Locally aggressive fibrous dysplasia

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Abstract Although fibrous dysplasia (FD) is a benign fibro-osseous lesion, locally aggressive behaviour has rarely been described but is poorly characterised. In this study, we document clinical, radiological and pathological (including molecular genetics) findings in three cases of locally aggressive FD, two of which involved the ribs. Lesions in these cases, one of which was a recurrent lesion, were followed up for 2–7 years. All of the lesions showed typical histological features of FD but were characterised by extension through the bone cortex into the extra-osseous soft tissue. The lesions did not exhibit overexpression/amplification of CDK4 and MDM2; in two of the cases, a GNAS mutation was identified. Our findings confirm that FD can rarely exhibit locally aggressive behaviour with extension beyond the bone compartment into the surrounding soft tissue; these lesions can be distinguished from low-grade intramedullary osteosarcoma by lack of amplification/-overexpression of CDK4 and MDM2 and the presence of a GNAS mutation.

Keywords Fibrous dysplasia · Bone tumour ·
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Introduction

Fibrous dysplasia (FD) is a relatively common benign fibro-osseous lesion in which irregularly distributed spicules of woven bone lie in a cellular fibrous stroma [1, 2]. Most cases involve only a single bone (monostotic FD), but in a significant percentage of cases, more than one bone is involved (polyostotic FD). FD usually presents as pain, swelling, deformity or a pathological fracture. It may present over a wide age range but is most often diagnosed in the first three decades of life. Patients with rib lesions alone tend to be older and are often asymptomatic. Males and females are affected equally. Activating missense mutations in the *GNAS* gene (20q13) that encodes the alpha subunit of the stimulatory G-protein, GS alpha (GSα), have been identified in monostotic and polyostotic FD [3–5].

FD, in most cases, is a relatively well-circumscribed intramedullary lesion that expands the bone and typically is surrounded by a relatively wide rim of sclerotic bone. FD enters into the differential diagnosis of many benign and malignant bone tumours. Growth of FD often stabilises when skeletal maturity is reached, but in some cases, there may be continued growth [2, 6]. Distinction of FD from other bone-forming tumours, such as low-grade intramedullary osteosarcoma, can in some cases be problematic. FD is typically confined to the affected bone, but lesions that extend beyond the normal confines of the bone compartment have rarely been documented [7–15]. Most of these cases have been reported in the craniofacial skeleton, particularly the maxilla and mandible, common sites of FD development [7–12]. This extra-osseous extension of FD needs to be distinguished not only from other aggressive bone-forming tumours but also rare sarcomatous transformation of FD.

In this report, we document the clinical, radiological and pathological findings in three cases of FD which exhibited extension of the lesion into the extraosseous tissues. We have examined whether these lesions showed evidence of the

Table 1 Clinical details of locally aggressive FD cases

Case No.	Age (years)[a]	Sex	Size of lesion	Other details	Follow-up (years)
1	32	Male	Left maxilla	Monostotic FD; primary lesion	7
2	60	Male	Right 11th rib	Monostotic FD; primary lesion	3
3	72	Female	Right 7th rib	Polyostotic FD; recurrent lesion	4

[a] Age at first presentation with locally aggressive FD

GNAS mutation characteristic of FD. We also determined whether these lesions expressed CDK4 and showed MDM2 amplification, markers which have recently been documented in low-grade forms of osteosarcoma [16–18].

Materials and methods

Clinical details of the three cases presented in this report are shown in Table 1. Imaging was not available for review in case 1, but the rib lesions of cases 2 and 3 were investigated radiologically using plain X-ray, CT and MRI.

For pathological investigation, 5-μm haematoxylin- and eosin-stained sections of the formalin-fixed, decalcified lesion were examined histologically. Immunohistochemistry was carried out using an indirect immunoperoxidase technique with the antibodies MIB-1 (Dako, UK) and anti-CDK4

(clone DCS-31), (Invitrogen, CA, USA) directed against Ki-67 and CDK4, respectively.

