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Fibrous dysplasia imitating malignancy

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ABSTRACT

Fibrous dysplasia is a benign bone disease, presenting as monostotic or polyostotic lesions, or as part of a syndrome (McCune-Albright/Mazabraud). Its clinical course shows a variegated picture and the progression of its growth is unpredictable. In the workup of 39 fibrous dysplasia cases in the cranio-facial area, four cases presented fast growth tendencies, of which two patients with McCune-Albright syndrome showed malignant-like rapid growth. This local aggressive form is extremely rare, and the concept of this issue has not been clearly defined. With regard to the speed of growth a volumetric-time analysis in one of our cases demonstrated a 74 days tumor doubling rate with an exponential growth curve. According to the literature the aggressive form presented extra-cranially mainly at an adult age, whereas its appearance in our cranio-facial patient collective was much younger. Distinguishing nonmalignant and malignant aggressive forms is difficult and highly inconsistent in the literature. We therefore implemented a quantitative growth measure analysis to define aggressive forms based on progression and speed of growth and impartial of type of FD, localization or functional incapacity. Due to our study findings and literature review we state a prevalence of an aggressive form might be possibly about 5 %.

1. Introduction

A cranial involvement of fibrous dysplasia occurs in 25–30% of cases of monostotic (MFD) and in nearly 90–100% of cases of polyostotic fibrous dysplasia (PFD) (Machida et al., 1986; Lee et al., 2012). In approximately 5% of all cases, polyostotic fibrous dysplasia is associated with the McCune-Albright Syndrome (MAS), in which in addition, a cutaneous hyper-pigmentation and hyper-functioning endocrinopathy is also present (Gorham et al., 1941; Shin et al., 2017). Fibrous dysplasia (FD) is the result of an early embryonic post-zygotic GNAS mutation (encoding cAMP pathway-associated G-protein, Gsα). It is, as a rule, characterized by slow, progressive growth, which develops over years and leads to deformities of the affected region. A rapid increase in size of fibrous dysplasia is exceptionally rare. In addition to cystic intra-lesional changes of FD (Fyrmpas et al., 2006; Anderson et al., 2015), a malignant transformation (Ruggieri et al., 1994; Salenave et al., 2014) or an aggressive benign progression of FD (Shapeero et al., 1993; Muthusamy et al., 2015) can both lead to a rapid increase in size with functional and morphological problems. In addition to unusual casuistry with obstruction of respiratory passages, massive masticatory functional problems and visual impairments, the speed of dynamic volume increase of an aggressive non-malignant progression is quantified here for the first time.

2. Materials and methods

In the framework of a retrospective study of 39 patients (17f, 22m) with fibrous dysplasia in the cranio-facial region who had been seen at the University Hospital Bonn from 2000 to 2017 were analyzed for an aggressive progression form. The age at the time point of first diagnosis was between 5 and 38 years with an average age of 31 ± 10.7 years. In 26 cases a monostotic form of a cranio-facial dysplasia (MFD) was diagnosed, in 10 cases, a polyostotic form (PFD) and in 3 cases a McCune-Albright Syndrome (MAS) was found. In at least 10 cases, post-pubescent disease progression was documented. The volumetric measurement of tumor growth was conducted with ROI-segmentation and subsequent evaluation with Philips software (IntelliSpace Portal V9.0; Hamburg, Germany).

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3. Results

From among the 39 patients, rapid progression of size was found in four patients in the craniofacial area within a short time, while in two cases, the absolute extension in size due to cystic change was still low, in another two cases, there was a high degree of suspicion of malignant transformation due to exponential growth. A fifth patient with craniofacial fibrous dysplasia showed a malignant transformation due to PFD at the age of 58 years (highly malignant central osteoblastic osteosarcoma with an KI 67 index of 30%). This appeared, however, in the area of the proximal femur after implantation of a hip-endoprothesis after repeated femur fracture. The analysis of the craniofacial part showed only subtle progression.

One of the patients with rapid progression but still comparatively little extension in overall size was a 16-year-old female patient with known monostotic fibrous dysplasia in the upper jaw, which was the result of an excessive reaction of the bone after the surgical extraction of a retained root (radix relicta regio 26). Spiral CT showed solid cystic tumor tissue that led to erosion of the maxillary sinus. Pathohistologically, there was a typical picture of an FD with a mitosis rate of <1/10 HPF (high-power field) with no indication of malignancy. The tumor measured 2 × 3cm.

A cystic FD change to rapid growth progression was also found in a 38-year-old male patient with MFD in the region of the horizontal lower jaw body accompanied by increasing pain. Four years after the first diagnosis, the lower jaw showed eroded cortex with a tumor size of 2 × 5 cm. Here, too, there was no pathohistological indication of malignancy.

In the last two cases, there was an impression of the tumor as being a solid neoplasia within the context of a McCune-Albright Syndrome, described in detail below.

