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Clival fibrous dysplasia in which short interval disease progression posed a diagnostic challenge in a skeletally mature patient: a case report

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Abstract

Background Fibrous dysplasia is an uncommon bone disorder in which medullary bone is replaced by disorganized fibro-osseous tissue. Fibrous dysplasia typically exhibits slow growth that stabilizes with skeletal maturity. We report a case in which rapid progression of a clival lesion otherwise typical for fibrous dysplasia in an adult male led to concern for a malignant rather than a benign lesion.

Case presentation A 38 year-old white male developed eye pain, and magnetic resonance imaging of the brain was interpreted as normal. A total of 2 years later, the patient again presented with eye pain, and a repeat magnetic resonance imaging study demonstrated interval development of a lesion replacing much of the clivus. Though the lesion appeared fairly typical of fibrous dysplasia, with magnetic resonance imaging and subsequent computed tomography revealing a well-defined and mildly expansile clival lesion, lesions of fibrous dysplasia do not typically appear in skeletally mature patients, and they are generally indolent. On the basis of concern for malignant degeneration or possibly an alternative diagnosis, as the patient had been referred to our center with a diagnosis of clival chordoma, the lesion was treated with endoscopic resection. The diagnosis of typical fibrous dysplasia was ultimately confirmed through histopathological, immunohistochemical, and genetic analysis.

Conclusion This case demonstrates the potential for development and progression of benign fibrous dysplasia lesions beyond skeletal maturity, a phenomenon rarely reported in literature and not previously demonstrated in the clivus.

Keywords Clivus, Fibrous dysplasia, MRI, Case report

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Background

Fibrous dysplasia (FD) is a nonhereditary genetic bone disorder linked to post-zygotic gain-of-function mutations in the *GNAS1* gene on chromosome 20, which encodes the α-subunit of the G_s signaling protein [1–4]. This condition leads to abnormal proliferation of fibroblasts and replacement of normal medullary bone with abnormal fibro-osseous connective tissue. The precise incidence and prevalence of FD remain uncertain owing to its variable clinical presentation, ranging from asymptomatic lesions incidentally detected on imaging studies to severely disabling multiple lesions with extra-skeletal involvement. FD can manifest in either monostotic or polyostotic forms [2, 5–10] and may be associated with multisystem disorders, such as McCune–Albright disease and Mazabraud syndrome [1, 2, 5–10]. Common sites of skeletal involvement by FD include long bones, ribs, craniofacial bones, and the pelvis [7]. Craniofacial FD is observed in approximately 30% of patients with monostotic disease and in 50% of those with polyostotic disease. Monostotic craniofacial FD typically involves the temporal bone, orbit, mandible, and paranasal sinuses [4, 11], while clival FD is relatively uncommon [3].

FD is a developmental disorder, and growth of FD lesions usually stabilizes once skeletal maturity is reached [1, 2, 5, 6, 10], though it has been suggested that lesions may progress under the hormonal influence of pregnancy [12]. If a bone lesion grows or symptoms worsen, further imaging with computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)/CT may be warranted to assess for potential complications such as pathological fracture, malignant transformation, or development of a secondary vascular anomaly such as aneurysmal bone cyst (ABC) or arteriovenous fistula. Progression of benign FD lesions as documented on cross-sectional imaging is rarely reported in literature. While two reports on craniofacial FD document an increase in size of lesions involving the maxilla [5, 13], with one showing sequential change in CT appearance from an egg-shell lesion to classic ground-glass density over time [13], we did not identify any cases of benign FD with progression on MRI, post-skeletal maturity or otherwise, on literature review.

This case report highlights striking short-interval progression on MRI of tissue-confirmed benign FD of the clivus in an adult male well past the age of skeletal maturity.

Case presentation

A 38 year-old white American male presented 2 years prior to being seen at our institution with intermittent sharp left eye pain. MRI of the brain performed at an outside hospital was interpreted as normal, though in retrospect, it demonstrated multiple small stippled foci throughout the basioccipital portion of the clivus that appeared iso- to hypointense on T1-weighted imaging (WI) and hypointense on T2-WI, suggestive of either prominent trabeculae or flow voids. There was no definite restricted diffusion, and minimal if any post-gadolinium enhancement was present (Fig. 1). The clival abnormality was not typical of FD. A total of 2 years later, the patient developed recurrent eye discomfort that had become bilateral. He denied headache, vision change, seizure, or issues with chewing or swallowing. Physical examination revealed no neurological deficit or evidence of cranial nerve palsy, and a repeat MRI of the brain was performed for further evaluation (Fig. 2). The imaging demonstrated interval development of a mildly expansile clival lesion that was isointense on T1-WI, heterogeneous but predominantly hypointense on T2-WI, and avidly enhancing following gadolinium administration. There was no diffusion restriction. The mass extended to the left occipital condyle and left jugular tubercle. Although the hypointense signal observed on the T2-WI was

