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(CASE REPORT)

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Recurrent frontal bone fibrous dysplasia as a high-grade pleomorphic sarcoma and unfavorable prognosis: Case report and brief review of literature

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Abstract

Malignant transformation of craniofacial fibrous dysplasia into high-grade undifferentiated pleomorphic sarcoma (UPS) is an exceptionally rare but aggressive phenomenon, posing a significant diagnostic and management challenge due to its initially benign appearance and sudden rapid progression.

We report a case of a 34-year-old woman who presented with an 8-year history of progressive, painless right frontal skull swelling, primarily causing cosmetic deformity without neurological symptoms. Initial imaging using CT showed a pathognomonic expansile "ground-glass" lesion (6.8 × 5.2 × 2.4 cm) of the right frontal bone consistent with monostotic FD. The patient was treated with an elective frontal craniotomy with intraoperative contouring and burring of the affected frontal bone through a bicoronal approach.

At the 30-month postoperative visit, repeat CT demonstrated recurrence at the site of the prior procedure in the form of high-grade UPS and pulmonary metastasis; there was no malignant osteoid formation. Molecular studies showed a GNAS mutation (Arg201His), confirming the origin from FD; a TP53 mutation supporting malignant transformation; and negative MDM2 amplification and CDK4 overexpression. The patient was treated with neoadjuvant chemotherapy, radical en bloc resection with craniofacial reconstruction, adjuvant radiation therapy (60 Gy) due to positive margins, second-line systemic therapy (gemcitabine + docetaxel) after progression, and finally, palliative care.

Ultimately, the decline in function led to death approximately 29 months post-malignant transformation. This case highlights the importance of consistent surveillance of the usually benign FD, as rapid transformation to high-grade sarcoma is associated with poor patient outcomes.

Keywords: Fibrous dysplasia; Undifferentiated pleomorphic sarcoma; Malignant transformation; McCune-Albright syndrome; Activating mutations in the GNAS gene; Immunohistochemistry

1. Introduction

Fibrous dysplasia (FD) is a benign skeletal disorder in which normal bone is replaced by fibro-osseous tissue, resulting in structural weakness, deformity, fractures, and pain. [1] This condition is caused by activating mutations in the GNAS gene that occur after fertilization. The gene encodes the Gαs subunit. These mutations increase cyclic AMP signaling,

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resulting in somatic mosaicism. The mutations are sporadic rather than inherited and may occur in association with McCune-Albright syndrome (MAS), a syndromic form characterized by endocrine hyperfunction and café-au-lait macules. [2,3]

FD may present as either monostotic or polyostotic disease and most commonly involves the craniofacial skeleton, ribs, femur, and pelvis. Clinical manifestations vary but frequently include bone pain, pathologic fractures, swelling, and, in cases of craniofacial involvement, facial asymmetry. [4] In most patients, FD follows a benign and slowly progressive course without significant complications. [1]

Malignant transformation of FD is a rare but well-recognized event, occurring in fewer than 1% of cases. When transformation occurs, it most commonly gives rise to osteosarcoma, chondrosarcoma, or fibrosarcoma. Less frequently, more aggressive and poorly differentiated sarcomas may develop, representing a clinically significant shift associated with unfavorable outcomes. [5] [6]

Given the rarity of this progression, particularly to high-grade pleomorphic sarcoma, individual case reports remain essential for improving understanding of its pathogenesis and clinical behavior. We present this case to illustrate the transformation of a previously benign FD lesion into an aggressive malignancy, highlighting the importance of careful clinical and radiologic surveillance. Recognition of concerning features, including cortical destruction and soft tissue extension, is critical for early diagnosis. This case further underscores the need for continued investigation into optimal detection and management strategies to improve patient outcomes in this uncommon but serious complication.

2. Case Presentation

2.1. Clinical Presentation

A 34-year-old woman presented with a progressive, painless bony expansion of the right frontal region of the skull that had been slowly enlarging over approximately eight years. She first noticed a subtle prominence in her mid-to-late twenties, which she initially attributed to normal variation. Over time, the lesion became increasingly visible, producing a marked cosmetic deformity that significantly affected her self-image and quality of life. She reported no neurological symptoms, no visual disturbances, no headaches attributable to the lesion, and no history of trauma to the area.

