Genes Associated with Fibro-Osseous Lesion: A Review Article

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Abstract

The Fibro osseous lesion is a group of diseases or lesions that are affecting the skeletal tissue which frequently includes maxilla and mandible. The disease can also be easily described as bone disorders. A lot of research and work has been done regarding this serious disease though due to similarities in its radiographical features or histopathology, it is been very complicating to diagnose and classify FOLs. The review article focuses on different diseases that come under the fibro-osseous lesion and the genes which have been associated with the respective one in an orderly manner with their Histopathological features. One to understand this lesion the clinical correlation with radiographic involvement is necessary to diagnose this kind of dysplasia. The article also throws light on that the mandible and maxilla also suffer from localized and generalized forms of skeletal dysplasia which results in disproportionate short stature. These dysplasias always remain in a confused manner for their nomenclature. Much classification has been proposed by the different authors in different years regarding the FOLs based on gene or protein defect in these disorders.

Keywords: *Fibro osseous lesion, Genes, Dysplasia, Skeletal.*

Introduction

The fibro-osseous lesions are very serious and complicated disease which can cause severity in the function of tissue including jaws and craniofacial bones. They consist of different type of pathological disorders which includes bone dysplasia, inflammatory lesion, neoplastic lesions, and metabolic disease. These maxillofacial lesions cannot be diagnosed by taking incisional or excisional biopsy alone but the correlation of clinical and radiological features is very crucial for detecting these serious disorders. As earlier mentioned many authors have proposed different classification and the article provides the latest classification which was given by ever sole et al in the 2008.[1]

Classification: In the year 2008 ever sole and their co fellows gives a classification of fibro-osseous lesion which was based on metabolic disorders, neoplastic lesions, inflammatory disorders, and reactive processes. Based on clinical features and radiographs with the adding of Histopathological diagnosis the behavior of this disorder can be judged and the final diagnose can be made, the ever sole et al have concluded in their classification or research.[2]

1. **Bone Dysplasia:**

a. Fibrous Dysplasia – This dysplasia includes its many types including monostotic,polyostotic,and polyostotic with endocrinopathy & osteofibrous dysplasia

b. Paget's disease

c. Pagetoid heritable bone dysplasia of childhood

d. Segmental odontomaxillary dysplasia

2. **Cemento osseous dysplasia:**

a. Focal Cemento osseous dysplasia

b. Florid cement dysplasia

3. **Inflammatory processes**

a. Focal sclerosing osteomyelitis

b. Diffuse sclerosing osteomyelitis

4. **Metabolic Disorder**

a. Hyperparathyroidism

5. **Neoplastic lesions**

a. ossifying fibroma

b. hyperparathyroidism jaw lesion syndrome

c. juvenile ossifying fibroma

d. gigantiform cementomas

Fibrous Dysplasia: This dysplasia compromises of bone-forming mesenchyme that manifests as a defect in osteoblastic differentiation and maturation which is skeletal developmental anomaly. The disorder is nonhereditary having unknown cause.[3]

Gene Associated for the Cause: Mutation in the GNAS1 (guanine nucleotide-binding protein, alpha stimulating activitypolypeptide) Gene. This gene encodes a G- protein which stimulates the production of c-AMP. The mutation results in the overproduction of cAMP due to the prolonged activation of G –protein. Due to this mutation hyperthyroidism, precocious puberty and overproduction of cortisol happens which results in hyperfunction of affected endocrine organs. Secondly large café au lait spots with irregular margins can be seen which is due to the increase in proliferation of melanocytes and at last fibrous dysplasia is caused as cAMP affects the differentiation of osteoblasts. Radiographic appearance is described as ground-glass appearance which appears radiolucent on radiographs which happens due to the fibrous tissue replacing medullary bone.[4]

Molecular Pathogenesis of Fibrous Dysplasia:

- The mutation of the GNAS1 gene activates the cyclic adenosine monophosphate(c-AMP),
- Which results in the elevation of c-AMP and stimulates the endocrine receptors
- In return which activates the c-fos (proto-oncogene)
- After which the impaired differentiation of osteoblasts results in bone lesion
- & the increased in the production of melanocytes results in cutaneous pigmentation
- & the hyperfunction of endocrine cells resulting in endocrine disturbances.
- The bone lesion giving rise to Fibrous dysplasia, cutaneous pigmentation concluding Mccune Albright syndrome & the endocrine disturbances lead to Jaffe Lichtensteinsyndrome.

