Review Article

FIBROUS DYSPLASIA – A REVIEW

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Abstract

Fibrous dysplasia is a common benign skeletal lesion that may involve one bone (monostotic) or multiple bones (polyostotic) and occurs throughout the skeleton with a predilection for the long bones, ribs, and craniofacial bones and is equally found in both genders and is not inherited. Most lesions are monostotic, asymptomatic, and identified incidentally and can be treated with clinical observation and patient education. Its etiology has been linked to an activating mutation of Gsα and the downstream effects of the resultant increase in Camp. Fibrous dysplasia may occur as a component of McCune-Albright syndrome or the rare Mazabraud syndrome. The radiological picture is somewhat variable, including a ground-glass appearance, expansion of the bone, and sclerosis surrounding the lesion. Histologically, fibrous dysplasia shows irregularly-shaped trabeculae of immature, woven bone in a background of variably cellular, loosely arranged fibrous stroma. It may be complicated by pathologic fracture, and rarely by malignant transformation. This review examines interesting issues surrounding the etiology of fibrous dysplasia, its clinical and laboratory manifestations, radiological picture, utility of bone biopsy, gross and microscopic pathology, complications, and its differential diagnostic considerations.

Key Words: - Fibrous dysplasia, McCune-Albright syndrome, Monostotic form, Polyostotic form

Introduction

Fibrous dysplasia a developmental tumour-like condition still remains as a clinico-pathologic challenge for many reasons. Although usually easily diagnosed, fibrous dysplasia may present with clinical and radiographic features that may border with other benign fibro-osseous lesions of the skeleton and (although rarely) may be confused with certain elusive types of malignancies.[1,2] Mention of fibrous dysplasia first appeared in the literature in 1937 when Albright and co-workers reported a disease showing cutaneous pigmentation and endocrine disorder in addition to fibrous dysplasia.[3]

The term fibrous dysplasia of bone was first used by Lichtenstein in 1938 to describe a condition to which attention had been drawn by Hunter and Turnbull (1931). Fibrous dysplasia is a rare benign intramedullary fibro-osseous lesion, which may present in either monostotic or polyostotic forms.[4,5] It is a genetic non-inherited condition caused by missense mutation in the *GNAS1* gene on chromosome 20. Fibrous dysplasia is characterized by abnormal proliferation of fibrous tissue interspersed with normal or immature bone, and may be associated with endocrine dysfunction, abnormal pigmentation, and precocious puberty in girls.[6] It occurs in equal proportions in males and females, most often during the first two decades of life.[7] The abnormal skin pigmentation also tends to be present on the same side.[8] The initial clinical sign is usually a painless enlargement of the affected bone. Other signs and symptoms include bone pain, pathologic fractures, and bone deformities.[9,10] Malignant transformation is rare, and is usually precipitated by radiation therapy[11]

Etiology and Pathophysiology

Fibrous dysplasia is postulated to occur as a result of a developmental failure in the remodelling of primitive bone to mature lamellar bone and a failure of the bone to realign in response to mechanical stress. Failure of maturation leaves a mass of immature isolated trabeculae enmeshed in dysplastic fibrous tissue that are turning over constantly but never (or very, very slowly) completing the remodelling process.[12] In addition, the immature matrix does not mineralize normally. The combination of a lack of stress alignment and insufficient mineralization results in substantial loss of mechanical strength, leading to the development of pain, deformity, and pathologic fractures.[13]

The etiology of fibrous dysplasia has been linked with a mutation in the *GNAS1* gene that encodes the alpha subunit of the stimulatory G protein-coupled receptor, Gsα, and is located at chromosome 20q13.2–13.3.[13,14] The activating mutations occur post-zygotically, replacing the arginine residue amino acid with either a cysteine or a histidine amino acid. All cells that derive from the mutated cells manifest the dysplastic features. The clinical presentation varies, depending on the location of the mutation in the cell mass and the size of the cell mass during embryogenesis when the mutation occurs.[15] Severe disease may be associated with an earlier mutational event that leads to a larger number or a more widespread distribution of mutant cells. The sporadic occurrence of these diseases and the characteristic lateralized pattern of skin and bone involvement in the polyostotic forms of fibrous dysplasia suggest this mosaic distribution of abnormal cells. The Gsα mutation was first identified in patients with McCune-Albright syndrome, and the Gsα gene has also been linked to other endocrine tumours and human diseases.[15] The strongest evidence to support a genetic link to the etiology of fibrous dysplasia was found in an experimental study by Bianco *et al* who isolated Gsα genes from patients with McCune-Albright syndrome, transplanted them into immunocompromised mice, and induced dysplastic bone production.[16]