She had sought evaluation from her primary care physician three years prior, at which time she was reassured and placed under observation. As the deformity became more conspicuous, she sought a second opinion from a craniofacial surgeon. Her primary motivation for the current consultation was cosmetic correction of the disfiguring frontal mass, which had become a source of significant psychosocial distress. There was no associated pain, no skin changes overlying the lesion, and no systemic complaints. She denied any history of fractures, endocrinopathies, or prior bone disease.

2.2. Physical Examination, History, Laboratory & Imaging

Physical examination revealed a firm, non-tender, bony-hard, immovable mass occupying a large portion of the right frontal calvarium, measuring approximately 6.5 × 5.0 cm on palpation. The overlying skin appeared normal with no erythema, warmth, or induration. There was no palpable cervical or regional lymphadenopathy. Cranial nerve examination was intact. Ophthalmologic assessment showed no proptosis, diplopia, or visual field defects. No café-au-lait macules were identified on the cutaneous survey. Her personal medical history was unremarkable. There was no prior history of radiation exposure, metabolic bone disease, or endocrine dysfunction. Family history was negative for FD, neurofibromatosis, or other skeletal dysplasias.

Routine serum chemistry, complete blood count, and coagulation studies were within normal limits. Serum alkaline phosphatase was mildly elevated at 148 U/L, consistent with active bone remodeling. Serum calcium, phosphorus, parathyroid hormone, and thyroid-stimulating hormone levels were all within normal ranges. Urinary N-telopeptide, a marker of bone resorption, was mildly elevated. These findings were consistent with a monostotic fibro-osseous process without systemic endocrinopathy.

Plain skull radiographs demonstrated a well-defined, expansile lesion of the right frontal bone exhibiting the classic "ground-glass" radiodensity, with no cortical destruction. Computed tomography (CT) of the head with bone windows confirmed an expansile, ground-glass, monostotic lesion of the right frontal calvarium with thinning but preservation of the inner and outer cortical tables, measuring 6.8 × 5.2 × 2.4 cm, without intracranial extension or dural involvement. Magnetic resonance imaging (MRI) with and without gadolinium showed the lesion to be heterogeneous on T1, hypointense on T2, and demonstrating mild homogeneous enhancement, without surrounding edema or mass effect on

adjacent brain parenchyma. Whole-body bone scintigraphy showed uptake limited to the right frontal calvarium, confirming monostotic disease.

The principal radiographic differential diagnoses considered included: (1) fibrous dysplasia, most consistent with the ground-glass matrix, monostotic distribution, and characteristic CT morphology; (2) Paget disease of bone, considered but less likely given the patient's young age and absence of cortical thickening or "cotton-wool" pattern; (3) ossifying fibroma, a fibro-osseous lesion with more well-defined margins and a more mineralized matrix; (4) low-grade intraosseous osteosarcoma, considered due to lesion size, but the non-aggressive radiographic features argued against malignancy.

2.3. Multidisciplinary Tumor Board: Initial Presentation

The case was formally presented at the multidisciplinary tumor board, attended by specialists in neurosurgery, craniofacial and plastic surgery, oral and maxillofacial surgery, neuroradiology, endocrinology, pathology, and oncology. The board acknowledged the characteristic radiographic and clinical features strongly suggestive of FD, while noting the need to histologically exclude a fibro-osseous malignancy given the lesion's size and the patient's age.

Discussion centered on the following key issues: the cosmetically significant nature of the lesion and the patient's stated preference for surgical correction; the importance of tissue diagnosis prior to any definitive resection; the need to rule out malignant transformation, particularly low-grade osteosarcoma; and the role of hormonal or bisphosphonate therapy as a potential adjunct. The board reached consensus that an incisional biopsy under image guidance was the appropriate next step. A CT-guided percutaneous core needle biopsy was subsequently performed, yielding adequate tissue.