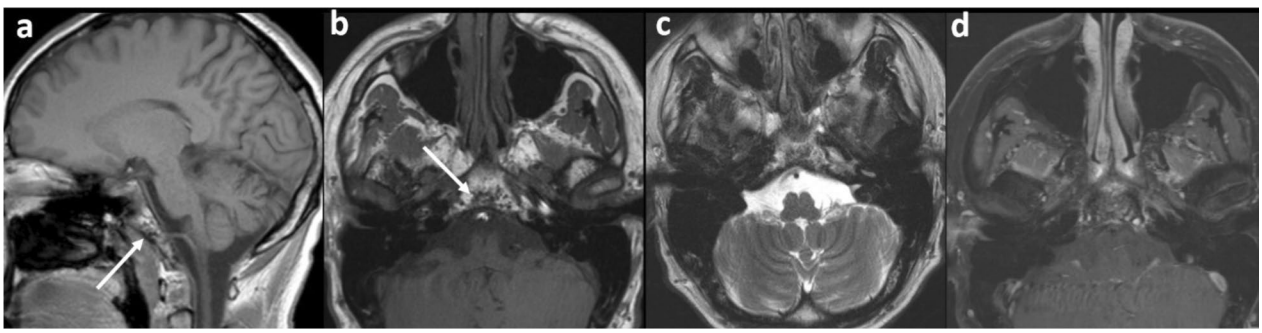

Fig. 1 Initial outside hospital magnetic resonance imaging obtained 2 years prior to presentation at our institution. **a** Sagittal T1-weighted imaging showing multiple foci of stippled hypointensity throughout the basioccipital portion of the clivus (arrow). **b** Axial T1-weighted imaging confirmed the stippled hypointensity (arrow). **c** Axial T2-weighted imaging showing similar stippled hypointensity. **d** Axial T1-weighted imaging post-gadolinium with fat suppression demonstrating minimal heterogeneous enhancement

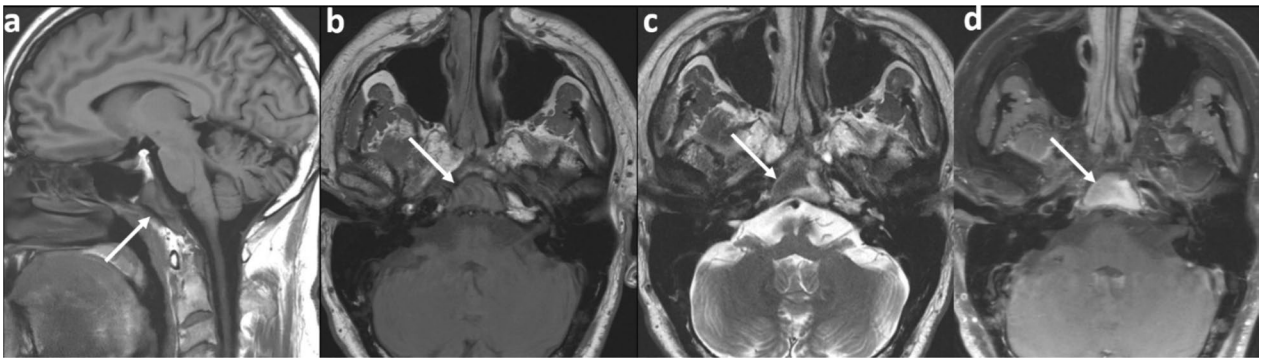

Fig. 2 Follow-up magnetic resonance imaging obtained 2 years after Fig. 1 (**a**) Sagittal T1-weighted imaging showing replacement of the stippled clival marrow fat by a homogeneous soft tissue signal intensity lesion (arrow). **b** Axial T1-weighted imaging confirmed the homogeneous nature of the marrow-replacing process that does not extend beyond the confines of the clival cortical bone (arrow). **c** The clival lesion was predominantly homogeneously hypointense on T2-weighted imaging (arrow). **d** The lesion demonstrated avid and homogeneous enhancement on axial T1-weighted imaging post-gadolinium with fat suppression (arrow)

inconsistent with the typical high T2 signal characteristic of chordoma, the diagnosis of chordoma was suggested. Subsequent CT imaging revealed a sharply demarcated, well-circumscribed, and mildly expansile marrow-replacing lesion without cortical disruption or erosion and with no periosteal reaction (Fig. 3). Additional aggressive differential diagnostic considerations such as metastatic disease and multiple myeloma were raised by the patient's physicians, and further evaluation with tissue sampling by endoscopic endonasal biopsy/resection was offered. At this point, the patient sought a second opinion at our institution.

