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Conceptual Paper

The Remodeled Ossein-Fibrous Dysplasia

Anubha Bajaj*

Department of Histopathology, Panjab University/A.B. Diagnostics, India

***Corresponding Author:** Anubha Bajaj, Department of Histopathology, Panjab University/A.B. Diagnostics, India.

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Preface

Fibrous dysplasia is a benign bone lesion demonstrating intramedullary fibro-osseous proliferation occurring on account of modified osteogenesis. Fibrous dysplasia was initially scripted by Lichtenstein and Jaffe in 1942 and chronicled as "Jaffe-Lichtenstein syndrome" [1]. Fibrous dysplasia was also designated as osteitis fibrosa or generalized fibrocystic disease of bone. Fibrous dysplasia can incriminate a singular bone, denominated as monostotic fibrous dysplasia or multiple bones, termed as polyostotic fibrous dysplasia.

The developmental bony disorder is associated with failure to configure mature lamellar bone. Tumefaction is comprised of immature woven bone and fibroblast-like, spindle-shaped cells. Absence and arrested maturation of woven bone is associated with distinct clinical or syndromic manifestations.

Age of incriminated subjects, occurrence of non aggressive lesions with predilection for diaphysis of long bones and a "ground glass" matrix on radiography are features indicative of fibrous dysplasia. Cogent sampling of bone is necessitated in order to exclude malignant metamorphosis where clinical representation and imaging studies are inconclusive. Malignant metamorphosis into a sarcoma is exceptional and may be engendered with previous exposure to irradiation.

Disease characteristics

Fibrous dysplasia displays an incidence of roughly 1: 5,000 to 1:10,000 individuals and comprises of around 5% of benign bone lesions. The condition is commonly discerned in children or young adults and usually manifests before 30 years. Polyostotic fibrous dysplasia usually represents in childhood. Fibrous dysplasia can be incidentally discovered in adults subjected to imaging for unrelated conditions. A specific gender predilection is absent and male are incriminated in equivalent proportion as females [2,3].

Monostotic fibrous dysplasia is preponderant and lesions can arise within the ribs, long bones as femur and craniofacial bones as maxilla or mandible although no site of tumour emergence is exempt. Lesions are uncommon within the hands, sternum and vertebral column [2,3].

Fibrous dysplasia occurs due to developmental arrest within the cortical bone with consequent emergence of irregular trabeculae of woven bone and immature, fibroblast-like spindle-shaped cellular aggregates. Fibrous dysplasia is associated with missense or gain in function mutation within the guanine nucleotide-binding protein/α-subunit (GNAS1) gene situated upon chromosome 20q13.2.3. Subsequent overexpression of Gsα protein and enhanced downstream activity of adenyl cyclase is observed. Activation of c-jun, c-fos and Wnt/β catenin accompanies activation of Gsα. The activating mutation engenders an aberrant proliferation of fibrous tissue. Variable manifestation of GNAS mutations contribute to diversity of clinical representation [2,3].

Monostotic fibrous dysplasia is a frequent variant and comprises of nearly 75% to 80% instances [2,3].

Fibro-osseous tissue replaces normal bone thus incurring complications such as pathological fracture and compression of adjacent soft tissues or neurovascular bundles. Malignant metamorphosis is exceptional and is discovered in around < 1% subjects. Malignant conversion may arise secondary to radiation therapy adopted for treating lesions confined to distant sites [2,3].

Clinical elucidation

Fibrous dysplasia is associated with gradual expansion of bone on account of proliferation of irregular trabeculae of woven bone devoid of peripheral accumulation of osteoblasts admixed with a fibrous tissue component composed of bland, spindle-shaped cells. Lesions are intramedullary and lack destruction of superimposed cortical bone. Monostotic fibrous dysplasia is frequently asymptomatic. Fibro-osseous replacement of incriminated bone can engender pathological fracture, particularly within weight-bearing bones or upper extremities in athletic, physically active individuals [4,5].

Fibrous dysplasia is associated with diverse conditions such as

- McCune-Albright syndrome which is an exceptional disorder demonstrating frequently unilateral polyostotic fibrous dysplasia along with cutaneous pigmentation and endocrine dysfunction, generally manifesting as female precocious puberty [4,5].

- Mazabraud syndrome is an extremely exceptional variant demonstrating polyostotic fibrous dysplasia associated with singular or multiple intramuscular or soft tissue myxomas [4,5].