Histopathologic examination of the biopsy specimen revealed irregular, curvilinear trabeculae of woven bone embedded within a cellular fibrous stroma, the hallmark "Chinese-letter" or "alphabet-soup" pattern, with no cytologic atypia, necrosis, or cartilaginous component. (Figure 1 A, B, C) A diagnosis of FD was rendered, and the tumor board proceeded to discuss definitive management options.

2.4. Management: Surgical Course, Recurrence & Final Pathology

Following multidisciplinary consensus, the patient underwent elective frontal craniotomy with intraoperative contouring and burring of the affected frontal bone through a bicoronal approach. Intraoperative navigation was employed to define lesion margins. The outer cortical table was meticulously burred and contoured to restore the normal frontal contour, while preserving the inner cortical table and overlying dura. Estimated blood loss was minimal, and the procedure was completed without complication. Pathology from the resected bony shavings confirmed FD with no evidence of malignant transformation.

The immediate postoperative course was uneventful, and the patient reported excellent cosmetic satisfaction at her six-month follow-up. Annual surveillance CT imaging was continued. At the thirty-month postoperative visit, repeat CT demonstrated progressive re-expansion of the frontal lesion with a new, lobulated, soft-tissue component measuring 4.1 × 3.8 cm, markedly enlarged relative to the prior study. The patient reported noticing a rapidly growing, firm mass over the past approximately 6 months. The tumor board was reconvened.

At the second tumor board meeting, the rapid growth, soft-tissue extension, and change in radiographic character raised concern for malignant transformation of the pre-existing FD. Radical resection and craniofacial reconstruction were recommended. The patient consented to radical resection with en bloc removal of the involved frontal bone segment and autologous calvarial bone graft. Preoperative planning included a high-resolution CT imaging to delineate lesion extent and plan harvest and reconstruction.

Gross pathological examination of the en bloc resection specimen revealed a poorly circumscribed, gritty, tan-white lesion extensively replacing the frontal bone, with focal areas of increased cellularity and a soft-tissue component at the outer cortical surface. Microscopic examination confirmed the background FD architecture with superimposed areas of increased stromal cellularity, nuclear pleomorphism, and atypical mitotic figures. No osteoid production by malignant cells was identified in the florid malignant zones. (Figure 2 A, B, C, D, E) Immunohistochemistry (IHC) demonstrated diffuse vimentin positivity and focal smooth muscle actin (SMA) positivity, with negativity for S-100, CD34, desmin, and AE1/AE3. Ki-67 proliferative index reached 32% in high-grade foci. Molecular studies identified a somatic activating mutation in the GNAS gene (Arg201His), confirming the origin from FD. MDM2 amplification and CDK4 overexpression, markers associated with secondary low-grade osteosarcoma, were absent. TP53 mutation was identified by next-generation sequencing, consistent with malignant transformation.

The pathologic differential diagnosis included: (1) recurrent/progressive FD with reactive atypia; (2) secondary high-grade sarcoma arising in FD; (3) low-grade central osteosarcoma; and (4) UPS, after multidisciplinary pathologic review and correlation with clinical and molecular findings, the final diagnosis was rendered as high-grade undifferentiated pleomorphic sarcoma (UPS) arising in pre-existing craniofacial FD (malignant transformation), with negative surgical margins on final specimen review. Whole-body PET-CT identified two lower lobe pulmonary nodules, 2.2 and 1.8 cm. Lung biopsy from the largest nodule confirmed metastatic pleomorphic sarcoma.

2.5. Outcome, Surveillance & Long-Term Follow-Up

The patient was referred to the multidisciplinary sarcoma oncology service. Staging workup was completed with whole-body PET-CT, which identified the known right lower lobe pulmonary nodules as metabolically active, one additional 0.6 cm subpleural left upper lobe nodule, and mildly increased uptake in a right hilar lymph node, raising concern for early nodal involvement. No osseous or visceral metastases beyond the lungs were identified at that time.

