiolucency that may be confused with an intraosseous neoplasm. The area does not represent a pathologic process, but its radiographic features may be confused with a variety of pathoses. The pathogenesis of this condition is unknown. Various theories include the following:

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

Clinical and Radiographic Features

The focal osteoporotic marrow defect is invariably asymptomatic and is detected as an incidental finding on a radiographic examination. The area appears as a radiolucent lesion, varying in size from several millimeters to several centimeters in diameter. In many instances, when discovered in panoramic radiographs, the area appears radiolucent and somewhat circumscribed; however, upon review of higher detailed periapical radiographs, the defect typically exhibits ill-defined borders and fine central trabeculations. More than 75% of all cases are discovered in adult women. About 70% occur in the posterior mandible, most often in edentulous areas. No expansion of the jaw is noted clinically.

Histopathologic Features

Microscopically, the defects contain cellular hematopoietic marrow, Lymphoid aggregates may be present. Bone trabeculae included in the biopsy specimen show no evidence of abnormal osteoblastic or osteoclastic activity.

Treatment and Prognosis

The radiographic findings, although often suggestive of the diagnosis, are not specific and may simulate those of a variety of other diseases. incisional biopsy, therefore, often is necessary to establish the diagnosis. Once the diagnosis is established, no further treatment is needed. The prognosis is excellent and no association between focal osteoporotic marrow defects and anemia or other hematologic disorders has been established.

Idiopathic osteosclerosis

Idiopathic osteosclerosis refers to a focal area of increased radiodensity that is of unknown cause and 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. These sclerotic areas are not restricted to the jaws, and radiographically similar lesions may be found in other bones. Similar radiopaque foci may develop in the periapical areas of teeth with non vital or significantly inflamed pulps; these lesions most likely represent a response to a low-grade inflammatory stimulus. Such reactive foci should be designated as condensing osteitis or focal chronic sclerosing osteomyelitis and should not be included under the designation of idiopathic osteosclerosis. Because past studies did not distinguish the idiopathic lesions from those of inflammatory origin, confusion in terminology has resulted.

Clinical and Radiographic Features Although previous studies often are difficult to interpret because of differences in diagnostic criteria, the prevalence appears to be

approximately 5%, with some investigators suggesting a slightly increased frequency in blacks and Asians. No significant sex predilection is seen. Upon review of several studies with long-term follow-up, a pattern has emerged. Although exceptions can be seen, most areas of idiopathic osteosclerosis arise in the late first or early second decade. Once noted, the lesions may remain static, but many reveal a slow increase in size. In almost all cases, once the patient reaches full maturity, all enlargement ceases and the sclerotic area stabilizes.

In a smaller percentage, the lesion diminishes or undergoes complete regression. The peak prevalence of osteosclerosis occurs in the third decade, with the attainment of peak bone mass seen in the fourth decade. Idiopathic osteosclerosis is variably asymptomatic, not associated with detectable cortical expansion, and is typically detected during a routine radiographic examination. About 90% of examples are seen in the mandible, most often in the first molar area. The second premolar and second molar areas also are common sites. In most cases, only one focus of sclerotic bone is present. A small number of patients have two or even three separate areas of involvement.

Radiographically

The lesions are characterized by a well-defined, rounded, or elliptic radiodense mass. Although the majority is uniformly radiopaque, occasional large lesions demonstrate a non homogeneous mixture of increased and reduced radiopacity. This is most likely due to variation in the three-dimensional shape of the lesion and is unrelated to differences in the mineral content of the mass. The lesions vary from 3 mm to more than 2.0 cm in greatest extent.

A radiolucent rim does not surround the radiodense area. Most examples of idiopathic osteosclerosis are associated with a root apex. In a lesser number of cases, the sclerotic area may extend into or be located only in the interradicular area is located in the jaw, with no apparent relationship to a tooth. Rarely, the sclerotic bone may surround all or portions of an impacted tooth. Root resorption and movement of teeth have been noted but are uncommon.

Histopathologic Features

In the few microscopic studies that have been reported, the lesion consists of 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 considered only if associated symptoms or significant cortical expansion is present. Although idiopathic osteosclerosis demonstrates radiographic and histopathologic similarities with a compact osteoma, the lack of cortical expansion and failure of continued growth rule against a neoplastic process.

Differentiation from condensing osteitis may be difficult; but in the absence of a deep restoration or caries, a periapical radiodense area associated with a vital tooth is likely to represent idiopathic osteosclerosis.

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 for idiopathic osteosclerosis, because there is little or no tendency for the lesions to progress or change in adulthood.

Paget's disease of bone (osteitis deformans)

Paget's disease of bone is a disease characterized by abnormal resorption and deposition of bone, resulting in distortion and weakening of the affected bones. The cause of Paget's disease is unknown, but inflammatory, genetic and endocrine factors may be contributing agents. In some studies, 15% to 30% of affected patients have a positive family history of the disease. The possibility that the disease is the result of a slow virus infection has received considerable attention in recent years, but a viral cause remains unproven, inclusion bodies identified as nucleocapsids from a paramyxo

virus have been detected in osteoclasts in patients with Paget's disease, but a cause-and effect relationship has not been established .

