Fibrous Dysplasia of Bone: A Comprehensive Review of Pathogenesis, Clinical Variants, and Evolving Management Strategies

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ABSTRACT

Fibrous dysplasia (FD) is a rare, non-hereditary, congenital developmental anomaly of the skeletal system characterised by the replacement of normal bone by proliferating fibrous tissue admixed with irregular, immature bony trabeculae. The underlying defect resides in the osteoblastic differentiation and maturation of bone-forming mesenchymal cells. With an estimated prevalence of approximately 1 in 30,000 individuals, FD accounts for nearly 5–7% of all benign bone tumours and 2.5% of all bone lesions. The disease is initiated by a postzygotic somatic gain-of-function mutation in the GNAS1 gene, located on chromosome 20q13.2–13.3, which encodes the alpha subunit of the stimulatory G-protein (Gsα). This mutation constitutively activates the Gsα–cAMP signalling axis, impairing osteoblastic differentiation and augmenting osteoclastogenesis through interleukin-6 (IL-6) upregulation. Clinically, FD is stratified into monostotic (70–80%), polyostotic (20–30%), and craniofacial forms; the most severe expression is McCune-Albright syndrome (MAS), which additionally encompasses café-au-lait macules and hyperfunctioning endocrinopathies. The craniofacial skeleton is among the most frequently involved regions, with nine out of ten craniofacial FD patients presenting before the age of five years. Radiographically, the hallmark 'ground-glass' appearance reflects replacement of normal trabecular bone by fibrous matrix. Histologically, the lesion is characterised by spindle-shaped fibroblasts in a storiform pattern with irregular woven-bone trabeculae resembling Chinese letters. Management remains predominantly surgical, with medical adjuncts including bisphosphonates and, more recently, denosumab (a RANKL inhibitor), offering promising results in refractory cases. This review comprehensively summarises the etiology, molecular pathogenesis, clinical features, oral manifestations, histopathology, radiographic features, differential diagnosis, treatment options, and long-term prognosis of fibrous dysplasia.

Keywords: fibrous dysplasia, McCune-Albright syndrome, GNAS1 mutation, monostotic, polyostotic, craniofacial dysplasia, bisphosphonate, denosumab.

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INTRODUCTION

Fibrous dysplasia was first described by Von Recklinghausen in 1891 and subsequently characterised in seminal works by Lichtenstein (1938) and Jaffe (1942), hence the eponym Jaffe-Lichtenstein syndrome.[1,2] It represents an intramedullary fibro-osseous lesion in which normal medullary bone is replaced by proliferating fibrous tissue interspersed with islands of immature, woven bony trabeculae.[3] This process results from a fundamental defect in osteoblastic differentiation and maturation within the bone-forming mesenchyme, rendering the affected bone structurally inferior and biomechanically compromised.[4]

Epidemiologically, fibrous dysplasia is estimated to affect approximately 1 in 30,000 individuals globally, accounting for 5–7% of all benign bone tumours and roughly 2.5% of all bone lesions.[5,6] There is no significant gender predilection overall, although some series report a mild female predominance, particularly for polyostotic disease. Initial clinical manifestations most commonly emerge in the first two decades of life, with the craniofacial form typically presenting before the age of five.[7]

The lesion is clinically and pathologically significant in the maxillofacial region owing to its capacity to cause progressive facial deformity, pain, pathological fractures, and, in severe craniofacial involvement, neurosensory deficits including blindness and hearing loss.[8] Although any bone may be affected, the long bones (especially the femur), craniofacial skeleton, and ribs are most frequently involved. The characteristic deformity of the proximal femur—termed coxa vara or shepherd's crook deformity—is a hallmark of severe polyostotic disease.[9] The spectrum of clinical expression ranges from asymptomatic, incidentally discovered solitary lesions to the debilitating triad of McCune-Albright syndrome (MAS), encompassing polyostotic FD, cutaneous café-au-lait macules, and multiple hyperfunctioning endocrinopathies.[4]

Despite decades of research, no pharmacological agent has been proven to definitively arrest or reverse the underlying pathological process. Treatment remains largely symptom-driven, combining surgical contouring, fracture stabilisation, and medical management with bisphosphonates.[10] Emerging evidence supports the role of denosumab, a RANKL inhibitor, in cases refractory to conventional therapy.[11,12] This review aims to provide an updated, comprehensive synthesis of the etiology, pathogenesis, clinical features, oral manifestations, radiographic and histopathological characteristics, differential diagnosis, and management of fibrous dysplasia, with emphasis on current evidence.