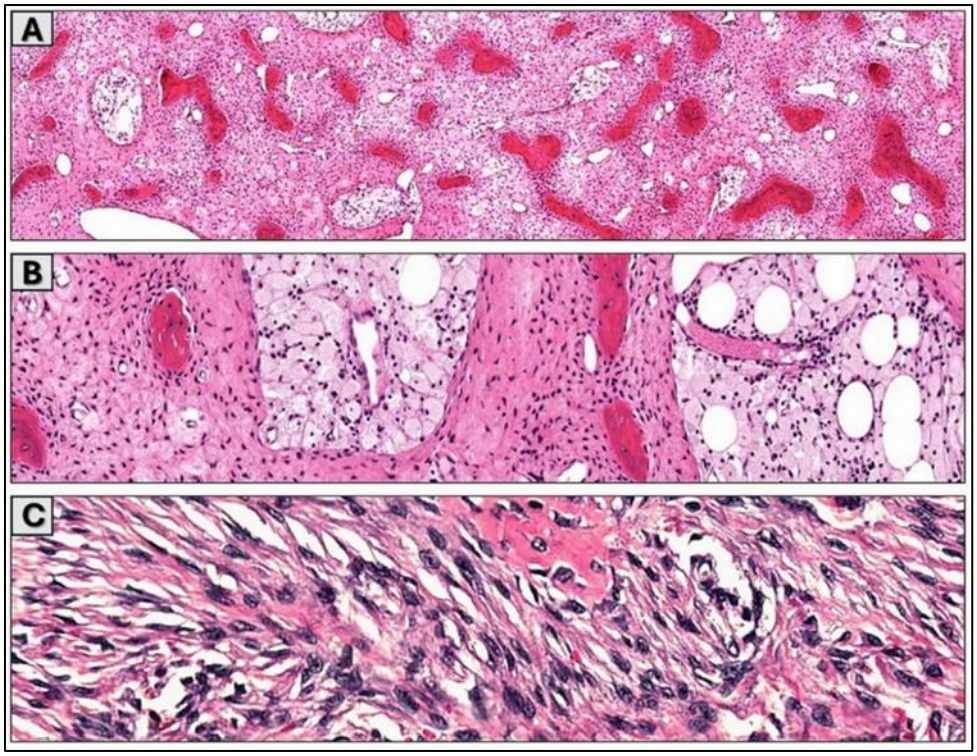
The patient was enrolled in a neoadjuvant chemotherapy protocol with high-dose methotrexate, Adriamycin (doxorubicin), and cisplatin (MAP regimen). She experienced significant treatment-related toxicity, requiring a dose reduction of cisplatin after cycle two, and persistent fatigue necessitating growth factor support. Response assessment CT at three months demonstrated a modest reduction in the primary frontal mass, from 5.3 to 3.8 cm, with stable pulmonary nodules and no new sites of disease. At follow-up surgery, histologic response of less than 10% necrosis was deemed poor by the Huevo grading system and indicated a worse prognosis.

Radical en bloc resection of the right frontal calvarium with dural excision and primary dural repair was performed, followed by cranioplasty reconstruction. Surgical margins were microscopically positive at the posterior dural margin. Given the positive margin and poor chemotherapy response, adjuvant external beam radiation therapy to the primary site was administered, totaling 60 Gy in 30 fractions, complicated by mild radiation dermatitis and transient frontal lobe edema on surveillance MRI.

The pulmonary metastases were assessed for resectability by thoracic surgery. At the time of planned metastasectomy, interval CT revealed progression from two to five pulmonary nodules bilaterally, precluding complete surgical clearance. Pulmonary metastasectomy was abandoned, and the patient was transitioned to systemic therapy with gemcitabine and docetaxel as second-line treatment.

