About a Rare Case of Low-Grade Chondrosarcoma of the Cranial Vault

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Abstract: Chondrosarcoma is a rare malignant tumour arising from the cartilage with a high variability in the clinical course and overall prognosis. This entity has, generally, a predilection for long bones of the limbs and pelvis and the location in the cranial bones is quite rare. We report a case of a 38 year male with a large and poorly symptomatic parafalcine chondrosarcoma of the cranial vault which was removed en bloc. The described location is extremely rare. Magnetic Resonance Imaging permitted to better delineate the lesion and plan the most appropriate therapeutic approach. Final diagnosis was based on histological examination, which confirmed the hypothesis of low-grade parafalcine chondrosarcoma. Even though surgery remains the mainstay of treatment for cerebral chondrosarcomas, adjuvant radiotherapy such as stereotactic, proton beam or carbon ion-beam therapy might be necessary in aggressive or incomplete removed cases.

Keywords: Chondrosarcoma, Computed Tomography, Magnetic Resonance Imaging, skull base, malignant tumor, adjuvant radiotherapy.

INTRODUCTION

Chondrosarcoma (CSA) is a slow growing malignant tumour arising from hyaline cartilage and represents the third most common malignant bone tumor after multiple myeloma and osteosarcoma. This entity is characterized by certain variability in macro- and microscopic features, clinical course and prognosis [1]. CSA mainly affects long bones of the limbs and pelvis, generally sparing spine and cranio-facial bones [2]. Among cranial and intracranial origin the most frequent location is at the skull base with an incidence around 0.16% [3] being the sphenoid bone the most affected [4]. Among the intracranial locations, the involvement of the frontal bone is extremely rare. Once it involves the intracranial location, the tumor is believed to originate from residual embryonic chondrogenic cells along synchondrosis and synfibrosis or from the pluripotential mesenchymal stem cells within the skull vault bones abnormally localized during intramembranous ossification [5-7]. Intracranial CSA usually remains silent for a long period of time because of its slow rate of growth and when the first symptoms appear the clinical picture may be very aspecific. Radiological findings are not typical and as matter of fact these lesions can be misdiagnosed for metastasis, solitary fibrous tumors, chordoma, meningimas and vascular lesions such hemangio-pericytoma [8].

CASE REPORT

A 38 years-old man was admitted to the emergency department of our hospital because he suffered from a single tonic clonic seizure. Past medical history was unremarkable. On admission, a brain computed tomography (CT) scan was performed and this showed the presence of a right side large intracranial extra-axial space-occupying mass (10 cm by 6 cm) arising from the inner surface of the frontal bone which was abnormally thick (Figure **1**). The lesion appeared to be non homogeneous but with a well defined margin and slightly hyperdense to brain tissue. There was no mass effect on the adjacent nervous structures or signs of bony erosion. A brain MRI confirmed the presence of an extra-axial non homogeneous expansive mass, arising from the inner surface of the cranial vault. The lesion determined only a moderate mass effect on adjacent nervous structures, without important brain oedema. On diffusion MRI there was a restricted water

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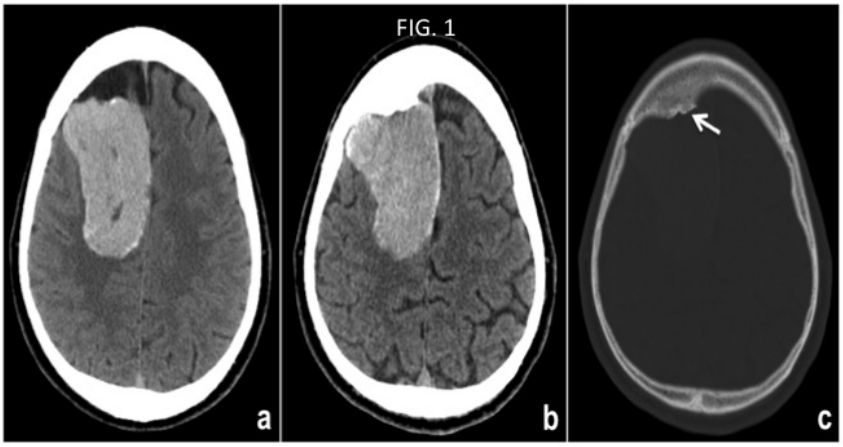