Our review of the outside imaging studies suggested a nonaggressive lesion. Though anaplastic or dedifferentiated chordoma may present as T2 dark instead of T2 bright owing to hypercellularity [14], there were no other imaging features to support an aggressive/malignant lesion such as chordoma other than change over time. The well-circumscribed, sharply marginated appearance on CT, including respect of the sphenooccipital synchondrosis, also suggested a benign lesion. At this stage, our leading differential consideration was benign FD, but the progression from the study 2 years earlier raised concern for malignant transformation. Repeat imaging at our institution was performed, demonstrating stability from recent imaging, continued absence of diffusion restriction, and the presence of hyperperfusion on arterial spin labeling (Fig. 4). Though these findings further supported the leading diagnosis of benign FD, obtaining tissue was considered warranted to confirm the nature of the lesion and to guide further management decisions. Subsequent endoscopic endonasal extradural approach to the skull base for tumor removal was performed. Pathology showed characteristic changes of FD, with a deposition of

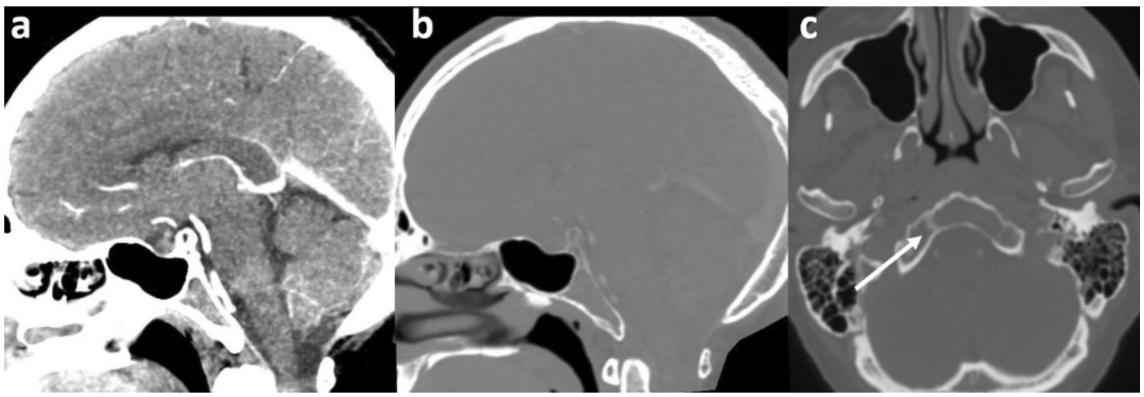

Fig. 3 Images from a computed tomography head angiogram. **a** Sagittal reconstruction in soft tissue algorithm demonstrating soft tissue signal intensity in the medullary space of the clivus, with no extension above the sphenooccipital synchondrosis. **b** Sagittal reconstruction in bone algorithm showing the bone to be subtly expanded with intact cortex. **c** Axial view demonstrating clear demarcation between the lesion and the adjacent uninvolved occipital condyle (arrow)

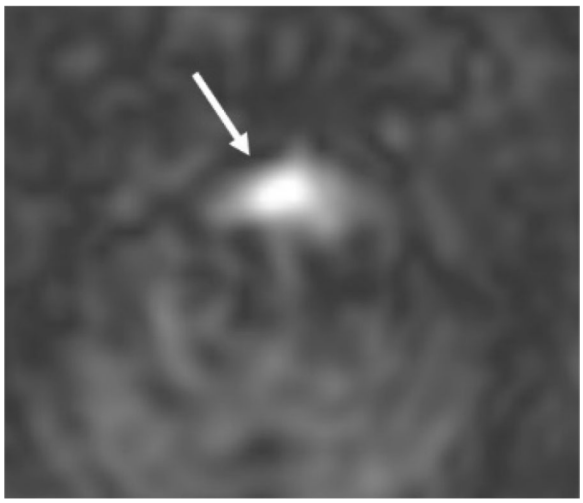

Fig. 4 Axial arterial spin label perfusion image demonstrates marked hyperperfusion associated with the clival lesion (arrow)

woven bone in a background of bland spindle cell proliferation (Fig. 5). No atypical features were seen. In addition, some regions displayed aneurysmal bone cyst-like changes, with multinucleated giant cells and foam cells (lipid-laden macrophages). The *GNAS* R201C mutation was identified by next-generation sequencing. At clinical follow-up, the patient was doing well, with mild headache but no cerebrospinal fluid (CSF) leak or cranial nerve palsy.