ETIOLOGY AND MOLECULAR PATHOGENESIS

Fibrous dysplasia is caused by a sporadic, postzygotic somatic gain-of-function mutation in the GNAS1 gene (guanine nucleotide-binding protein, alpha-stimulating activity polypeptide), located on chromosome 20q13.2–13.3.[4] This gene encodes the alpha subunit of the stimulatory G-protein (Gsα), a crucial component of intracellular signal transduction pathways.[13] The specific mutation most frequently involves arginine 201 in exon 8, substituted by either histidine (R201H) or cysteine (R201C), with R201H being the more prevalent variant.[6] Less commonly, a mutation at codon 227 (Q227L) has been identified. A 2024 meta-analysis confirmed that GNAS mutations show a high detection rate in FD and that mutation type is significantly associated with FD subtype (OR = 3.51, 95% CI = 1.05–11.72; $p < 0.05$).[6]

At the cellular level, the R201 substitution impairs intrinsic GTPase activity of Gsα, rendering the protein constitutively active. This results in persistent, unregulated adenylyl cyclase stimulation and consequent overproduction of cyclic adenosine monophosphate (cAMP) in affected cells.[4,6] Elevated intracellular cAMP profoundly disrupts skeletal stem cell differentiation: mutant stromal progenitor cells fail to undergo normal osteoblastic maturation, instead producing structurally abnormal, immature woven bone embedded in a fibrous matrix.[4,8] The WNT/β-catenin signalling pathway, which governs osteoblastogenesis, is also aberrantly activated downstream of the mutant Gsα.[4] Furthermore, excess cAMP stimulates osteoclastogenesis through the upregulation of interleukin-6 (IL-6), resulting in accelerated bone resorption within dysplastic lesions.[8]

Because the mutation is postzygotic, it creates a mosaic organism: only cells derived from the originally mutated stem cell carry the defect. The timing of the mutation during embryogenesis is the primary determinant of clinical severity.[14] Mutations arising early in embryonic life, when the mutant cell can propagate into multiple germ layers, produce the triad of MAS affecting bone, skin, and endocrine organs. Mutations occurring later, during postnatal bone remodelling, restrict the defect to a single skeletal site, yielding monostotic fibrous dysplasia.[15] The affected endocrine organs exhibit hyperfunction, manifesting clinically as precocious puberty (most common), hyperthyroidism, growth hormone excess, and hypercortisolism. Cutaneous melanocytes harbouring the mutation display increased proliferation, producing large café-au-lait macules with characteristic irregular ('coast of Maine') borders, in contrast to the smooth-bordered lesions of neurofibromatosis.[4]

CLINICAL FEATURES

The clinical presentation of fibrous dysplasia is heterogeneous, determined primarily by the number of bones involved, the anatomical location of lesions, and the severity of the underlying GNAS mutation. There is no significant gender predilection, and initial manifestations typically arise between the ages of 3 and 15 years, although lesions may occasionally be discovered incidentally in adults.[4] The disease is conventionally classified into three subtypes: monostotic FD (MFD), polyostotic FD (PFD), and craniofacial FD (CFD).

McCune-Albright syndrome represents the most severe systemic variant.[4,8]
Bone pain is the most common presenting complaint, often attributable to microfractures within the weakened fibrous matrix or to periosteal stretching from expanding lesions. Progressive deformity, swelling, and pathological fractures constitute the other major presenting features. Cranial nerve involvement may result in visual impairment, hearing loss, hyposmia, or anosmia when relevant foramina are encroached upon by expanding craniofacial lesions.[8] Females with FD may experience exacerbation of bone pain during pregnancy and menstruation, attributed to the presence of oestrogen receptors within dysplastic bone.[9]

Monostotic Fibrous Dysplasia (MFD)