A girl of five years underwent surgery due to rapid FD growth and the suspicion of a malignant transformation of a known right supraorbital FD lesion. She presented with a known McCune-Albright Syndrome, pseudopubertas praecox (pseudo-precocious puberty), hyperthyreosis, and recurring ovarian cysts with hormone suppressant therapy. Clinically the lesion showed a progressive volume expansion with increasing exophthalmos (Protrusio bulbi) and constriction of the eye socket. Bone scintigraphy showed multilocular craniofacial involvement as well as the involvement of the lower extremities on both sides. The CT examination showed the typical ground-glass phenomenon with displaced growth in the orbita. Intraoperatively, the findings were described as gray solid tumor masses. The pathohistological evaluation confirmed fibrous dysplasia, and yet no indication of a malignant transformation. The molecular biological examination of the Gsα-Protein-Gene was positive. The defect in the forehead area was reconstructed using titan mesh but showed continued growth in the following years despite pamidronate therapy commencing in 2003. Just after the end of puberty the growth began to slow down (see pictures Fig. 1a–c) though meanwhile pathological fractures in the area of the upper thigh, the right lower leg as well as the supracondylar region of the humerus and the radius were incurred due only to minor trauma. These were cared for, and a malignoma of the thyroid was surgically removed. Chemical laboratory examination showed alkaline phosphatase continued to be high with values between 994 U/l (1998), 494 U/l (2008) and 645 U/l (2011). Concerning the craniofacial FD lesion the patient is currently stable with no further growth observed.

The second case was a 16-year-old male patient operated in 2015, with an alio loco diagnosis of McCune-Albright Syndrome that had been genetically validated four years ago. In 2014 a modeling osteotomy in the facial area was conducted and repeated 6 months later. Due to a recurrent progressive swelling, he finally presented at our clinic with increasing respiratory problems. Clinically, a progressed facial deformity with a dislocation of the nose and upper jaw was conspicuous (see Fig. 2a–c). The digital CT examination showed an irregular thickening of the skull base with the typical ground-glass texture, which affected the facial skull and narrowed the optic nerve on the left side. In comparison to the original CT at the age of 11 years, three years later (05/2014) a doubling in the size of the lesion to 45 × 38 mm was apparent. The FDG-PET-CT examination (2014) showed mild activity but no indication of malignity. Six months later a renewed doubling of the volume occurred and now compromised broad areas of the alveolar crest of the nasal skeleton and hard palate. The CT examination conducted at his first presentation in our hospital in January 2015 showed further tumor growth with a size of 122 × 102 mm which expanded three months later to 141 × 109 mm and displayed clear mineralization of parts of the tumor and cortical destruction with mild activity enrichment of the tracer in the 3-phase bone scintigraphy. Laboratory chemistry assessments showed increase of alkaline phosphatase from 732 U/l (2014) to 1439 U/l (2015), which fell postoperatively (06/2015) to a value of 338 U/l. Vitamin D was within normal limits. Raised levels of parathyroid hormone were found in the hormone status [129.8 pg/ml (2014)] and thyroid-stimulating hormone (normal range 0.4–4 μU/ml) with 6.5 μU/ml (2014), 2.57 μU/ml (2015) and 4.22 μU/ml (2017), while the adrenocortico tropic hormone and cortisol level was within normal limits. Likewise, the follicular stimulating hormone, luteinizing hormone, prolactin and testosterone level and C-ANCA all lay within the normal range.

In the course of the first presentation a Percutaneous Endoscopic Gastrostomy (PEG) was inserted and a tracheotomy in local anesthesia was conducted. The analysis of the alio loco performed brain imaging showed an exponential trajectory of the tumor volume within a time frame of a few months and a tumor doubling time of 74 days (see Fig. 3).

During the tumor resection (05/2015) the reconstruction of nasal anatomy, the periorbital anatomy, reconstruction of the midface as well as the orbital floor and the masticatory functional rehabilitation of the patient were taken into account. The final result was a light raised position of the bulbous with far visual acuity of 0.05 on the left (see Fig. 4a–c).

3.1. Histology

According to the pathohistological assessment, the nature of the tumor was “biphasic” with no indication of malignancy. No atypias or raised mitosis-rates were found. The immunohistochemical Ki67-proliferation Index amounted to <2 % (Fig. 5). No MDM2-amplification was found, so that a low malignant central osteosarcoma could also be excluded. In two DNA-samples of the tumor-tissue, a GNAS-mutation R201H in Exon 8 was found (c.602G > A p. Arg201His).

1. Bone components (A): irregular curved bone trabeculae without cement lines, which appeared to derive from the tissue and corresponded to the structure of the lamellar bone with osteoblasts at the margins.
2. Connective tissue components (B): spindle cell proliferates in a storiform layout with massive cell density in hyaline/edematous/fibromyxoide supporting tissue. The cell nuclei appeared bland and showed oval cell nuclei and no mitoses.

3.2. Follow up

Just one week after the operation orthoptical findings for visual acuity of the right eye was 0.6 and 0.4 for the left eye. The motility

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