Discussion

FD is a benign process in which medullary bone is replaced by fibro-osseous tissue, resulting in architectural distortion and overgrowth/expansion of the affected bone [10]. Craniofacial FD, though often asymptomatic, may manifest with enlargement of an affected area leading to cosmetic disfigurement, encroachment on the paranasal sinuses and their ostia leading to nasal obstruction, cranial nerve symptoms due to encroachment on skull base foramina, and/or nonspecific symptoms such as headache or visual disturbance.

Imaging findings of FD are typically described in three patterns on plain film and CT: pagetoid, sclerotic, and cyst-like [11, 15]. All FD patterns generally exhibit bony expansion along with sharply demarcated borders and no cortical destruction. Loss of corticomedullary distinction giving rise to a characteristic "ground glass" appearance is also common and is essentially diagnostic of FD when present. The pagetoid pattern is characterized by mixed areas of radiopacity and radiolucency that are reminiscent of the changes of Paget disease. The sclerotic form is characterized by increased density of the ground-glass medullary space surrounded by intact cortex. The cyst-like form lacks the characteristic ground-glass change in the medullary space and is characterized on plain film and CT by a lucent area with a sclerotic border. As plain radiographs are limited in the diagnosis and characterization of craniofacial FD, CT, and/or MRI are preferred owing to their ability to more precisely characterize

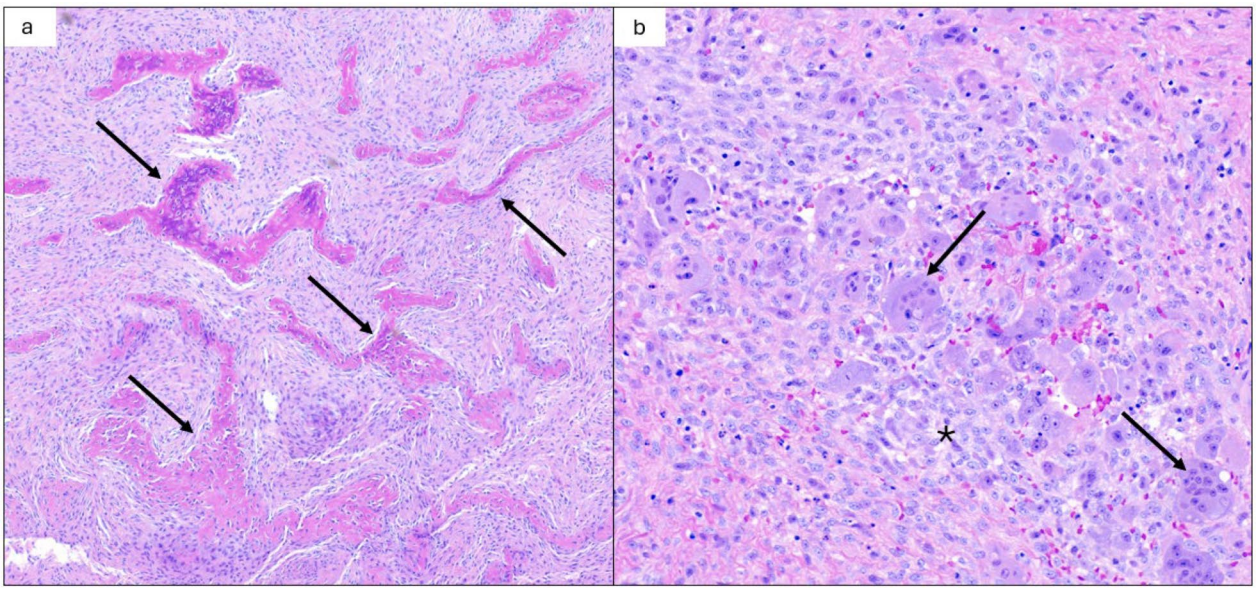

Fig. 5 Photomicrograph of resection specimen (**a**) demonstrates characteristic deposition of woven bone (arrows) in a background of bland spindle cell proliferation, typical of fibrous dysplasia (hematoxylin and eosin, original magnification 40×). No atypical features were observed. Several regions of the patient specimen (**b**) display aneurysmal bone cyst-like changes, including multinucleated osteoclastic giant cells (arrows) and foam cells (*) against a background of numerous capillaries (hematoxylin and eosin, original magnification 100×)

lesions and to evaluate the extent of disease [2, 16]. On MRI, FD is typically hypointense on both T1-WI and T2-WI and brightly enhancing post-gadolinium owing to hypervascularity. These characteristics are not consistently displayed, however. As signal intensity and contrast enhancement vary depending on the quantity and density of fibrous and osteoid matrix present, some lesions may appear bright on T2-WI [7].