Monostotic fibrous dysplasia is frequently asymptomatic. Bone pain is occasional and may enhance with occurrence of pathological fracture arising due to minimalistic trauma and appearing as initial clinical manifestation. Pregnant female subjects display an enhanced possible occurrence of pain and pathological fracture. Features such as bone tenderness, bony protuberances, osseous asymmetry, associated endocrine disturbances and dermatological manifestations require evaluation [4,5].

Assessment of skeletal deformity, bone asymmetry, leg length discrepancy, classic “shepherd’s crook” deformity of proximal femur or facial involvement with orbital asymmetry is necessitated. Additional possible facial manifestations are proptosis, frontal bossing or mandibular enlargement [4,5].

Severe bone deformity is accompanied by bowing, musculoskeletal dysfunction or rapid progression of osteoarthritis. Lesions of spine predispose to scoliosis and subsequent functional impediment. Craniofacial tumefaction delineates associated deficits of cranial nerves such as loss of vision or hearing and mandate appropriate evaluation. Hereditary forms of fibrous dysplasia such as cherubism are accompanied by a pertinent family history. Malignant transformation into a sarcoma may be significantly delayed and can be assessed when associated with aggressive evolution of lesions [4,5].

Histological elucidation

On gross examination, a well circumscribed, cortical lesion is circumscribed by a sclerotic perimeter. Expansion of lesion results in an attenuated bone cortex [6,7].

On microscopy, irregular, branching and anastomosing trabeculae of woven bone appear devoid of a peripheral osteoblastic layer. Particularly, "C" and "S" shaped trabeculae of woven bone can be exemplified [6,7].

Fibrous dysplasia is composed of immature collagen and immature bone trabeculae intermingled within a fibrocellular matrix. Osteoblastic maturation arrest contributes to an absence of osteoblastic rimming of trabeculae of woven bone. Therefore, metamorphosis from normal bone to aberrant bone is sudden and abrupt [6,7].

Fibrous tissue stroma commingled with the bone trabeculae is composed of bland, spindle-shaped cells. Cytological atypia and mitotic activity is exceptional. Intervening stroma may depict foci of myxoid and adipose tissue metaplasia. Secondary aneurysmal bone cyst-like alteration can be enunciated [6,7].

Additionally, lesions of fibrous dysplasia may undergo cartilaginous metaplasia or aneurysmal bone cyst-like modification [6,7].

Immune histochemical elucidation

Majority (90%) of bone forming neoplasms express SATB2. Fibrous dysplasia is immune non reactive to keratin [2,3].

Differential diagnosis

Fibrous dysplasia incriminates diverse osseous sites and a variable representation upon imaging. Therefore, the neoplasm re-

quires segregation from various benign and malignant neoplasms such as

- Central and parosteal osteosarcoma which are destructive, low grade, gradually progressive bone neoplasms. Characteristic amplification of MDM2 gene is exemplified [8,9].

Central osteosarcoma is a tumefaction depicting cellular permeation with replacement of medullary spaces, erosion of native bone trabeculae, cortical destruction and infiltration of adjacent soft tissue. Neoplastic cells are pleomorphic, hyperchromatic and depict multiple morphologies as epithelioid, plasmacytoid, spindle-shaped, miniature spherical, clear cell and multinucleated tumour giant cells. Foci of neoplastic osteoid are deposited upon pre-existing bony trabeculae. Non neoplastic giant cells may be scattered within the tumour parenchyma [8,9].

Parosteal osteosarcoma is a gradually progressive surface neoplasm originating from extraneous periosteal layer and contributing to roughly 65% of surface osteosarcomas. The low grade, hypo-cellular neoplasm is composed of well formed bony trabeculae, osteoid, cartilaginous component and a fibrotic, malignant, spindle-shaped cellular stroma. Mitotic figures or osteoclast-like, multinucleated giant cells are absent

- Ossifying fibroma is composed of irregular bony trabeculae, akin to fibrous dysplasia. However, rimming of trabeculae with osteoblasts is prominent [8,9].
- Liposclerosing myxofibromatous tumour (LSMFT) is a condition which simulates fibrous dysplasia on clinical and morphological grounds.

Characteristically, activation of protein G is observed. The neoplasm is typically located within proximal femur. Tumefaction depicts an amalgamation of diverse histological patterns such as curvilinear trabeculae of woven bone intermingled within a paucicellular myxofibromatous tissue. Additionally, foci of ossification and adipose tissue or cartilaginous metamorphosis are delineated [8,9].