Histologic Features:

- Fibrillar connective, woven immature bone, irregular in shape can be seen in the lesion.
- Large osteocytes and collagen fibers can be noticed extending out in the fibrous tissue.
- Stellate osteoblasts that form the bone can be observed.
- Osteoblastic riming can be seen.
- Wide osteoid seams can be observed in the trabeculae.
- Osteoclastic activity can be noticed in the histological slide.

Treatment & Prognosis: In the maxilla the lesion is been treated non surgically maximally.

No specific medical treatment is for bone diseases. Although the use of vitamin –D and bisphosphonates can be useful in relieving pain and possibly in reconstituting lesions with normal bone. The surgical procedure includes the curettage technique and replacing the bone with autograft or allograft.[5]

The malignant transformation for this lesion is very low which can be estimated 0.4%-1%.In most times the facial and skull bones went a malignant change in polyostotic disease. The fibrosarcoma and osteosarcoma are the most common tumors. The lesion size increases with an increase in pain can be noticed in the malignant transformation with enlarged soft tissue mass.

Paget's disorder: It can also be called as osteitis deformans. The disorder commonly affects the middle-aged and elderly ones. It is a disease which is non-malignant. Usually, this disorder is asymptomatic, but the patient may develop symptoms like pain in the affected bone, neurological, and cardio complication can also be seen in complicated cases. Almost 3-5% of people in the United States of America are been affected by this disease.[6,7]

Genes and other associated Factors for the cause: The etiology of this disease is still unknown but two main theories for its cause have been proposed which include Viral i.e. paramyxoviral infection & genetic.

Genes associated with it include: TNRSF(Tumor necrosis factor receptor superfamily member -11A), Sequestrome 1 (SQSTM1), and Valosin containing protein (VCP).

Different Phases includes:

This disorder occurs in 3 phases, which includes:

- **Initial Phase:** In this phase intense Osteoclastic activity and resorption of bone occurs.
- **Secondary Phase:** In this phase osteoblasts start to produce woven bone and the mineralization is ineffective.
- **Final Phase:** In the final phase trabecular and dense cortical bone dominates the deposition.

The bones which are commonly affected by this disorder include pelvis, femur, skull, humerus, cervical spine, and thoracic spine. This disease mostly affects the axial skeleton. Pelvis, which has a high percentage in its involvement.[9]

Radiologic Findings: In the affected person one can notice these findings as;

- In skull we can noticed osteoporosis circumscripta
- Sclerotic bone can be observed
- Banana or chalk pattern transverse fractures can be seen.
- Bowed limbs

Diagnosis: Imaging tests which include x-ray and bone scan & lab tests is been performed to diagnose the disorder. In the bone scan method, radioactive material is injected into the body, and the materials directly affect the areas which include the Pagets disease and thus they are light up in the scan. In laboratory testing elevated levels of Alkaline phosphatase can be observed in the blood. [10]

Histologic Features:

- Disordered areas of resorption with an increasing number of large osteoclasts is been noticed in the initial osteolytic phase.
- Jigsaw or mosaic pattern can be observed which is a result of continuous bone removal giving small bone fragments which are irregular in shape.
- The above-mentioned pattern can be considered as the hallmark for this disease.
- The pattern is mosaic with irregular cement lines joining the area of lamellar bone.

Treatment and Prognosis: In the present scenario no specific treatment is there for osteitis deformans but the use of radiation and hormone therapy, vitamins have been used to challenge this disorder. Very better and product results have been found nowadays by using the Calcitonin, which is a parathormone antagonist produced by the thyroid gland which suppresses bone resorption. Overall the complication of this disease is not so wide and less than 1% of osteosarcoma is noticed from Paget's disease.[11,12]

Ossifying Fibroma: It is a benign neoplasm that affects the jaw which has been enlarged. This fibro-osseous lesion is featured by substitution of normal bone by newly formed calcified products like bone, cementum, or both and fibrous tissue. It is commonly seen in teenagers and young adults. It is a rare and slow-growing tumor that is non-cancerous.[13]

Gene associated with it: HRPT2 gene mutation is found to be cause for this fibro-osseous lesion. The radiographic feature reveals a radiolucent area with an increase in calcification, displacement of adjacent tooth is common. The Histologic features include interlacing collagen fibers, proliferating fibroblasts and mitotic figures can be noticed. Small foci of irregular bony trabeculae can also be observed.[14]

The treatment includes excision of the tumor and the recurrence rate is very less.