FD typically presents as a slowly growing lesion prior to skeletal maturity that then becomes inactive and stabilizes following skeletal maturity. Kuznetsov *et al.* proposed an explanation for why FD stabilizes over time, suggesting that as a lesion ages, residual normal stem cells permit the growth of a normal tissue, while mutant stem cells lack the ability to self-renew, and their progeny are eliminated by apoptosis [17]. Hart *et al.* followed 109 subjects for up to 32 years using ^{99}Tc-MDP bone scans and found that 90% of the total body disease skeletal burden of FD was established by the age of 15 years [1]. Of new confirmed FD lesions identified during their follow-up, over 50% occurred before age 10 years, and only 18% occurred after age 20 years, with only 2% in the craniofacial region [1]. This could be attributed to the fact that the craniofacial skeleton develops from the mesoderm and ectoderm and is influenced by neural crest cells, distinct from the rest of the skeleton that develops from mesodermal tissue [18]. FD lesions may be classified on the basis of their growth characteristics as quiescent (stable with no growth), nonaggressive (slow growing), or aggressive (rapid growth), which is helpful for guiding management [6]. As previously noted, growth typically occurs prior to skeletal maturity, and rapid growth should always raise a concern for malignant degeneration.

Malignant transformation can occur in both monostotic and polyostotic FD, typically past the fourth decade of life and with a notable predominance in males—it is, however, extremely rare in monostotic FD [19]. Osteosarcoma represents the most common histological sarcoma subtype, although sarcomas associated with FD may also include fibrosarcoma, chondrosarcoma, and malignant fibrous histiocytoma [9, 19, 20]. Sarcomatous degeneration should be considered when a patient has rapid progression of pain and swelling. Radiographic findings associated with sarcomatous degeneration include poor margination or incomplete sclerotic margins and osteolytic destruction, often accompanied by thinned or frankly eroded cortices. There is variable association with soft tissue masses or periosteal reaction. In a report of ten patients with malignant transformation of FD, long bones and the pelvis were most commonly affected [18]. Malignant sarcomatous degeneration of FD of the craniofacial bones occurs, but it is rare [21].

Apparent progression of FD may also result from the development of secondary vascular lesions such as aneurysmal bone cysts (ABCs) and arteriovenous fistulae, presumably related to the hypervascular nature of many FD lesions [22, 23]. ABC formation has been most frequently documented within preexisting FD of the skull [2, 8]. In our patient, findings characteristic of ABC were observed pathologically in some areas of the lesion. It is hypothesized that local hemodynamic abnormalities caused by pathological fracture-related bleeding or bone resorption stimulate ABC formation. These lesions may expand rapidly, leading to increased bone pain and the characteristic imaging feature of fluid–fluid levels seen on MRI studies. Secondary high-flow vascular lesions associated with FD are rare, with only a few reported cases. One report described an arteriovenous fistula arising from FD in the occipital bone [22], while two reports detailed arteriovenous malformations in long bones [24, 25]. These vascular anomalies present as rapidly growing, aggressive osteolytic lesions with overlying dilated vessels; they presumably develop from the dilated vascular channels that are common in FD [22]. In our case, the MRI scan from 2 years prior to presentation at our institution shows findings that are potentially suggestive of prominent flow voids, with no characteristic lesion of FD seen on that study.

Conclusion

While the presence of a clival lesion in an adult patient typically raises clinical concern for an aggressive pathology such as chordoma, plasmacytoma, or metastasis, FD is an important consideration in the differential diagnosis. In this case report, we highlight that FD may develop or progress rapidly in a skeletally mature patient, a finding that does not necessarily connote malignant degeneration or suggest an alternative diagnosis if the imaging findings otherwise conform to the spectrum of imaging findings of FD. We highlight that new or progressive lesions of FD may occur after skeletal maturity, and we present an example of such a lesion in the clivus that is documented on serial MRI studies.

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Author contributions
ST and NF carried out conceptualization, drafted the article, and reviewed it critically for important intellectual content. NP drafted the article and reviewed it critically for important intellectual content. JN and JFM cared for the patient and reviewed the article critically for important intellectual content. HV provided the pathological figure and discussion of pathological findings. All authors read and approved the final manuscript.

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Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent
Informed consent was obtained from the patient included in the case report.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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