The mutation selectively inhibits GTPase activity, leading to constitutive activation of adenylate cyclase, increased cell proliferation, and inappropriate cell differentiation, resulting in overproduction of a disorganized fibrotic bone matrix in polyostotic and monostotic fibrous dysplasia.[17,18] It is now apparent that the constitutive elevation in cAMP level induced by Gsα mutations leads to alterations in the expression of several target genes, the promoters of which contain cAMP-responsive elements, such as c-fos, c-jun, interleukin-6, and interleukin-11. This, in turn, affects the transcription and expression of downstream genes and results in alterations of osteoblast recruitment and function in dysplastic bone lesions.[19,20] Interleukin-6 may be responsible for the increased numbers of osteoclasts and the bone resorption seen in fibrous dysplasia.

Weinstein *et al*. analyzed DNA from four patients with McCune-Albright syndrome and found that all four had mutations of the gene that rendered it active for the α subunit of the guanine-nucleotide binding protein (Gsα) that inhibit GTPase activity and lead to constitutive activation of adenylate cyclise and increased cyclic adenosine monophosphate (cAMP) formation.[14] Mutations were found within coding region 8 of the Gsα gene when polymerase chain reaction analysis was used to amplify the patients' genomic DNA. Other molecular studies were also used to screen for mutations. The specific location of the mutation is position 201, which usually is occupied by an arginine (R201) and is replaced by either a cysteine (R201C) or a histidine (R201H). In a multi-institution study in which similar techniques were used, Shenker *et al*. identified the mutation of residue Arg201 of Gsα in three additional patients with McCune-Albright syndrome.[21] The strongest evidence to support a genetic link to the etiology of fibrous dysplasia was found in an experimental study by Bianco *et al*., who isolated the Gsα genes from patients with McCune-Albright syndrome, transplanted them into immunocompromised mice, and induced dysplastic bone production.[22] This in vivo cellular model of fibrous dysplasia illustrated the importance of both normal and mutant cells in the development of fibrous dysplasia. Marie *et al*. showed that an activating mutation of Gsα in osteoblastic cells of patients with McCune-Albright syndrome and monostotic disease leads to constitutive activation of adenylate cyclase, increased cell proliferation, and inappropriate cell differentiation, resulting in overproduction of a disorganized fibrotic bone matrix in polyostotic and monostotic fibrous dysplasia.[23]

With the help of genetic amplification techniques, such as polymerase chain reaction, it is now possible to test for the genetic mutation in peripheral blood samples. This novel technique may have application in the diagnostic and therapeutic monitoring of patients with fibrous dysplasia.[24]

Histologic Features

The key histologic features of fibrous dysplasia are delicate trabeculae of immature bone, with no osteoblastic rimming, enmeshed within a bland fibrous stroma of dysplastic spindle shaped cells without any cellular features of malignancy. The ratio of fibrous tissue to bone ranges from fields that are totally fibrous to those filled with dysplastic trabeculae. Examination of macrosections of intact lesions reveals the margins of the lesion to be separated from surrounding bone by a thin shell of mature lamellar reactive bone. The overall impression is of a variable number of immature, non-stress oriented, disconnected dysplastic trabeculae floating in a sea of immature mesenchymal cells that have little or no collagen about them. The pattern of the bizarrely shaped trabeculae has been likened to "alphabet soup." The mesenchymal stroma surrounding the dysplastic trabeculae is relatively hypocellular and is composed of spindle-shaped primitive mesenchymal cells that produce little or no collagenous fibrils. There is a characteristic absence of plump osteoblasts rimming the isolated immature trabeculae, which often have abnormally thick seams of osteoid, similar to those seen in osteomalacia. These trabeculae, which fail to undergo remodelling, seldom contain cement lines. Multiple delicate capillaries are found throughout the lesion and, when injured, incite a giant-cell reactive process. Lobules of cartilage are infrequently seen and, when present, are composed of mature hyaline cartilage

Differential diagnosis

Entities that come into the differential diagnosis of fibrous dysplasia include non-ossifying fibromas, osteofibrous dysplasia, cemento-osseous dysplasia, simple bone cysts, adamantinoma, low-grade intramedullary osteosarcoma, and Paget's disease, sarcoma, and cartilaginous tumors.[25,26] Non-ossifying fibromas are common benign fibrous lesions of bone. They originate eccentrically in the growing metaphysis, are usually asymptomatic, and spontaneously regress with age. Non-ossifying fibromas can be distinguished from fibrous dysplasia by their intra-cortical origin, smaller size, lack of intra-lesional ossification, and spontaneous regression.[13] Osteofibrous dysplasia, or ossifying fibroma, first identified as a distinct entity in 1976 by Campanacci, is a rare lesion localized almost exclusively to the distal third of the tibia or fibula. It is usually identified in children younger than 10 years of age, and has a remarkable radiographic resemblance to fibrous dysplasia.[27] Histologically, osteofibrous dysplasia can be distinguished from fibrous dysplasia by the presence of lamellar bone and osteoblastic rimming of bone trabeculae. Immunohistochemically, in contrast with fibrous dysplasia, it is commonly reactive for keratin, neurofibromin, S-100 protein, and Leu 7.[28] When a differential diagnosis is not possible on the basis of clinical and radiographic features, a molecular analysis can be helpful.