Molecular genetic investigations included polymerase chain reaction (PCR) and mutation-specific restriction enzyme digestion (MSRED) for GNAS1 mutation. DNA was extracted from 5-μm sections cut from the tissue blocks and MSRED of exon 8 or exon 9 PCR products used to screen for the ten previously reported GNAS1 codon 201 and 227 mutations as previously described [19]. In addition, MDM2 FISH using the ZytoLight SPEC MDM2/CEN12 Dual Color Probe kit (Zyto Vision GmbH, Bremerhaven, Germany) was performed and evaluated on a full tissue section as previously described [20]. All FISH findings were reviewed by at least two individuals experienced in interpreting FISH.

Results

Clinical findings

As shown in Table 1, all cases in our series were adults (age range 32–72 years). One patient had a lesion of the left maxilla; the other two patients had lesions in the right 11th rib and right 7th rib. Cases 1 and 2 presented without a prior
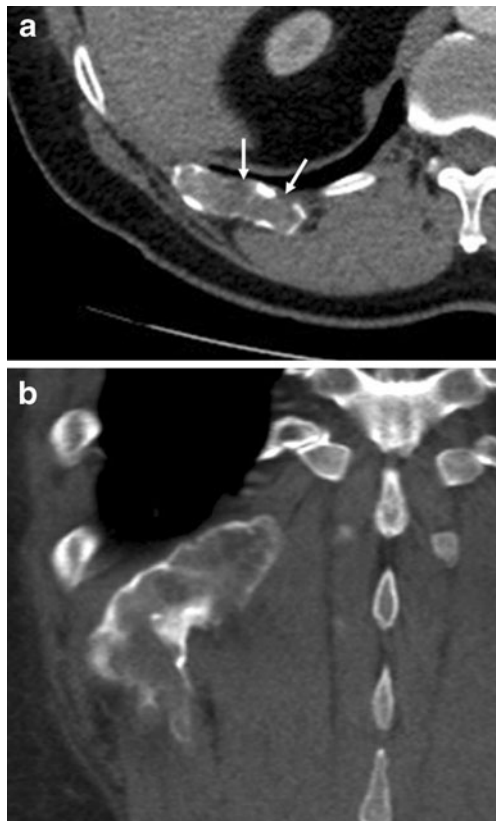

Fig. 1 Case 2. **a** Axial and **b** coronal reformatted CT images showing expansile lesion with breach of the cortex (*arrows*)
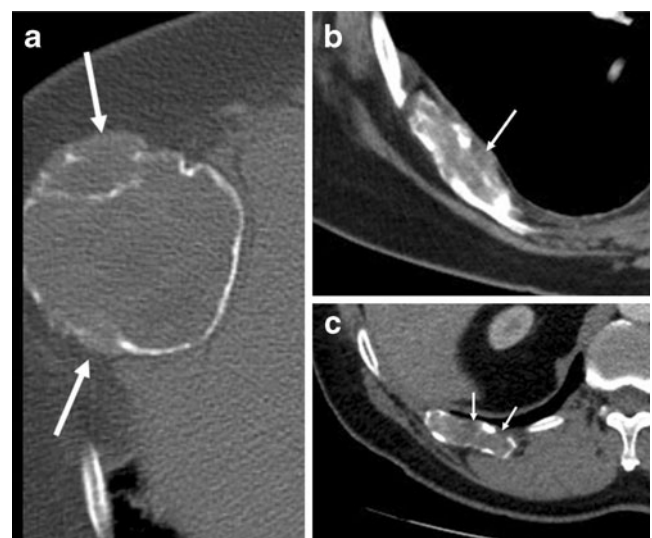
Fig. 2 Case 3. CT of the **a** anterior, **b** middle and **c** posterior 7th rib lesions. All three lesions show breach of the cortex (*arrows*)