Figure 1: Unenhanced CT scan shows a well-defined, hyperdense and inhomogeneous extra-axial lesion (**a-b**), with mass effect on the adjacent brain structures. CT scan with bone algorithm (**c**) shows a clear planting base on the inner surface of the cranial vault, with thickening of the internal wall of the frontal bone (*white arrow*).

diffusion, consistent with the hypothesis of a slow-growing tumour (Figure **2a-d**). After intravenous gadolinium administration there was a minimal enhancement at the periphery of the mass (Figure **2e-f**). According to these apparent benign radiological findings a complete removal of the lesion was planned and managed by a right side craniotomy. The tumor was removed en bloc together with the infiltrated dura and the overlying bone. It was hard in consistency and whitish in colour with good dissection margins from the surrounding tissue (Figure **3**). About 1.5 cm tumor free of dural margin and bony borders, histologically proven, were achieved. A cranioplasty with cement was performed as well. The post operative course was unremarkable and the patient was discharged home a week later. Histological examination demonstrated immature amorphous chondroid matrix with a few multicellular nests mixed with scanty atypical, hyper-chromatic and bi-nucleated chondrocytes. High power examination revealed a mild grade of dedifferentiation,

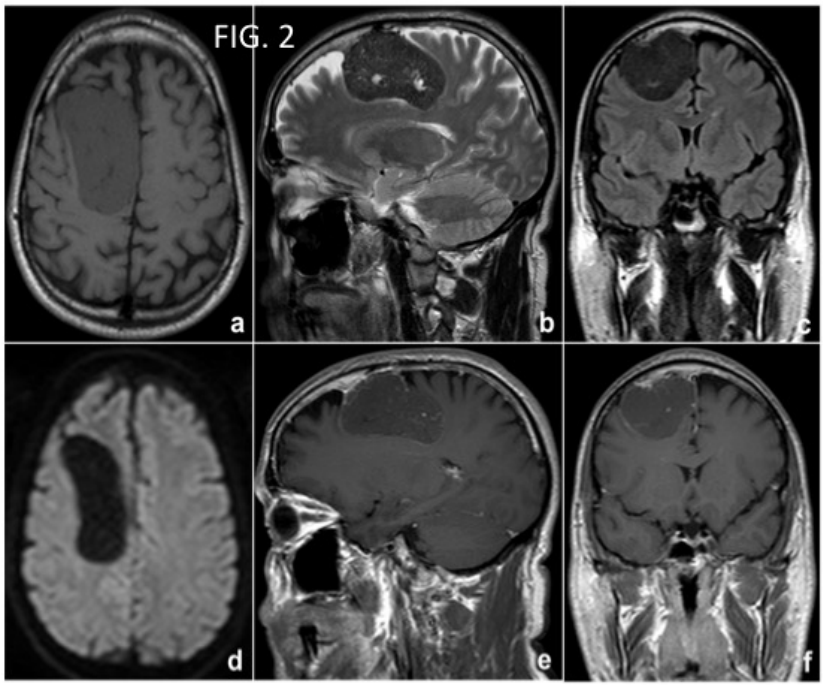

Figure 2: Transverse T1-weighted Spin-Echo (**a**) and sagittal T2-weighted Turbo Spin-Echo (**b**) MR images show a slightly inhomogeneous hypointense mass compared to cortex, arising from the inner surface of the cranial vault, with a thin rim of CSF between tumour and brain parenchyma (*cleft sign*) and no clear evidence of dural invasion. Coronal FLAIR MR image (**c**) shows moderate mass effect on adjacent structures, without brain tissue oedema. At Single Shot Diffusion Weighted Image (DWI) (**d**) no evidence of restricted diffusion was present. Sagittal and coronal T1-weighted Spin-Echo MR images after intravenous administration of Gadolinium (**e-f**) show poor contrast enhancement, limited to planting base and peripheral part of the lesion.