Tissue from an area of osteofibrous dysplasia does not have the characteristic genetic mutation seen with fibrous dysplasia.[13] These two lesions can also be distinguished by testing for proliferating cell nuclear antigen expression on osteoblasts within the lesion. In a retrospective clinic-pathologic analysis, Maki *et al* demonstrated that bone-lining cells in fibrous dysplasia are negative for proliferating cell nuclear antigen expression, whereas

osteoblasts in osteofibrous dysplasia are positive.[29] Cemento-osseous dysplasia is a fairly common fibroosseous lesion of the jaw, which can be described as a benign, self-limiting fibro-osseous condition, occurring possibly as a reaction to local injury. It can have a similar radiologic appearance to that of fibrous dysplasia. However, biopsy can help in differentiating the two. Cemento-ossifying dysplasia in histopathologic section shows a fibrous connective tissue stroma with numerous areas of hemorrhage. Within this connective tissue background is seen a mixture of woven bone and numerous irregularly shaped cementum like particles.[25]

Simple bone cysts tend to be more radiolucent than lesions of fibrous dysplasia, produce greater enlargement of the affected area, be surrounded by a thinner amount of lamellar bone, and move away from the growth plate with skeletal growth. If clinically indicated, aspiration may be helpful for differentiating between the two lesions. Straw colored fluid aspirated from the cyst and complete filling of the radiolucent lesion with contrast material strongly favour the diagnosis of a unicameral bone cyst.[13] Adamantinoma is a low-grade malignant tumour found almost exclusively in the anterior aspect of the tibia. Its two distinct histiogenic components include an epithelioid component of epithelial histogenesis and a fibro-osseous component of mesenchymal histogenesis. Because the anatomic site and radiographic features may resemble those of osteofibrous dysplasia and because of the histologic resemblance of the mesenchymal component, some believe that adamantinoma is a malignant variant of osteofibrous dysplasia.[30] Biopsy is often needed to differentiate between the two lesions. Maki and Athanasou recently investigated the relationship between adamantinoma and osteofibrous dysplasia using histochemistry to analyze the expression of several proto-oncogene products and extracellular matrix proteins in specimens from 25 tumours (18 osteofibrous dysplasias, three differentiated adamantinomas, and four classic adamantinomas).[31] The investigators found common expression of a number of oncoproteins and bone matrix proteins, including ones associated with mesenchymalto-epithelial cell transformation. Because of this, they concluded that osteofibrous dysplasia may represent a precursor lesion of adamantinoma.

Paget disease has a distribution that is similar to that of fibrous dysplasia, with a monostotic occurrence (skull or flat bones) or polyostotic occurrence (long bones), but it is seen in the middle, rather than the early, decades of life. It also occurs more frequently in males and in those with a Northern European ancestry. Radiographic features can vary, but on occasion the resorptive phase of Paget disease may resemble fibrous dysplasia. Juvenile Paget disease, or hereditary hyperphosphatasia, is a rare form of Paget disease that usually appears in infancy or early childhood, and it can even be present at birth. This disorder affects virtually every bone in the body, and its effects are seen easily on radiographs. The disorder is characterized by a generalized widening and often bowing of the long bones and thickening of the skull. It is readily distinguishable from fibrous dysplasia by the accompanying marked elevation in serum alkaline phosphatises level.

In conclusion, fibrous dysplasia is an uncommon benign bone disease, although severe and devastating cases have been described. It is found to exist in monostotic and polyostotic forms and is a component of McCune-Albright and Mazabraud syndromes. Biopsy is indicated for confirmation if the radiographic findings are not characteristic of fibrous dysplasia. The histopathology of fibrous dysplasia is characterized by a fibrous tissue stroma in which spicules of woven bone may be found, which are present as curled disconnected trabeculae resembling letters of the alphabet. Characteristic absence of osteoblastic rimming of the bony trabeculae is seen. Complications include occasional pathologic fracture, secondary aneurysmal bone cyst formation, and rare malignant change. Awareness of the varied histopathology, complications, and extra-osseous manifestations of fibrous dysplasia is important to ensure early accurate diagnosis and appropriate management of this disease.

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