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CASE REPORT

Recurrent adult-type fibrosarcoma of the frontal bone in a child

Mariangela Novello[1] · **Concezio Di Rocco**[2,3] · **Gianpiero Tamburrini**[2] · **Paolo Frassanito**[2] · **Daniel T. Aguirre**[3] · **Andrew E. Rosenberg**[4] · **Antonella Coli**[1]

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Abstract
Introduction Primary, adult-type bone fibrosarcoma is an uncommon, malignant spindle-cell tumor of fibroblastic origin, rarely affecting children. Most frequently diagnosed among bone malignancies in the past, improved diagnostic techniques and further restrictive classification criteria have currently made the diagnosis of fibrosarcoma very unusual.
Case report We hereby report the case of a 7-year-old child with a right frontal swelling mass. A computed tomography scan showed an osteolytic lesion of the right frontal bone, involving the diploe and the outer table of the skull. An en bloc surgical excision, followed by a thorough immunohistological evaluation, led to the diagnosis of fibroblastic proliferation, with low cellularity and minimal atypias. The patient had four recurrences during the 4-year follow-up. With an increasing histological grade at recurrences, a diagnosis of adult-type fibrosarcoma was made.
Conclusion To the best of the authors' knowledge, this is the first reported case of an adult-type fibrosarcoma arising in the frontal bone of a child.

Keywords Fibrosarcoma · Tumor progression · Frontal bone · Pediatric · Immunohistochemistry · Molecular biology

✉ Antonella Coli
antonella.coli@rm.unicatt.it

[1] Department of Anatomic Pathology, Catholic University, Largo F. Vito 1, 00168 Rome, Italy

[2] Pediatric Neurosurgery, Catholic University, Rome, Italy

[3] Pediatric Neurosurgery, International Neuroscience Institute, Hannover, Germany

[4] Division of Anatomic Pathology, Miller School of Medicine, University of Miami, Miami, FL, USA

Introduction

Adult-type bone fibrosarcoma (FS) is a rare, malignant tumor arising from fibroblasts, generally affecting adults and very rarely children [1–17], more commonly occurring in the long bones of the extremities, with exceedingly rare localization in the cranial bones [18]. Histologically, it consists of a proliferation of uniform spindle-shaped cells with a fibroblastic immunophenotype, arranged in a fascicular or "herringbone" pattern, with a variable presence of collagen. Since these histological features can be observed in a broad spectrum of benign and malignant spindle-cell bone tumors, the diagnosis of FS is now considered of exclusion, particularly after the advent of ancillary techniques [1].

We present a rare case of recurrent adult-type FS arising in the frontal bone of a child, which progressively increased in histological grade at recurrences, investigated by immunohistochemical and molecular techniques.

Case report

A 7-year-old boy presented with a right frontal swelling, progressively increasing in size over the last year. A computed tomography (CT) scan showed an osteolythic lesion of the right frontal bone, involving the diploe and the outer table of the skull. Sagittal T2 and T1-weighted magnetic resonance imaging (MRI) with gadolinium showing a hyperintense bone enlarging lesion (Fig. 1a, b). Surgical resection of the lesion was performed through a bicoronal skin flap and en bloc craniotomy, to obtain a marginal resection. Macroscopic examination showed a white lesion with a rubbery consistency expanding the diploic space, breaking through the outer table and infiltrating the periosteum, that was accordingly resected (Fig. 1c). Macroscopically, the tumor appeared completely