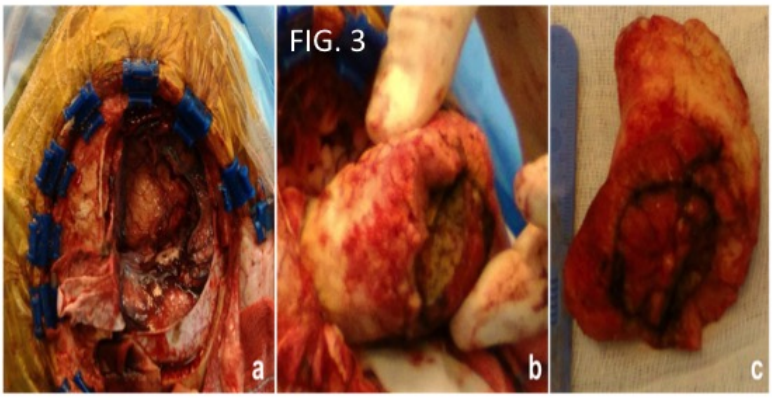

Figure 3: After craniotomy, intraoperative images (**a-b**) shows an ovalar well-defined parafalcine mass, arising from the inner surface of the frontal bone with apparent invasion of the underlying dural membrane in few points. Gross specimen (**c**) shows a large (10 x 6 cm), white and lobulated tumor, poorly vascularized and hard to the touch.

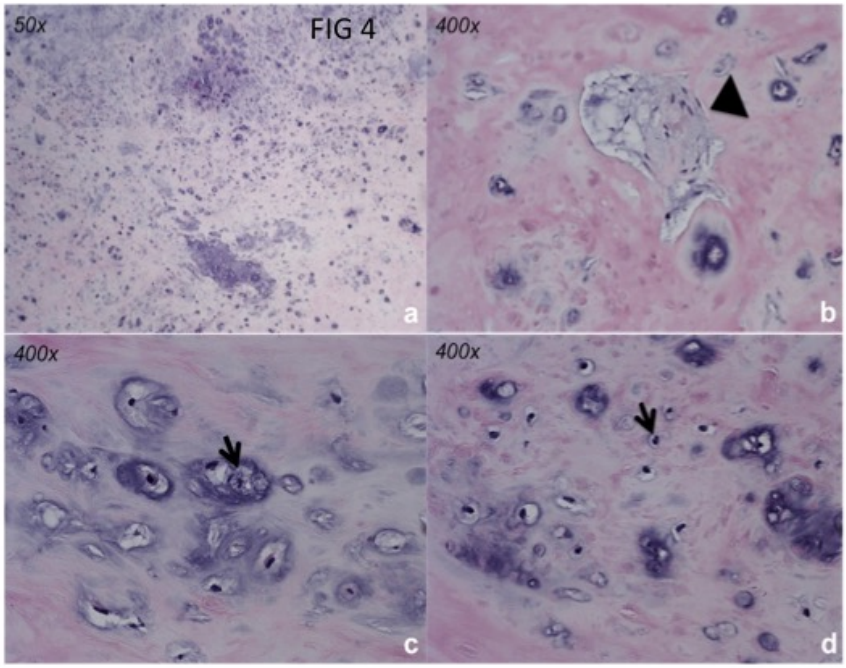

Figure 4: Hematoxylin-eosin stain 50x (**a**) shows immature amorphous chondroid matrix with pauci multicellular nests and some atypical chondrocytes. High power slide 400x reveals dedifferentiation and myxoid changes of the matrix (*black arrowhead*) (**b**); hyperchromatic and binucleated cells (*black arrow*) and nuclear pleomorphism are clearly visible (**c-d**).

with myxoid changes of the matrix; no necrotic areas were observed (Figure **4**). The final diagnosis was grade II CSA according to the World Health Organization classification. We advice the patient to undergo stereotactic radiosurgery but he strongly refused this option. At the latest out patient follow up (30 months) he was fine and on MRI there was no signs of tumor recurrence.