MFD is the most prevalent form, constituting 70–80% of all FD cases.[4,7] It involves a single bone and typically runs a relatively benign course. Lesions tend to expand during periods of skeletal growth and stabilise following skeletal maturity, though incomplete stabilisation may occur in some patients. The rib is the most commonly affected site in the general skeleton, followed by the femur, tibia, craniofacial bones, and humerus. In the craniofacial region, the maxilla is more frequently involved than the mandible, although mandibular lesions are well documented.[4] When the maxilla is involved, the condition may produce a characteristic leonine facial appearance, historically termed leontiasis ossea, owing to marked facial expansion and coarsening of facial features.[4] Although MFD predominantly occurs without extraskeletal manifestations, isolated café-au-lait macules have occasionally been documented. Bisphosphonate therapy, specifically intravenous zoledronic acid, has recently demonstrated efficacy in managing bone pain and trismus even in paediatric monostotic mandibular cases.[16]

Polyostotic Fibrous Dysplasia (PFD)

PFD accounts for 20–30% of FD cases and is characterised by involvement of multiple bones, most commonly in a unilateral distribution, though bilateral involvement is possible.[9] Symptoms typically manifest before the age of 10 years, reflecting the earlier embryonic timing of the causative mutation. Bone pain and pathological fractures of the extremities are frequently the initial presenting features. The shepherd's crook deformity (coxa vara) results from progressive curvature of the femoral neck and proximal shaft under weight-bearing forces, representing a classic complication of femoral involvement. Spinal lesions may produce scoliosis or vertebral collapse. Cutaneous café-au-lait macules are the most common extraskeletal manifestation, observed in approximately 50% of PFD patients, typically appearing on the same side as the skeletal lesions and respecting the midline.[4] When endocrine abnormalities co-exist—most commonly precocious puberty in females—the constellation constitutes McCune-Albright syndrome. In rare instances, PFD is associated with multiple intramuscular myxomas, a condition termed Mazabraud syndrome.[4]

Craniofacial Fibrous Dysplasia (CFD)

CFD refers to FD restricted to contiguous craniofacial bones, involving the frontal, temporal, sphenoid, ethmoid, maxillary, and/or zygomatic bones in varying combinations. It accounts for 10–25% of monostotic cases and up to 50% of polyostotic cases.[4] Strikingly, nine out of ten patients with craniofacial involvement present before the age of five years.[7] While many patients are initially asymptomatic, progressive expansion produces facial asymmetry, orbital displacement, and nasal obstruction. The involvement of the skull base is particularly challenging, as expansion into the optic canal can precipitate visual impairment or blindness, while temporal bone involvement leads to conductive or mixed hearing loss.[8] Sequelae include chronic nasal congestion, hyposmia, malocclusion, and dental crowding. Computed tomography (CT) with three-dimensional reconstruction is indispensable for surgical planning, enabling precise delineation of the extent of craniofacial involvement and proximity of critical neurovascular structures.[9]

COMPARISON OF FD SUBTYPES

Feature	Monostotic FD	Polyostotic FD / MAS	Craniofacial FD
Bones involved	Single bone	Multiple bones, often unilateral	Contiguous craniofacial bones
Prevalence	70–80% of FD cases	20–30% of FD cases	10–25% (MFD); ~50% (PFD)
Age at onset	Childhood–adolescence	Before age 10 in many cases	Usually before age 5
Extraskeletal features	None typical	Café-au-lait macules, endocrinopathies	Rare; mainly local effects
Typical complications	Local deformity, fracture	Severe deformity, limb discrepancy	Visual/hearing deficits, cosmetic deformity

ORAL MANIFESTATIONS

The oral and maxillofacial region is one of the most clinically important sites of fibrous dysplasia owing to the functional and aesthetic significance of the jaws. When jaw bones are affected, the earliest and most consistent clinical sign is a painless, slow-growing bony expansion of the labial or buccal cortical plate; lingual plate involvement is comparatively rare.[17] As the lesion enlarges, it may become associated with mild pain and tenderness, particularly if the alveolar nerve is compressed or if pathological microfractures occur within the affected bone.
Progressive expansion of the lesion disrupts the normal eruption pattern and position of teeth,

producing malalignment, tipping, displacement, or delayed eruption. Root resorption of adjacent teeth may occur in advanced lesions. Endocrinal disturbances associated with MAS may further compound these dental abnormalities, leading to altered eruption sequences and malposition.[17] On periapical radiographs, the periodontal ligament space of involved teeth may be widened or indistinct, and the lamina dura may be poorly defined or absent—features that can pose diagnostic challenges and mimic other periapical pathoses.[9] The inferior alveolar nerve canal may also be displaced from its normal position, a critical consideration in surgical planning.