Clinical and Radiographic Features

Paget's disease is relatively common, although there is a marked geographic variance in its prevalence. It is more common in Britain than in the United States, whereas it is rare in Africa and Asia. The disease principally affects older people and is rarely encountered in patients younger than 40 years of age. Men are affected more often than women, and whites are affected more than blacks. Reviews have estimated that 1 in 100 to 150 individuals greater than 45 years of age have Paget's disease. Subclinical disease is not rare, and an increased number of cases are being seen as the population ages. Asymptomatic disease often is discovered in radiographs taken for unrelated reasons or from an unexpected elevation in serum alkaline phosphatase. The frequency increases with age and the true prevalence (including undiscovered subclinical disease) probably ranges from 1% in the fifth decade to 10% in the tenth decade. Although the disease may be monostotic (limited to one bone), most cases of Paget's disease are polyostotic (more than one bone is affected). Symptoms vary; and some patients may remain relatively asymptomatic. Bone pain, which may be quite severe, is a common complaint. Affected bones become thickened, enlarged, and weakened. An involvement of weight-bearing bone often leads to a bowing deformity, Paget's disease affecting the skull generally leads to a progressive increase in the circumference of the head. Jaw involvement is present in approximately 17% of patients diagnosed with Paget's disease. Maxillary disease, which is far more common than mandibular involvement, results in enlargement of the middle third of the face. In extreme cases, the alteration results in a lion like facial deformity (leontiasis ossea). Nasal obstruction, enlarged turbinates, obliterated sinuses, and deviated septum may develop secondary to maxillary involvement. The alveolar ridges tend to remain symmetric but become grossly enlarged. If the patient is dentulous, the enlargement causes spacing of the teeth. Edentulous patients may complain that their dentures no longer fit because of the increased alveolar size.

Radiographically

The early stages of Paget's disease reveal a decreased radiodensity of the bone and alteration of the trabecular pattern. Particularly in the skull, large circumscribed areas of radiolucency may be present (osteoporosis circumscripta). During the osteoblastic phase of the disease, patchy areas of sclerotic bone are formed, which tend to become confluent. The patchy sclerotic areas often are described as having a "cotton wool" appearance. On radiographic examination, the teeth often demonstrate extensive hypercementosis.

On initial discovery of Paget's disease, bone scintigraphy should be performed to evaluate fully the extent of involvement. When the mandible is affected, the bones can may demonstrate marked uptake throughout the entire mandible from condyle to condyle, a feature that has been termed black beard or Lincoln's Sign. Radiographic findings of Paget's disease may resemble those of cemento-osseous dysplasia. Patients with presumed cemento-osseous dysplasia who demonstrate clinical expansion of the jaws should be evaluated further to rule out Paget's disease.

Histopathologic Features

Microscopic examination shows an apparent uncontrolled alternating resorption and formation of bone in the active resorptive stages, numerous osteoclasts surround bone trabeculae and show evidence of resorptive activity. Simultaneously, osteoblastic activity is seen with formation of osteoid rims around bone trabeculae. A highly vascular fibrous connective tissue replaces the marrow. A characteristic microscopic feature is the presence of basophilic reversal lines in the bone. These lines indicate the junction between alternating resorptive and formative phases of the bone and result in a "jig saw puzzle." or "mosaic." appearance of the bone. In the less active phases, large masses of dense bone showing prominent reversal lines are present.

Diagnosis Patients with Paget's disease show :

1-high elevations in serum alkaline phosphatase levels but usually have normal blood calcium and phosphorus levels.

2-Urinary hydroxyl proline levels also may be elevated markedly.

3-Newer and more sensitive markers of bone resorption are N-telopeptides and pyridinoline cross-link assays. The clinical and radiographic features, combined with supportive laboratory findings, are typically sufficient for diagnosis. Histopathologic examination can be confirmatory but often is unnecessary for a strong presumptive diagnosis

Treatment and Prognosis

Although Paget's disease is chronic and slowly progressive, it is seldom the cause of death. In patients with more limited involvement and no symptoms, treatment often is not required.

1-In asymptomatic patients, systemic therapy is usually not initiated unless the alkaline phosphatase is more than 25% to 50% above normal.

2-Use of parathyroid hormone antagonists, such as calcitonin and biphosphonates, can reduce bone turnover and improve the biochemical abnormalities.

3-Edentulous patients may require new and larger dentures periodically to compensate for progressive enlargement of the alveolar processes.

4-Dental complications include difficulties in extraction of teeth exhibiting significant hypercementosis.

5-Development of a malignant bone tumor, usually an osteosarcoma, is a recognized complication of Paget's disease. Osteosarcoma in adults over the age of 40 is quite uncommon in individuals who do not have Paget's disease.

6-Benign and malignant giant cell tumors also may develop in bones affected by Paget's disease. Most of these occur in the craniofacial skeleton.

Idiopathic osteosclerosis

Idiopathic osteosclerosis refers to a focal area of increased radiodensity that is of unknown cause and 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.

These sclerotic areas are not restricted to the jaws, and radiographically similar lesions may be found in other bones.

Massive osteolysis (gorham disease; gorham stout syndrome; vanishing bone disease; phantom bone disease)

Massive osteolysis is a rare disease that is characterized by spontaneous and usually progressive destruction of one or more bones. The destroyed bone initially is replaced by a vascular proliferation. The affected area does not regenerate or repair itself; eventually, the site of destruction fills with dense fibrous tissue.