DISCUSSION

Intracranial extra-axial CSA was reported, for the first time, by Mott in 1899 [9]. About 75% of CSAs are primary lesions while the remaining are histologic variants and secondary forms which include solitary osteochondroma, multiple osteochondromatosis, enchondroma and primary synovial chondromatosis which generally originate from the skeletal axis [8]. CSA originating from the cranial bones represents only 0.15% of all intracranial space-occupying masses and when the cranium is involved there seems to be a predilection for skull base, sphenoid and occipital bone. The origin from the cranial vault is very seldom [3]. In a review of CSAs by Korten *et al.* [6], 37% of tumors were located in the petrous bone, 23% occurred in the occipital and clival bone, 20% in the sphenoid bone and 14% in the frontal, ethmoidal and parietal bones;

the remaining 6% used to arise from dural tissue. Also a location in the choroid plexus and brain parenchyma have been reported [10]. Histologically, intracranial CSAs are classified into three subtypes: well-differentiated (classical type), intermediate (myxoid type) and undifferentiated (mesenchymal type) [11]. In a review of 192 CSAs cases by Chandler *et al.* [12], 62% were of the classical subtype, while the mesenchymal and myxoid types accounted, respectively, for 30% and 8%. Korten *et al.* [6] reported that the mesenchymal type is the most malignant subtype and it may spread to distant areas. The classical type is, instead, the most benign one. Intracranial CSA typically affects patients in the fourth and fifth decades of life, with no gender preference [13]. The mesenchymal subtype has, on the contrary, a younger peak of incidence in the II and III decades [6]. The clinical presentation of CSA is generally, related to increased intracranial pressure and reflects the anatomical location of the mass [14,15]. As in our case, seizures may be the first sign [12,16]. The correct diagnosis largely relies on neuroradiological assessment and may expose the radiologist to higher risk of error, considering the frequently atypical presentation on CT and/or MRI imaging [16,17,18]. MRI usually reveals a hypointense mass on T1-weighted images and a hyperintense mass on T2-weighted images [1,15]. Histological examination posed the diagnosis of grade II parafalcine CSA, highlighting the presence of few atypical chondrocytes. This aspect required us to have an open discussion with the patient for possible adjuvant x-ray treatment despite the certain total removal of the lesion. The patient, however, refused such treatment for personal reasons. The most accurate radical surgery, if feasible, should always be attempted for these types of tumor, in order to reduce the risk of recurrence [8,19,20]. Another point to keep in mind is the possible association of these tumors with other systemic pathologies like Ollier and Paget disease, Maffucci syndrome and osteochondromas, [7]. When total surgical resection cannot be achieved due to the location of the tumour and its relationship with important functionally relevant structures postoperative adjuvant radiotherapy has been reported to improve patient outcomes [19] while chemotherapy does not seem to be so effective [14]. In same articles is recommended radiotherapy even after successful radical resection due to the invasive nature of these lesions [21]. According to a previous study, the 5-year recurrence rate for CSA patients treated with surgery alone is 44%, which is reduced to 9% following the addition of adjuvant radiation therapy [17]. Also other forms of radiotherapy like postoperative proton beam therapy has also demonstrated promising results with regard to tumor control [18,22]. As matter of fact proton therapy is already a part in the multidisciplinary management of sarcomas in contiguity to sensitive structures [22]. Demizu *et al.* [23] conducted a retrospective, nationwide multicenter study to evaluate the clinical outcomes of proton beam therapy for bone sarcomas of the skull base and spine in Japan. Among 96 patients 20 (20.8%) were affected by CSA and in 70.8 % the most frequent tumor location was in the skull base. At a median follow-up of 52.6 months (range, 6.3-131.9) the 5-year overall survival, progression-free survival, and local control rates were 75.3%, 49.6%, and 71.1%, respectively. Li *et al.* [24] evaluated retrospectively, the clinical chart and radiographic data of 106 consecutive surgically treated cases of CSA (18 mesenchymal and 88 conventional type) in order to find out the adverse factors important for progression-free survival (PFS) and overall survival (OS) and try to propose a treatment strategy. Gross total resection was achieved in 43 patients (40.6%) and adjuvant radiotherapy was administered in 45 patients. After a mean follow-up duration of 47.8 months, 38 patients (37.3%) experienced recurrence tumor. Progression free survival and disease-specific overall survival at 5 years was 57.7% and 74.4%. Independent adverse factors were previous surgery ($P = 0.028$), increased lesion size ($P = 0.026$), extent of surgical resection ($P < 0.001$) and malignant subtype pathology ($P = 0.003$). In the incomplete resection subgroup ($n = 63$), steretactic radiosurgery significantly benefited tumor control ($P = 0.016$). In a study from the neuroncology unit at the University of Cambridge [25] high-dose photon radiotherapy improved the 5 year disease-specific survival for CSAs patients treated with radical intent to 100% while the local control rate was 83%. Another form of radiotherapy used for these tumors is the carbon ion-beam therapy but a study comparing this modality of treatment with the proton beam therapy did not show any significative difference [26]. Raza *et al*. [27] wanted to focus on the multimodality management of CSAs arising in the skull base and especially they wanted to see the impact of histological subtype/grade on PFS, the indications for surgery, radiation, and chemotherapy based on histology. They conducted a retrospective review on 37 patients. Among these 81% were conventional type, 16.2% mesenchymal type and 2.7% dedifferentiated. Histological grade/subtype and treatment factors were assessed for impact on median PFS as primary