Mandibular involvement typically manifests as unilateral facial swelling, producing progressive facial asymmetry. In some cases, protuberant excrescence of the inferior border of the mandible is observed. Maxillary involvement tends to be more severe in clinical consequence: the lesion frequently spreads into contiguous structures including the zygomatic process, orbital floor, maxillary sinus, and skull base, making complete surgical extirpation virtually impossible without disfiguring resection.[4] Severe malocclusion, extension of the lesion into the canine fossa, and prominence of the zygomatic process are characteristic complications. Importantly, maxillary FD may not conform strictly to either monostotic or polyostotic classification, representing an intermediate form.[4] Cone beam CT (CBCT) is recommended preoperatively to map lesion extent, locate neurovascular structures, and facilitate planning of conservative surgical recontouring.[9]

RADIOGRAPHIC FEATURES

Radiographic evaluation plays a pivotal role in the diagnosis, characterisation, and monitoring of fibrous dysplasia. Conventional radiographs, CT, MRI, and bone scintigraphy each contribute complementary information. Three principal radiographic patterns are recognised: cystic, sclerotic, and mixed, reflecting the evolving composition of fibrous and osseous tissue within the lesion.[18]

On plain radiographs and CT, the 'ground-glass' appearance—a smooth, homogeneous, hazy opacity resembling frosted glass—is the pathognomonic finding of FD, resulting from the replacement of normal trabecular bone by disorganised fibrous matrix containing irregular calcified foci.[18] The normal trabecular pattern is lost, and endosteal scalloping is frequently observed. A characteristic peripheral dense sclerotic rim, termed the 'rind sign', surrounds the radiolucent lesion and corresponds to a zone of reactive cortical thickening.[4] Early lesions of both monostotic and craniofacial forms may display unilocular or multilocular radiolucency, while mature lesions show the ground-glass or 'orange peel' matrix. Craniofacial FD is characterised on plain films by diffuse thickening and sclerosis of the skull base.

The three radiographic patterns include: (1) Cystic type — unilocular or multilocular radiolucency, predominant in early lesions; (2) Sclerotic type — dense, homogeneous opacity characteristic of mature lesions with abundant woven bone; (3) Mixed type — coexisting radiolucent and radiopaque areas, representing transitional pathology between the above two forms. Lesion size varies considerably, from small focal areas to lesions involving most of a long bone.

Computed tomography (CT) is the modality of choice for craniofacial FD owing to its superior delineation of cortical bone, lesion extent, degree of cortical thinning, and proximity to critical structures such as the optic canal, foramen rotundum, and inferior alveolar canal.[18] CT is also valuable for detecting soft-tissue involvement and raising suspicion for malignant transformation when aggressive features such as cortical destruction or periosteal reaction are identified. Magnetic resonance imaging (MRI), while less specific for FD, is superior to CT in characterising the internal signal pattern of the lesion and evaluating soft tissue or extra-osseous extension. On MRI, FD lesions typically demonstrate low-to-intermediate signal intensity on T1-weighted sequences and variable signal on T2-weighted sequences, depending on the proportion of fibrous versus osseous tissue. MRI is particularly important when malignant degeneration is suspected, as it can identify permeative bone marrow involvement and extra-osseous soft tissue masses.[18] Bone scintigraphy with technetium-99m is useful for mapping the full skeletal extent of polyostotic disease and monitoring metabolic activity of lesions.

HISTOPATHOLOGY

Core needle biopsy or surgical curettage provides definitive histopathological confirmation of fibrous dysplasia. The microscopic hallmark is the presence of numerous irregularly shaped, curvilinear (C-shaped or 'alphabet soup') trabeculae of immature woven bone arranged loosely within a moderately cellular fibrous connective tissue stroma.[18,19] These trabeculae arise directly from the fibrous stroma without the normal osteoblastic rimming that characterises reactive or neoplastic bone formation—a key distinguishing feature from ossifying fibroma, in which osteoblastic rimming is typically prominent.

The fibrous stroma is composed of bland, spindle-shaped fibroblasts arranged in a distinctive whorled or storiform pattern within a dense collagenous matrix.[18,19] The stroma is relatively avascular in mature lesions, but multiple delicate capillaries traverse early and active lesions. Osteoclast-like giant cells are frequently identified, predominantly on the concave surface of the bony trabeculae. Intralesional haemorrhage may trigger a more pronounced giant cell reaction, necessitating histological exclusion of giant cell tumour of bone as a differential diagnosis. Early lesions are characterised by a greater proportion of fibrous tissue relative to bone, while advanced lesions display a higher density of woven bone trabeculae.