Additionally, radiological expression of monostotic fibrous dysplasia requires a segregation from conditions such as simple bone cyst, giant cell tumour, fibroxanthoma, osteoblastoma, haemangioma, osteofibrous dysplasia or Paget's disease [8,9].

Investigative assay

Plain radiography contributes significantly to cogent discernment and assessing disease extent of fibrous dysplasia. Upon plain radiography, singular or multiple, well circumscribed intramedullary lesions are encompassed by zones of sclerosis. Tumefaction is usually confined to metaphysis or diaphysis and demonstrates a "ground glass" appearance. Expansion of lesion is associated with attenuation of superimposed bone cortex [10,11].

Computerized tomography (CT) and magnetic resonance imaging (MRI) can be optimally employed to demarcate adjunctive bone lesions, assessment of soft tissue injuries secondary to fractures, neurovascular complications arising from craniofacial lesions and malignant metamorphoses. CT and MRI may also be adopted for assessing endocrine dysfunction engendered by adrenal hyperplasia, thyroid nodules and pituitary neoplasms [10,11].

Classically, plain radiographs and computerized tomography (CT) of bone lesions delineates an intrinsic "ground glass" matrix. However, aforesaid appearance may vary on account of lytic or sclerotic tumour components, probable bone expansion and attenuation of bone cortex. Bowing deformities such as femoral shepherd's crook deformity, discrepant limb length and short stature secondary to premature fusion of growth plates can be distinguished with precise imaging [10,11].

Bone scan can exemplify enhanced uptake of Technetium-99m radiotracer within polyostotic lesions which aids the assessment of disease extent [10,11].

Pertinent evaluation of tumour tissue may be mandated in lesions where imaging features indicate malignant metamorphosis [11].

Alkaline phosphatase levels are elevated in progressive neoplasms [10,11].

Therapeutic options

Fibrous dysplasia can be managed conservatively. Appropriate management of clinical symptoms is usually sufficient. Instances associated with pathological fracture or bony deformity can be subjected to surgical intervention. Asymptomatic monostotic fibrous dysplasia can be periodically monitored and does not require therapy [10,11].

Bisphosphonates are appropriately employed in order to alleviate bone pain and disease-associated osteoporosis in adults. Bisphosphonates prohibit osteoclastic bone resorption and conserve cortical bone mass, thereby reducing possible occurrence of fractures [10,11].

Surgical management is employed for treating symptomatic fibrous dysplasia and is achieved by prophylactic internal fixation of pathological fractures, especially within weakened weight-bearing bones [10,11].

Additionally, surgical manoeuvers such as correction of extremity and spine deformities or limb length discrepancies may be adopted. Craniofacial surgery can relive symptoms of nerve compression [10,11].

Cogent surgical procedures are curettage, bone grafting or insertion of fixatives such as metallic rods, plates and screws [10,11].

Figure 1: Fibrous dysplasia delineating immature bone trabeculae with immature collagen admixed within a fibrous tissue matrix [12].

Figure 2: Fibrous dysplasia exhibiting immature bone trabeculae with absent osteoblastic rimming and a surrounding cellular matrix [13].

Figure 3: Fibrous dysplasia enunciating immature bone trabeculae, immature collagen and an abundantly cellular fibrous tissue stroma [14].

Figure 4: Fibrous dysplasia exemplifying immature trabeculae of woven bone, immature collagen fibrils and an encompassing fibrotic stroma [15].

Figure 5: Fibrous dysplasia demonstrating trabeculae of immature woven bone devoid of osteoblastic rimming enmeshed within a cellular fibrous tissue stroma [16].

Figure 6: Fibrous dysplasia depicting trabeculae of immature woven bone with absent osteoblastic rimming, immature collagen and a circumscribing fibrotic stroma [17].

Figure 7: Fibrous dysplasia exhibiting immature bone trabeculae and immature collagen fibres surrounded by a stroma rich in fibrous tissue [17].

Figure 8: Fibrous dysplasia delineating trabeculae of immature woven bone devoid of osteoblastic rimming surrounded by a cellular fibrous tissue stroma [18].

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12. Image 1 Courtesy: Turkish Journal of Pathology.
13. Image 2 Courtesy: Webpathology.com.

14. Image 3 Courtesy: Wikipedia.
15. Image 4 Courtesy: Wikimedia Commons
16. Image 5 Courtesy: Asian journal of Neurosurgery.
17. Image 6 and 7 Courtesy: Pathology outlines.
18. Image 8 Courtesy: Orthobullets.com.

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