Fig. 3 FD of 11th rib in case 2 showing **a**, **b** irregular woven bone trabeculae lying in a bland cellular fibrous stroma; **c**, **d** osteoclastic giant cells in the haemorrhagic fibrous stroma and on the surface of woven bone
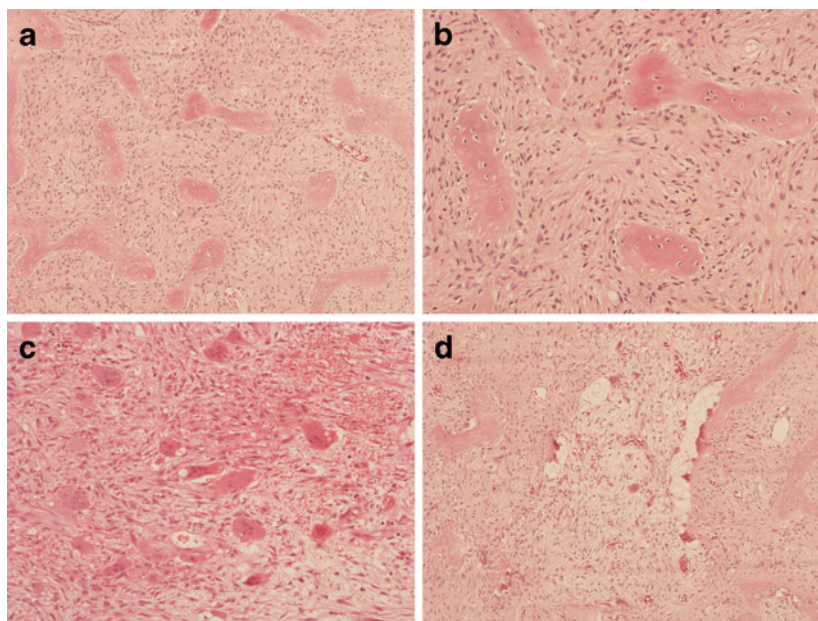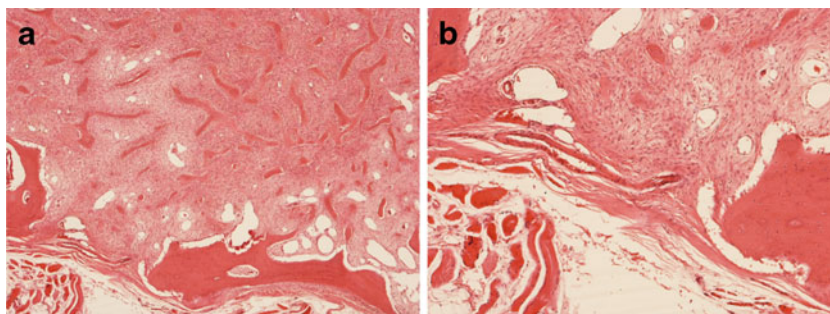

history of FD; case 3 had multiple rib lesions and was considered a case of polyostotic FD.

Radiological findings

In case 2, MRI showed a single expansile lesion arising from the posterior portion of the 11th rib with uniform intermediate signal on T1-weighted sequence and mixed high and low signal on the STIR sequence. CT showed an expansile lytic lesion with multiple breaches of the thinned cortex (Fig. 1).

In case 3, CT showed two lytic lesions arising from the 7th rib at the resection margins and an additional lesion involving the posterior end of the rib. The small posterior lesion was lytic and non-expansile and had a sclerotic border with a breach in the cortex anteriorly. The other two lesions were expansile and were surrounded by a thin cortex with intermittent breaches. The more anterior of the two lesions was spherical and measured 5 cm in diameter. The smaller more posterior lesion showed modest expansion of the rib along a 5-cm length (Fig. 2).