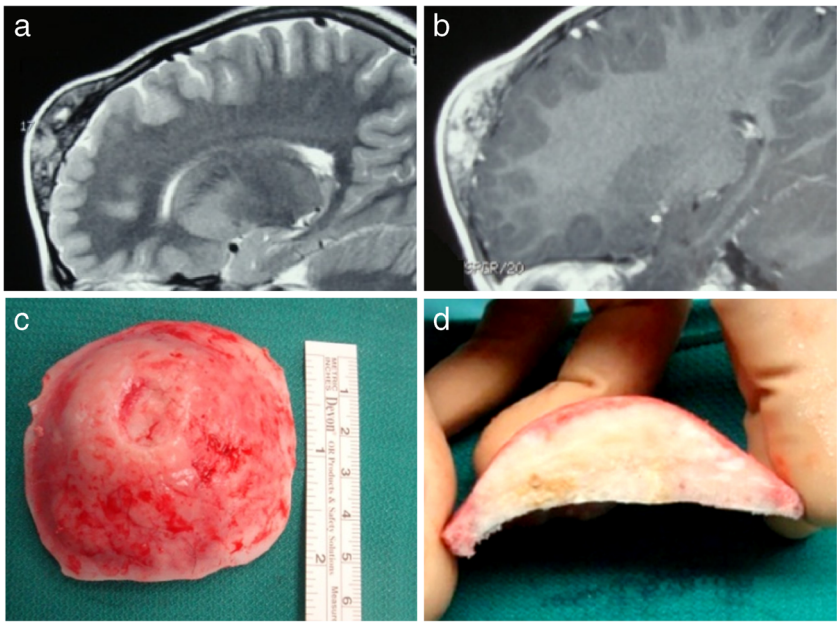

Fig. 1 Sagittal T2 and T1-weighted magnetic resonance imaging with gadolinium showing a hyperintense bone enlarging lesion (**a**, **b**, respectively). Resected frontal bone with tumor breaking the outer table (**c**). Section of the tumor with rubbery fibrous consistency (**d**)

removed (Fig. 1d). The skull defect was repaired by means of autologous bone, harvested by splitting two parietal bone flaps. The histological examination showed a lesion composed of spindle cells, arranged in a fascicular pattern with a moderate amount of collagen bundles. The lesion was hypocellular and did not show significant cellular atypia; infiltration of the pre-existing cancellous and cortical bone was focally detected (Fig. 2a, b). Mitotic activity was very low (<1 × 10 HPF), with a Ki-67 proliferation labeling index <1 % (Fig. 2c). Immunohistochemistry showed that the tumor cells expressed vimentin and focally smooth muscle actin. The tumors cells were negative for S-100, desmin, caldesmon, epithelial membrane antigen, PGM-1, CD21, CD35, CD68, ALK, and cytokeratins. A diagnosis of fibroblastic proliferation with minimal atypias was made.

Given an apparently total resection, a close follow-up was decided. Six months later CT scan revealed a local recurrence in the orbital margin of the cranioplasty. The recurrent tumor, which presented histological features superimposable to those of the first examination, was resected and the new cranial defect was repaired by splitting the frontal bone. Chemotherapy was decided and carried out weekly according to the trial for aggressive fibromatosis [19]. Seven months later, the patient showed a rapidly growing swelling in the frontal region and a new CT scan confirmed a second recurrence of the lesion, with complete erosion of the cranioplasty, mild compression of the brain parenchyma and infiltration of the dura mater. Surgery was performed, with en bloc resection of the lesion. Duraplasty was also performed, since local infiltration of the dura mater was observed, while cranial repair was

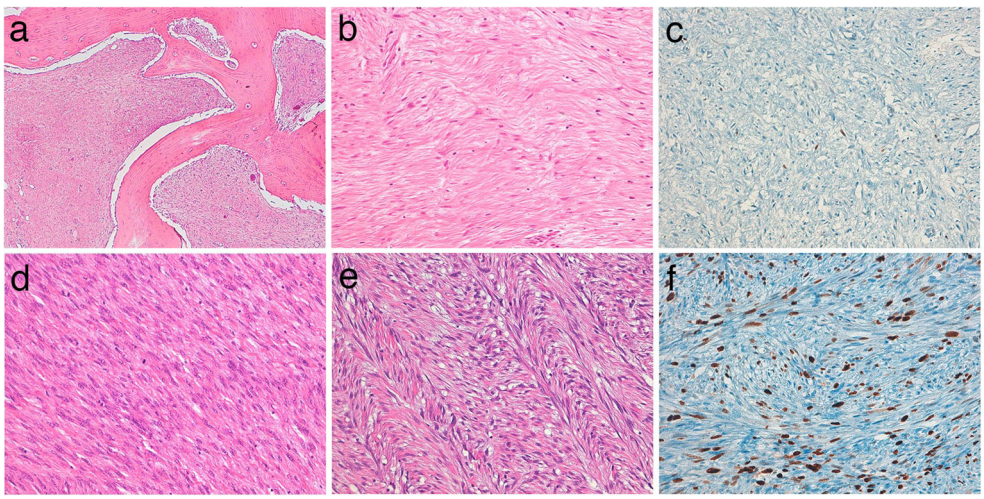

Fig. 2 Fibroblastic proliferation with minimal atypias and infiltration of the pre-existing cancellous and cortical bone (**a**). Hypocellular spindle cell tumor at presentation (**b**), with 1 % Ki-67 labeling index (**c**). At third recurrence, high cellularity, moderate atypias, and rare mitoses were observed (**d**). High grade fibrosarcoma with "herringbone pattern" (**e**) and 30 % Ki-67 labeling index (**f**). (**a** ×50; **b–f** ×200)