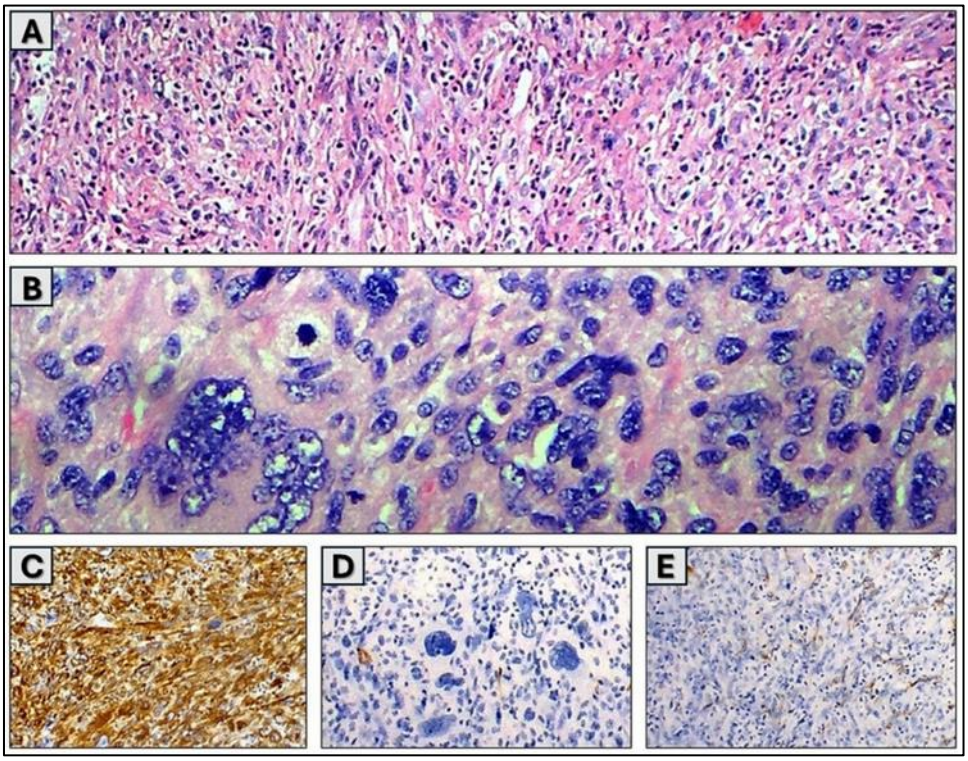
At the four-year mark from initial presentation, and approximately twenty-six months from the diagnosis of malignant transformation, the patient's disease course had been characterized by relentless progression despite multimodal therapy. Surveillance imaging demonstrated multiple bilateral pulmonary metastases, a new hepatic lesion measuring 2.1 cm in segment VI, suspicious for metastatic disease, and local recurrence at the right frontal operative site with a 2.8 cm enhancing soft-tissue mass along the posterior dural repair margin. The patient reported worsening fatigue, progressive dyspnea on exertion, 14 lbs. of unintentional weight loss over six months, and intermittent right-sided frontal headaches. Performance status had declined to ECOG 2.

She was referred to palliative care for symptom management and goals-of-care discussions. The case was reviewed at a dedicated sarcoma tumor board to assess eligibility for a clinical trial targeting GNAS-mutant or MDM2-amplified sarcomas. Quality of life had been significantly compromised, and psychosocial support services, including oncology social work and psychiatric liaison, were actively engaged. The patient died twenty-nine months after malignant transformation was diagnosed.



1A: Low power view showing irregular, curvilinear trabeculae of woven bone embedded within a cellular fibrous stroma, the hallmark "Chinese letter" (H&E X20). 1B: High power view showing focus of lipid-laden macrophages surrounded by fibroblastic stroma and irregular bony trabeculae. (H&E X40). 1C: High power view showing foci of hypercellular stroma but without significant atypia or abnormal mitosis (H&E X40).

Figure 1 Microscopic examination of the initial frontal fibrous dysplasia



1A: Low power view showing solid sheets of atypical pleomorphic and spindle cells (H&E X20). 1B: High power view showing bizarre, highly atypical, hyperchromatic pleomorphic cells with multinucleation, hyperchromasia, and irregular nuclear membranes (H&E X40). 1C: Tumor cells are strongly positive for Vimentin 1D: Tumor cells negative for Desmin 1E: Tumor cells negative for Actin

Figure 2 Microscopic examination and immunohistochemistry of the recurrent high-grade pleomorphic sarcoma

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification)