Histological and molecular genetic findings

The diagnosis of FD was confirmed in all cases histologically. The fibro-osseous lesions contained abundant cellular fibrous tissue in which there were scattered irregular woven bone trabeculae (Fig. 3). Bone trabeculae were lined by flattened cells, and there was no marked cellular or nuclear pleomorphism. Mitotic activity was not pronounced and atypical mitotic figures were not identified. Focal myxoid change was seen in the fibrous stroma in which there were many small collections of osteoclastic giant cells, some of which were associated with small areas of haemorrhage; neighbouring woven bone trabeculae in the lesion often showed evidence of osteoclastic bone remodelling (Fig. 3). Other morphological changes which have been noted in FD such as cementum-like bodies, island of cartilage or extensive cystic change within the fibrous stroma were not seen in these lesions.

In all three cases, there was extension of FD through the bone cortex into the covering soft tissue. In cases 1 and 2, the cortex had been breached but the lesion was still covered by

Fig. 4 Case 2 **a**, **b** of FD showing extension of the lesion through the bone cortex. The lesion remains covered by periosteal fibrous tissue

periosteum (Fig. 4). In case 3, the lesion extended into extraosseous fat, fibrous tissue and muscle (Fig. 5).

Immunohistochemistry showed a low proliferating fraction (<5 %) on Ki-67 staining and no evidence of CDK4 expression in all cases.
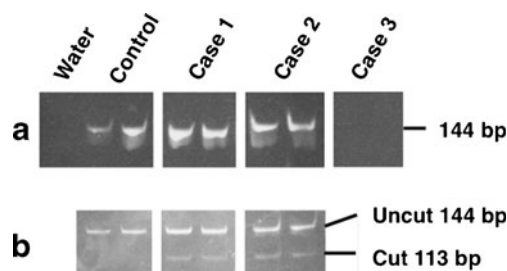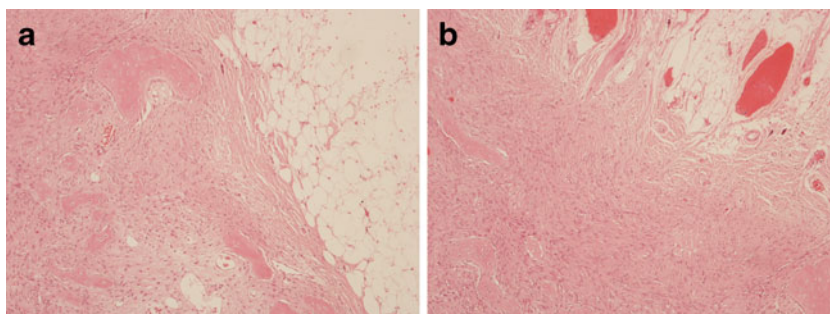
Molecular genetic investigation showed evidence of a R201H GNAS mutation typical of FD in cases 1 and 2 (Fig. 6). There was no evidence of MDM2 amplification by FISH. Molecular genetic investigation was not informative due to inadequate DNA quality in case 3.

Fig. 6 Eight percent polyacrylamide analytical gel showing **a** PCR-amplified fragments from exon 9 of the GNAS1 gene. **b** The *Nco*I restriction digest analysis of mutations R201H. Normal PCR product 144 bp uncut (wild type). *Nco*I digests reveal bands at 144 and 113 bp (heterozygous mutations)

Discussion

In this report, we document three cases of FD, two arising in the rib and one in the maxilla, where unusually there was histological evidence of extension of the lesion through the bone cortex into the covering soft tissues. The lesions showed typical histological features of FD with disorganised, irregular woven bone trabeculae lying in a cellular fibrous stroma. There was no marked nuclear pleomorphism or mitotic activity. Focal myxoid change and small collections of osteoclast-like giant cells were noted in the fibrous stroma, and there was prominent osteoclast remodelling of FD woven bone trabeculae. All cases were negative for CDK4 and did not have a high proliferating fraction. Two of these cases were negative for MDM2 amplification and showed a R201H GNAS mutation.