Table 1 Reported cases of bone adult-type fibrosarcoma in children

Author, year, ref	Age (year)/sex	Location	Positive IHC	Molecular analyses	Adjuvant therapies	Follow-up
Van Blarcom et al., 1971, [2]	13/M	Mandible	NR	NR	NR	NR
Dehner, 1973, [3]	7/M	Mandible	NR	NR	None	NED, 5 ½ yrs
Slootweg et al., 1984, [4]	11/F	Mandible	NR	NR	RXT	R at 1 year, D after 2 years
Bang et al., 1989, [5]	2.5/M	Mandible	Vimentin	NR	None	5R in 15 years, NED for 7 years
Grundfast et al., 1991, [6]	8/F	Temporal	NR	NR	NR	NR
Lo Muzio et al., 1998, [7]	4/M	Mandible	Vimentin	NR	None	NED, 4 years
Daw et al., 2000, [8]	NR	Occipital	NR	NR	None	NED, 5.8 years
Gosau et al., 2008 [9]	9/F	Mandible	NR	SYT: neg.	None	NED, 3 years
Divya et al., 2009, [10]	10/F	Mandible	NR	NR	None	NED, 8 months
Nanda et al., 2013, [11]	17/F	Mandible	Vimentin	NR	NR	NR
Swain et al., 2013, [12]	8/M	Maxilla	Vimentin	NR	None	D after 6 months
Present case	7/M	Frontal	Vimentin, SMA§	SYT, ETV6: neg.	ChT	4 R, D after 4 years

IHC immunohistochemistry, *NR* not reported, *ChT* chemotherapy, *RXT* radiotherapy, *NED* not evidence of disease, *D* died, *R* recurrence, *SMA* smooth muscle actin, § focally

postponed. Radiotherapy (60 Gy) and chemotherapy according to the protocol EpssG non RMS were administered [20].

The patient had two further recurrences during the next 14-month follow-up. Histologically, the tumor showed a progressive increase of cytological atypias at recurrences. In particular, from the third recurrence, a higher cellularity, mild nuclear atypias, and occasional mitoses became evident (Fig. 2d) and a progressive shift from a low grade fibroblastic proliferation to a high grade, extremely cellular spindle cell proliferation, with a characteristic "herringbone pattern", was observed (Fig. 2e). Increased mitotic activity (up to 6 × 10 HPF) with a Ki-67 labeling index about 30 % (Fig. 2f) and small foci of necrosis were also present in the last two recurrences. Therefore, all the histological material was revised by one of the authors (AER), with a diagnosis of adult-type FS (grades 2 and 3), supported by fluorescent in situ hybridization analysis, showing negativity for SYT and ETV6 gene rearrangements. The child eventually died 4 years after initial surgery.

Discussion

Bone FS is a rare, malignant fibroblastic tumor occurring in adults (from the second to sixth decade of life). The distal femur is the most common location, followed by the distal humerus and proximal tibia; localization in the skull bones is extremely rare [1]. From large brain tumor series, primary adult-type FS in the meninges and brain parenchyma shows a very low incidence—with only seven reported cases, almost all in adult patients—among about 35,000 cases of CNS tumors [21, 22]. Large series of bone FS present in literature contain only few pediatric cases, lacking accurate clinical information [13–17]. Single case reports of bone FS in children, although rare, show a prevalent facial bone localization, particularly in the mandible (Table 1) [2–12]. Only a single pediatric case arising in the occipital bone has been reported [8]. Unfortunately, almost all reported cases of adult type bone FS in children lack deep immmunohistochemical and molecular analysis [2–12]. To our knowledge, this is the first case of primary adult-type bone FS of the frontal bone in children.