FD is a rare, benign skeletal disorder characterized by the replacement of normal bone with fibro-osseous tissue, leading to structural weakness, deformity, and potential functional impairment. [1,4] The pathological characteristics of this condition were initially documented by Friedrich Daniel von Recklinghausen in 1891. However, analogous lesions have also been observed in prehistoric skeletal remains. [7] The term "fibrous dysplasia" was later introduced by Leo Lichtenstein in 1938. FD is estimated to have a prevalence of 1 in 100,000 to 1 in 1,000,000 individuals [4]. Others suggest the incidence is higher, sometimes cited as 1 in 5,000 to 10,000 for all types of FD, including asymptomatic cases. [4] It may present in monostotic or polyostotic forms, with the latter often associated with MAS, a condition characterized by café-au-lait macules and endocrine hyperfunction. FD most frequently involves the craniofacial skeleton, skull base, and proximal femur. While it is generally benign, it may lead to complications such as bone deformity, fracture, pain, and, in rare cases, malignant transformation. [1,4]

Malignant transformation of FD is an uncommon but well-documented complication, occurring in a small percentage of cases. The risk is higher in patients with polyostotic disease and in those with syndromes such as MAS. [8,9] Among environmental risk factors, prior radiation exposure is the most significant, with studies reporting that up to 46% of sarcomas arising in FD patients are associated with previous radiotherapy. [10,11] The craniofacial bones represent the most frequent site of sarcomatous transformation (approximately 46%), followed by long bones such as the femur (25%). [10,11]

UPS, previously termed malignant fibrous histiocytoma (MFH), is a rare and aggressive mesenchymal malignancy. MFH was introduced to the literature in 1961 by Ozzello, O'Brien, and Stout, and was famously characterized by Kauffman and Stout. [12] The World Health Organization (WHO), in its 2002 third edition, reclassified MFH as Undifferentiated Pleomorphic Sarcoma (UPS) to better reflect its lack of specific differentiation. The 2013/2012 classification further cemented this change. [13] UPS accounts for less than 2% of primary malignant bone tumors and typically presents in older adults, with a reported median age at diagnosis of approximately 59.5 years and no significant sex predilection. [9]

3.2. Pathogenesis, Pathophysiology

The development of high-grade pleomorphic sarcoma in craniofacial fibro-osseous disease involves a multistep oncogenic process driven by abnormal bone remodeling. Postzygotic, somatic, gain-of-function mutations in the GNAS gene cause FD. These mutations convert the GNAS protein (R201H or R201C), resulting in constitutive Gαs signaling. These molecular alterations disrupt the differentiation of bone and stromal cells, promote the proliferation of immature osteogenic precursors, and replace normal lamellar bone with fibro-osseous tissue characterized by abnormal trabecular architecture and increased osteoclast activity. [2,3,14]

FD may occur as part of MAS, a mosaic disorder characterized by endocrine hyperfunction and cutaneous pigmentation, reflecting the involvement of pathogenic variants in GNAS-mediated signaling pathways. [2,15] Although these lesions are typically benign, they exhibit persistent cellular proliferation and impaired maturation, creating a microenvironment conducive to genomic instability and the accumulation of secondary oncogenic mutations. [16]

Malignant transformation, reported in <1% of cases, occurs more frequently in craniofacial disease and after radiation exposure. Progression is mediated by additional genetic alterations within the context of GNAS-driven signaling, including disruption of tumor suppressor pathways, such as TP53 and RB1, which facilitates the evolution to high-grade sarcoma. [15,17]

Osteosarcoma is the most frequently reported malignancy, although fibrosarcoma and UPS have also been described. All malignant transformations exhibit aggressive histologic features, including marked pleomorphism, increased mitotic activity, and necrosis. [15,17]

3.3. Comparative Analysis of Our Case with Existing Literature. (Clinical, radiology, pathology, Lab, diagnosis, management, and outcome)