Most of the previously published reports of aggressive behaviour or soft tissue extension of typical FD have been noted in the craniofacial skeleton, particularly in the maxilla and mandible [7–12]. These cases arose mainly in young patients in whom FD had recurred locally following an initial surgery. We also report a case (case 1) of locally aggressive FD that arose in the maxilla, but in our case, the patient had reached skeletal maturity and the lesion was not a recurrence. The other two cases in this series arose in the ribs of patients that had reached skeletal maturity. One of these (case 3) was a recurrent lesion developing in the seventh rib of a 72-year-old female; the other (case 2) was a primary lesion arising in the 11th rib of a 60-year-old male. Spread beyond the bone cortex into the surrounding connective tissue was relatively limited in cases 1 and 2 where the lesion was largely covered by periosteal fibrous tissue. Infiltration beyond the periosteum was seen in case 3 where the extraosseous component was covered by muscle and fat.

FD usually presents in the first three decades of life; it may often remain asymptomatic but can present later in life as an incidental radiological finding or as pathological fracture. Most monostotic lesions of FD cease to enlarge after skeletal growth has ended. Lesions are usually confined to bone and have a sclerotic border. It should be noted that FD can rarely be attached to bone by a bony stalk, producing an exophytic lesion on the bone surface (fibrous dysplasia protuberans); this occurs mainly in short tubular bones of the hands and feet but has also been reported in the ribs [21]. In this series of lesions which showed a locally aggressive behaviour, typical histological features of FD were noted. No evidence of cystic change was seen, but focal myxoid change and small collections of osteoclastic giant cells were noted in the fibrous stroma; the latter were often associated with small areas of stromal haemorrhage and in most cases with osteoclastic activity on the surface of the neighbouring woven bone trabeculae. It is possible that stromal haemorrhage may have resulted from lesional trauma and that this increased osteoclast activity is significant with regard to osteolysis of the cortex and expansion of the lesion into extraosseous soft tissue.

As all these FD cases had extended through the bone cortex, the principal differential diagnosis was an aggressive bone-forming tumour, such as aggressive osteoblastoma or

Fig. 5 Case 3 **a**, **b** of FD showing extension of the lesion beyond the periosteum into muscle and fat

low-grade (FD-like) intramedullary osteosarcoma. However, unlike osteoblastoma, these lesions did not show evidence of prominent osteoblastic rimming of woven bone and had an inter-trabecular stroma composed mainly of cellular fibrous tissue. The possibility of low-grade osteosarcoma was a concern in these cases as a FD-like variant of this tumour is known to exist [22, 23]. However, the absence of nuclear pleomorphism or increased mitotic activity made a diagnosis of osteosarcoma difficult to substantiate morphologically. Immunohistochemistry showed a low proliferating fraction on Ki-67 staining, and CDK4 expression and MDM2 amplification, which have recently been described as markers of low-grade osteosarcoma [16, 17], were not identified in this case or any of the other lesions examined. Evidence of a R201H GNAS mutation typical of FD was seen in two of our cases where there was DNA of adequate quality. Pollard et al. also concluded that mutational analysis for GNAS mutation was useful in the differential diagnosis of FD and low-grade central osteosarcoma [24].

One of the features that distinguish FD from other bone-forming tumours is that even when it is large and has replaced cancellous bone, there is a rim of cortical bone which limits the lesion to the bone compartment. This series of cases provides evidence that FD is not always confined to bone and can rarely extend through the bone cortex into extra-osseous soft tissues. Full-thickness cortical bone destruction is a feature that characterises aggressive or malignant lesions of bone. With regard to FD, it is important to bear in mind that such cortical penetration could represent rare (approximately 0.5 % of monostotic cases) sarcomatous transformation [25]. Distinction of locally aggressive FD from a low-grade (FD-like) osteosarcoma can be difficult but, as this study shows, absence of cellular and nuclear pleomorphism and mitotic activity, a low-proliferating fraction on Ki-67 staining, absence of CDK4 overexpression and MDM2 amplification, and the presence of GNAS mutation should be useful in distinguishing rare examples of locally aggressive FD.

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