In the previous literature, the term FS was applied to any primary spindle cell neoplasm showing tumor cells organized in a fascicular pattern [13–16]. Histologically, bone FS, as its soft tissue counterpart, is composed of a population of uniform, spindle cells exhibiting a typical herringbone growth pattern and variable amounts of intercellular collagen. Although most often observed in FS, these histological features are also evident in other bone tumors, such as synovialsarcoma, infantile fibrosarcoma, osteosarcoma, leiomyosarcoma, and mesenchymal chondrosarcoma. However, after the advent of ancillary techniques, FS has been diagnosed with caution, being mainly an exclusion diagnosis, and its incidence is considered exceedingly low [1]. In fact, recent retrospective studies, using modern diagnostic criteria based on immunohistochemistry and molecular genetic analyses, placed the vast majority of previously reported FS in other categories [23, 24].

Histological grading of bone FS is based on cellularity, pleomorphism, mitotic activity, amounts of collagen produced by the tumor cells, and extent of necrosis. Cases with marked cytological pleomorphism and storiform growth patterns are separated from FS and classified as undifferentiated pleomorphic sarcoma [1]. These tumors can be graded according to the AJCC or FNCLCC grading systems [25, 26]. Since FS tumor cells are unreactive for Desmin, Myogenin, MyoD1,

Caldesmon, epithelial markers (Cytokeratins), S-100, and ALK, immunohistochemical stains are necessary to rule out other malignant spindle cell tumors. Furthermore, molecular genetic analyses may contribute to a more accurate diagnosis, as negativity for specific transcripts allow to exclude other sarcomas with characteristic molecular signatures, such as synovialsarcoma and infantile FS, which harbor peculiar translocations, t(X;18)(p11;q11) and t(12;15)(p13;q26), respectively [27, 28]. Moreover, the tumor should be devoid of bone and osteoid formation in order to rule out central low-grade osteosarcoma and fibrous dysplasia.

Well-differentiated FS may be misdiagnosed as desmoplastic fibroma, a benign fibroblastic proliferation. The presence of cellular areas, mitotic figures, plump nuclei, and hyperchromasia foster a diagnosis of FS, although the diagnosis is often difficult and subjective [29]. According to the literature, this distinction is of no clinical interest, as both these lesions are locally aggressive and the treatment depends on a wide surgical excision [29].

In our case, at time of presentation, the lesion showed a very low cellularity without significant cytological atypia and absence of mitoses, the only feature in favor of an aggressive malignant behavior consisting of a focal infiltration of the preexisting cancellous and cortical bone, and a diagnosis of fibroblastic proliferation with minimal atypias was made. The patient had four recurrences during the follow-up, and only at third recurrence the tumor showed overt fibrosarcomatous features.

Bone FS can often recur locally, both marginal and intralesional surgical excisions being followed by a high risk of recurrence rates (about 70 %), either in high and in low-grade lesions. Wide surgical margins ensure local control of the tumor in low-grade lesions, although, do not always exclude local recurrences in high-grade lesions. As assessed by Bertoni et al., the percentage of local recurrences in the stump, following amputation, (26 %) was higher than in osteosarcomas (4.3 %) and comparable only to that observed in malignant fibrous histiocytoma of bone [16].

The treatment of choice of bone FS is radical surgery. However, wide surgical margins in the skull are difficult to obtain, in particular when the soft tissues are involved or where the margins of craniectomy are extended with bone rongeurs or drilling (i.e., close to the orbit or in general to the skull base). Radiation therapy and chemotherapy can be administered for inoperable cases or as a palliative treatment, as their effectiveness is still unclear [30]. In our case, notwithstanding adjuvant chemotherapy and radiation therapy, local disease progression was shortly observed. Interestingly, no cases of distant metastasis have been reported in adult-type bone FS in children, despite the absence of adjuvant treatment. Prognosis of the tumor is dependent on the histological grade, tumor size and adequate surgical treatment with wide margins. The 5-year survival rate disease is poor, ranging from 20 to 30 % [16].

In conclusion, bone FS is a very uncommon entity, especially in pediatric patients. Its diagnosis may be challenging and deep sampling and use of modern diagnostic criteria based on immunohistochemistry and molecular genetic analyses are necessary in order to make a proper diagnosis. As observed in the present case, marginal excision does not exclude local recurrences also in low-grade lesions and adjuvant therapies do not seem to guarantee local control of the disease. The present case, despite adjuvant therapies, showed multiple recurrences with a progressive increase in histological grade and death of the patient. Due to the rarity of adult-type bone FS in children, reports of new cases with accurate clinical information, utilizing molecular and immunohistochemical techniques, could provide useful information concerning the biology and behavior of this rare tumor.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement The present report was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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