outcome. They found that increasing conventional grade inversely correlated with median PFS ($P < 0.05$). Gross total resection positively impacted PFS, adjuvant radiotherapy significantly impacted PFS in conventional grades 2 and 3 (182 vs 79 months; $P < 0.05$) and had a positive trend with mesenchymal/dedifferentiated CSAs. Chemotherapy improved PFS for mesenchymal/ dedifferentiated CSAs ($P = 0.089$). So they postulated a histological subtype/grade specific treatment protocols. For conventional CSAs (grade 1) surgery alone provides optimal results, while resection with adjuvant radiotherapy yields the best outcome for grade 2 and 3 CSAs. Yakkioui *et al.* [28] performed an interesting study in order to assess if a molecular switch due to oncogenic viruses could be responsible for the malignant behavior of chordomas and chondrosarcomas. They isolated DNA and RNA from snap-frozen specimenns of 18 chordomas and 15 chondrosarcoma and performed real-time PCR or RT-PCR to assess the presence of multiple oncogenic viruses. Immunohistochemistry and in situ hybridization were used as well to validate the eventually positive results. Parvovirus B19 (PVB19) DNA was detected in 4 of 18 chordomas (22%) and in 1 of 15 chondrosarcomas (7%). The authors concluded that viral involvement in the etiology of chordomas is likely, with PVB19 the most distinguishing but no conclusion were made for chondrosarcomas.

CONCLUSION

Intracranial CSA is a rare malignant cartilaginous tumor of the skull which requires multispecialty management. The mainstay of therapy is, when possible, the completely removal of the lesion with clear margins followed, according to the histologic result, by adjuvant therapy to avoid the risk of recurrence. New modality of radiotherapy like the proton beam or carbon ion-beam therapy seems to be very promising in order to achieve long period of PFS.

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