Hyperparathyroidism–jaw tumor syndrome: It is a syndrome which is an autosomal dominant disorder. It is associated with fibro-osseous jaw tumors, renal lesions and featured by parathyroid tumors. The patient who suffers from hyperparathyroidism may develop symptoms of muscle weakness, pain in the joint or bone, fatigue, and may develop kidney stones with a decrease in the density of bone.

HPT-JT is a jaw tumor which is fibro-osseous lesions that consists both the maxilla and mandible and mostly affect in the 3rd decade of life. Ossifying fibromas generally slow-growing and benign tumors that arise from the periodontal ligament in molar or premolar areas are reported to be highly involved with HPT-JT.

Gene associating for its cause: The HRPT2 gene localizes to 1q24-32 which encodes a 531-amino acid long protein, which is called parafibromin, which exerts anti-proliferative activities via interacting with cyclin D1. Germline mutation and somatic inactivation of the HRPT2 gene which lead to hyperparathyroidism –jaw tumor syndrome. The treatment involves the management

of hypercalcemia. The focus of the treatment is to reduce the level of calcium to below 11.5mg/dl.[15]

Cherubism: It a skeletal dysplasia and an autosomal dominant fibro-osseous lesions of the jaw. It is a non-neoplastic hereditary bone lesion that has a similar type of histopathological features as central giant cell granuloma. It was first described by jones in 1993. It mostly affects the children. It is also known as disseminated juvenile fibrous dysplasia or familial multilocular cystic disease of jaws.[16]

Gene associated with its cause: The mutation in the SH3BP2 (SH3 domain-binding protein 2) gene is the most identifying cause for 70-80% cases in Cherubism. In the remaining cases, the etiology is unknown. The SH3BP2 gene gives instructions for producing a protein whose exact function is still not clear. This protein has an important role in transferring chemical signals within cells, especially involving in replacing the old bone tissue with a new one which is a bone remodeling procedure. Thus mutation in the SH3BP2 gene results in producing an overactive version of this protein which can lead to the disrupting of the critical signaling pathways among cells that maintain the bone tissue. This overactive protein leads to the inflamed jawbones and alters the osteoclasts production, which on return results in the breakage of the bone tissue during remodeling.[17]

Clinical and Radio graphical Features: The children who are been affected are normal at birth until 14 months to 3 years of age, after that clinical evidence can be seen which includes the symmetrical enlargement of the jaws. The symptom starts with deforming maxillary and mandibular overgrowth with a problem in respiration and defects in hearing and vision. Noonan's syndrome can be observed in some cases of Cherubism which involves obstructive sleep apnea, gingival fibromatosis with orbital involvement.

The radiograph is characterized by multilocular cystic expansion of the jaws. Numerous unerupted teeth with the destruction of alveolar bone will displace the teeth which results in floating tooth syndrome.

Histopathology: Multinucleated giant cells can be seen, fibroblasts are spindle-shaped present in the connective tissue stroma, water logged & granular. Numerous small vessels can be noticed.

The treatment is done by surgery to correct the deformities of the jaw and is very rarely indicated. The surgery is usually done after puberty when the remission phase reached.

Periapical Cemento–Osseous Dysplasia: This dysplasia is a kind of fibro-osseous lesion which is associated with the apex of a tooth. The disorder has a dominant autosomal inheritance pattern. The etiology of this fibro-osseous lesion is unknown. Usually the unifocal or multifocal dysplasia does not need any treatment but the larger lesion requires surgery to prevent further complication.[18]

Differential Diagnosis: The fibro-osseous lesion should be differentiated from the other lesion which can produce the same radiographic and histological features. Some of the important lesion which should be differentiated from fibro-osseous lesion are-

- Osteoblastoma
- Giant cell reparative granuloma
- Sclerosing osteomyelitis

Conclusion

The fibro-osseous lesion should not be diagnosed or classified only based on histological features as they all can show almost similar features. These craniofacial lesions should be judged by clinical correlation and radiographic involvement. The classification can only be done by radiographic appearance and their growth pattern. The genes which are involved in this type of lesion and their mutation provide a better idea of knowing the pathogenesis of these disorders. However, in this era, some of the cause of this lesion is found to be unknown. Research is been made for detecting the important causative factors which can further lead to the prevention and proper diagnosing of this lesion.

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