Malignant transformation of FD is rare but acknowledged, with reported rates typically under 1%. However, the craniofacial series suggested a somewhat higher observed frequency in selected referral populations. Our case shared several features with published reports, including female sex, craniofacial involvement, a prolonged antecedent benign phase, and the later emergence of radiologic alarm features that signaled transformation. [6,19] Similar to prior series,

the change from a relatively indolent fibro-osseous lesion to an aggressive sarcoma was heralded by accelerated enlargement and the development of a new soft-tissue component, findings repeatedly emphasized as warning signs in craniofacial FD. [5,19]

At the same time, this case differed from much of the existing literature in clinically important ways. Studies indicate that malignant craniofacial FD most often develops in the maxilla or mandible and most often presents as osteosarcoma. [6,18] Unlike typical cases, our patient's frontal calvarium transformed into high-grade UPS, a rare secondary malignancy in FD. [5,6]

The molecular profile further strengthened the association with pre-existing FD, as the persistence of a GNAS mutation supported an origin from dysplastic bone. In contrast, the absence of MDM2 amplification and CDK4 overexpression argued against a secondary low-grade osteosarcoma. Finally, the subsequent pulmonary metastases, poor response to multimodal therapy, local recurrence, and early death paralleled the unfavorable survival reported in modern reviews, underscoring that once malignant transformation occurred, prognosis was frequently poor despite aggressive treatment. [6,19]

4. What Have We Learned from This Case?

This case reinforced several practical clinical lessons. First, craniofacial FD should not be considered permanently indolent after an initial benign biopsy or satisfactory contouring procedure. A history of longstanding stability did not exclude later malignant change, particularly when follow-up imaging demonstrated rapid regrowth, interval radiologic heterogeneity, or a new extraosseous soft-tissue component. These findings should prompt urgent re-evaluation, repeat tissue diagnosis, and multidisciplinary review rather than continued routine surveillance. [5,19]

Second, the case highlighted that malignant transformation may occur even in monostotic disease and in relatively young adults, thereby challenging the tendency to reserve heightened suspicion only for polyostotic or syndromic patients. [5,18] Third, integration of pathology, immunohistochemistry, and molecular testing was clinically decisive. Demonstration of GNAS-supported sarcomatous transformation within FD, while exclusion of MDM2/CDK4-associated osteosarcoma refined classification and prognosis. [6]

From a management perspective, this case supported early radical treatment once transformation was suspected. However, it also illustrated the limitations of current multimodal therapy in high-grade secondary sarcoma of the craniofacial skeleton. For future practice, maybe clinicians should adopt surveillance strategies such as using advanced radiographic techniques and frequent assessment aimed at detecting early accelerated growth, soft-tissue invasion, and metastatic spread at the earliest possible stage, rather than purely cosmetic in intent.

Abbreviations: Undifferentiated pleomorphic sarcoma (UPS); Fibrous dysplasia (FD); Immunohistochemistry (IHC); McCune-Albright syndrome (MAS)

5. Conclusion

We reported this case to document an exceptionally uncommon but devastating event: high-grade undifferentiated pleomorphic sarcoma arising in recurrent monostotic frontal bone fibrous dysplasia, confirmed by clinicopathologic and molecular correlation. Its value lay in showing that a lesion initially diagnosed and managed as benign craniofacial FD could later recur with aggressive behavior, pulmonary metastasis, treatment resistance, and fatal outcome. It expanded the literature to include osteosarcoma transformations outside the commonly reported maxillary or mandibular cases.

For the medical community, the principal message was practical: previously stable craniofacial FD that rapidly enlarges, causes pain, shows altered imaging features, or develops a new soft-tissue component should be promptly reassessed for malignant transformation. Early multidisciplinary evaluation is essential because, although rare, this complication carries major prognostic consequences. By reporting this case, we aimed to strengthen awareness of these red flags and support earlier diagnosis, definitive management, and more purposeful surveillance in patients with craniofacial FD.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations:

- Payment/services information: All authors have declared that they received no financial support from any organization for the submitted work.
- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

Ethical review and approval were not required for this study involving human participants. The paper has been sufficiently anonymized to maintain the patient's confidentiality.

Statement of informed consent

The patient expired, and all attempts to reach the family members were unsuccessful. Therefore, the paper has been sufficiently anonymized to maintain patient confidentiality.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

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