Under polarised light microscopy, the woven-bone trabeculae demonstrate a haphazard, irregular birefringence pattern—in contrast to the parallel, organised pattern of lamellar bone—constituting an important diagnostic feature.[19] Dense ossifications and lamellar bone may be encountered specifically in craniofacial sites. Key microscopic features include: (1) absence of osteoblastic rimming of trabeculae; (2) immature woven-bone islands in a storiform fibrous background; (3) no cellular atypia or abnormal mitoses unless malignant transformation has supervened; (4) occasional giant cell reaction secondary to haemorrhage; and (5) absence of cartilage unless a fracture callus is present.

DIFFERENTIAL DIAGNOSIS

The diagnosis of fibrous dysplasia may be confounded by several clinically and radiologically similar fibro-osseous lesions, particularly in the jaw. A thorough correlation of clinical, radiological, and histopathological findings is mandatory before arriving at a definitive diagnosis.[20] Ossifying fibroma (OF) represents the most important differential diagnosis in jaw lesions. Unlike FD, OF is well-demarcated with a distinct capsule on imaging and shows prominent osteoblastic rimming of trabeculae on histology; it is also amenable to surgical enucleation due to its defined margins, in contrast to FD which blends imperceptibly with adjacent normal bone. Paget's disease of bone shares radiographic similarities in advanced stages, but primarily affects individuals above the fifth decade, exhibits the classic 'cotton-wool' radiopacity, and is associated with markedly elevated serum alkaline phosphatase. Histologically, Paget's disease displays the characteristic mosaic or 'jigsaw puzzle' pattern of lamellar bone. Cemento-osseous dysplasia is confined to the tooth-bearing regions of the alveolar bone and is typically asymptomatic and bilateral, usually requiring no treatment. Low-grade central osteosarcoma may closely mimic FD radiographically and even histologically, and must be excluded, particularly when lesions appear aggressive, demonstrate cortical perforation, or occur in older patients. Aneurysmal bone cyst may develop secondarily within an FD lesion, manifesting as a rapidly expanding lytic lesion with fluid levels on MRI. Central giant cell granuloma, non-ossifying fibroma, simple bone cyst, and cherubism complete the differential spectrum. Molecular testing for GNAS mutation via polymerase chain reaction (PCR) on biopsy tissue is increasingly employed as an adjunct diagnostic tool, with high sensitivity for confirming FD when morphological features are equivocal.[6,21]

TREATMENT

No pharmacological therapy has yet been proven to definitively arrest, reverse, or cure fibrous dysplasia. Treatment is therefore individualised, symptom-guided, and multidisciplinary, based upon the extent of skeletal involvement, the presence of functional deficits, degree of deformity, and the patient's age and general health status.[9] Surgical management is the cornerstone of treatment for FD. In monostotic jaw lesions, surgical recontouring (osteoplasty) is performed primarily for cosmetic correction and functional rehabilitation. Timing of surgery is critical: operating during active skeletal growth carries a significant risk of lesion recurrence, and most authorities recommend delaying elective recontouring until after skeletal maturity where possible.[4] Optic canal decompression is indicated urgently when craniofacial FD threatens visual acuity through compression of the optic nerve. In patients where decompression is contraindicated, or where surgical risk is prohibitive, medical management with vitamin D supplementation and bisphosphonate therapy is recommended to relieve bone pain and reduce osteoclastic activity.[9] For fractures or impending fractures of long bones, cortical allograft supplementation or intramedullary fixation of the entire bone provides the best biomechanical support. Polyostotic FD necessitates a multidisciplinary approach involving orthopaedic surgery, endocrinology, ophthalmology, and maxillofacial surgery, as appropriate, alongside treatment of associated endocrine abnormalities.[18] Bisphosphonates—particularly intravenous pamidronate and zoledronic acid—inhibit osteoclast activity and have demonstrated efficacy in reducing bone pain, decreasing fracture rates, and improving bone density within FD lesions in multiple studies.[22] A paediatric case report confirmed prompt resolution of bone pain and trismus in mandibular FD following intravenous zoledronic acid administration.[16] Denosumab, a fully human monoclonal antibody against RANKL, has emerged as a promising therapeutic option for FD refractory to bisphosphonate therapy. A clinical study demonstrated that denosumab 60 mg every three months was well-tolerated and resulted in pain reduction, decreased bone turnover markers, and increased lesion density on CT in the majority of treated patients.[11] Longer follow-up data indicate that therapeutic effects of denosumab persist for up to two years after treatment discontinuation, though recurrence is associated with rising bone turnover markers.[12] Rebound hypercalcaemia following denosumab discontinuation is an important adverse effect requiring monitoring and management with bisphosphonates.[12] In McCune-Albright syndrome, hormonal therapies targeting specific endocrinopathies—including aromatase inhibitors for precocious puberty, thyroid-suppressive agents for hyperthyroidism, and somatostatin analogues for growth hormone excess—are essential adjuncts.[14] Novel investigational therapies targeting the Gsα–cAMP pathway directly are under active preclinical and clinical evaluation. Radiotherapy is absolutely contraindicated in FD owing to the established risk of malignant transformation to osteosarcoma following irradiation.[23] Postoperative radiological follow-up is recommended at six-monthly intervals to assess for lesion progression, recurrence, or signs of malignant degeneration.[18]

PROGNOSIS AND LONG-TERM OUTCOMES

Fibrous dysplasia is generally a slowly progressive condition that tends to stabilise following skeletal maturity, particularly in its monostotic form. Patients with limited skeletal involvement may remain largely asymptomatic and maintain a good quality of life with minimal or no intervention across their lifetime.[14,20] By contrast, individuals with extensive polyostotic FD or MAS experience chronic pain, recurrent pathological fractures, progressive deformity, and significant functional limitations, often necessitating repeated surgical procedures and long-term interdisciplinary follow-up care.[22,23]

Malignant transformation of FD—most commonly to osteosarcoma, but also to fibrosarcoma or undifferentiated pleomorphic sarcoma—is rare, with reported rates generally below 1% in the absence of prior radiotherapy.[24] The risk of malignant transformation is highest in patients with extensive polyostotic disease or MAS and in those who have received prior radiation therapy. This risk underscores the absolute contraindication of radiotherapy for FD management.[23] Surveillance with periodic clinical examination and CT or MRI is therefore essential in all patients, with accelerated follow-up warranted when lesion behaviour changes or pain increases unexpectedly.

The psychosocial burden of FD, particularly the impact of facial deformity, chronic pain, and repeated hospitalisation on children, adolescents, and their families, is substantial and frequently underestimated.[24] Multidisciplinary teams should incorporate psychological support, patient education, and appropriate reconstructive options as integral components of long-term management. Patient advocacy organisations such as the FD/MAS Alliance have played an important role in raising disease awareness and facilitating access to specialised care for this rare condition.

CONCLUSION

Fibrous dysplasia is a benign yet clinically significant intramedullary fibro-osseous lesion arising from a postzygotic activating mutation in the GNAS1 gene. Its clinical spectrum ranges from asymptomatic solitary bone lesions to the debilitating triad of McCune-Albright syndrome involving widespread skeletal, cutaneous, and endocrine involvement. The craniofacial region is particularly vulnerable, and the potential for neurosensory compromise—including blindness and hearing loss—demands early recognition and prompt, multidisciplinary management. Early and accurate diagnosis, underpinned by a thorough understanding of the pathognomonic radiological and histological features, is indispensable for avoiding overtreatment and for differentiating FD from its important mimics, particularly low-grade osteosarcoma and ossifying fibroma.

Although no curative pharmacological therapy currently exists, bisphosphonates and the emerging RANKL inhibitor denosumab provide meaningful symptomatic relief and lesion stabilisation in refractory cases. Surgical management must be carefully timed, with elective recontouring deferred until after skeletal maturity where feasible. The absolute contraindication to radiotherapy must be emphasised given the risk of sarcomatous transformation. Advances in molecular diagnostics—particularly GNAS mutation testing—are refining diagnostic accuracy and opening potential avenues for targeted therapies directed at the Gsα–cAMP signalling cascade. Clinicians across disciplines—dentistry, oral and maxillofacial surgery, paediatrics, endocrinology, and orthopaedics—must maintain heightened awareness of this rare condition to ensure timely diagnosis, appropriate treatment planning, and informed long-term follow-up.

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