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Case Report

Post Radiation Transformation to a Sarcomatous Meningioma: a Case Report in an Adolescent Male with NF2 Genetic Mutation

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Abstract

Atypical meningioma is often treated adequately by complete surgical resection and subsequent radiation therapy. Nevertheless, radiation therapy should be reassessed in the management of younger patients and particularly in individuals harboring NF2 genetic mutation. To the best of our knowledge this is the third case of post radiation transformation of atypical meningioma in an adolescent male after reviewing the available English literature. Kew wards: Post radiation, atypical meningioma, transformation, sarcomatous meningioma, NF2 mutation.

Keywords: Post radiation, atypical meningioma, transformation, sarcomatous meningioma, NF2 mutation.

INTRODUCTION

Meningioma in general is an indolent neoplasm; it constitutes approximately 36% of all primary intracranial tumors. The WHO classifies it into three main grade groups, CNS grade 1 meningioma, atypical (CNS grade 2) and anaplastic (CNS grade 3) meningiomas. Surgical resection is considered to be the gold standard modality of treatment. The addition of radiotherapy may positively influence disease free life survival in the higher-grade tumors. However, compared to CNS WHO grade 1 meningioma, CNS WHO grade 2 and 3 meningiomas have a significantly higher rate of recurrence [1]. Several resections may be required in patients with recurrent meningioma, and consequently, the percentage of cure is reduced. There are few reported cases of histological malignant transformation following radiotherapy treatment [1]. Herein we report a case of a frontoparietal meningioma in a 17-year-old adult male with NF2 genetic mutation, initially diagnosed as CNS grade 2 'atypical meningioma' that progressed after surgical treatment and subsequent radiotherapy to a malignant sarcomatous type meningioma. This article has been presented in the annual neuroscientific research held on 27 October 2022.

CASE PRESENTATION

A 17-year-old adolescent male, presented to our department at the age of ten, with a giant extra-axial fronto-parietal tumor measuring 8.7 x 7.7 cm (Figure 1). The patient had no significant past medical history or family record of any genetic diseases. Staged near total surgical resection was performed due to the tumor high vascularity and risk of significant blood loss, but a small residual (less than 2 cm) persisted. Subsequently, histopathological assessment of the resected tumor revealed an atypical meningioma (CNS WHO grade 2), featuring increased mitotic activity in the neoplastic cells, ranging between 5 to 12 mitotic figures per 10 HPF (figure 2). Later after surgery, he received radiotherapy treatment 59.4 Gy in 33 fractions, along with brain fractioned stereotactic radiotherapy 25 Gy in 5 fractions for the residual disease. During a three-year clinical and radiological surveillance, the patient remained stable, and his residual tumor did not increase in size. Almost five years after his first presentation, he developed a sudden onset of acute neurological deficit, his brain images revealed significant progression of his residual tumor (Figure 3a). He underwent near total resection for the sagittal sinus invasion and the tumor progression, then followed by a course of radiation to the operative bed. The histology of these samples showed a meningothelial neoplasm with its characteristic whorling pattern but with significant increased mitotic activity around 12 mitoses per 10 high power fields with findings similar to the previously resected tumor (Figure 2). Six months following his last course of radiotherapy, his MRI scan

showed marked increase in size with areas of necrosis and substantial progression of the residual disease, (Figure 3b). The radiological impression was radiotherapy related necrosis, but tumor recurrence couldn't be ruled out. Surgery was conducted and the samples were examined to reveal a different histological picture. The tumor cells lost its whirling pattern and exhibited predominantly spindle cell morphology with numerous apoptotic bodies, large areas of necrosis and marked cytological atypia. The mitotic index in the hot spots reached 20 mitotic figures per 10 high power fields. The tumor cells displayed in some areas a sarcomatous /rhabdoid phenotype. Immunohistochemical showed EMA and progesterone immunoreactivity, confirming a meningothelial phenotype, (Figure 4). Ki67 (proliferative index) changed from 20 % in the previous samples to reach approximately 40% in this last sample, (Figure 5). The case was discussed in the neuro-oncology multidisciplinary tumor meeting and the decision was to manage the patient with palliative and salvage chemotherapy. Next generation sequencing was performed on the paraffin embedded tissue to estimate tumor mutational burden, investigate microsatellite instability (MSI) status, and detect any genetic mutations. The results showed an absence of high mutational burden or any microsatellite instability, but an inactivating mutation in NF2 gene P135fs*39 was identified.

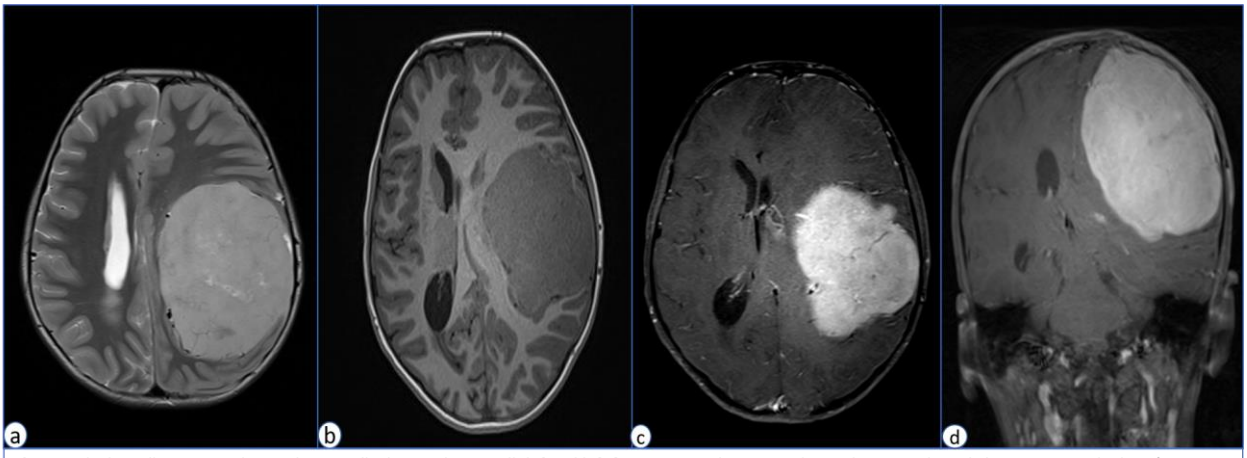

Figure 1: (a, b, c, d) MRI scan, (sagittal, coronal), shows a large well defined left fronto-parietal extra-axial mass lesion irrelatively homogeneous high T2/FLAIR and low T1 signal intensity measuring about 8.7cm x 7.1cm x7.7cm in it's maximum AP, TR, CC dimensions respectively. Post contrast images the lesion showed avid mostly homogeneous contrast enhancement with some none enhancing central component likely representing necrosis. The lesion is causing mass effect on the brain parenchyma causing 12mm midline shift.

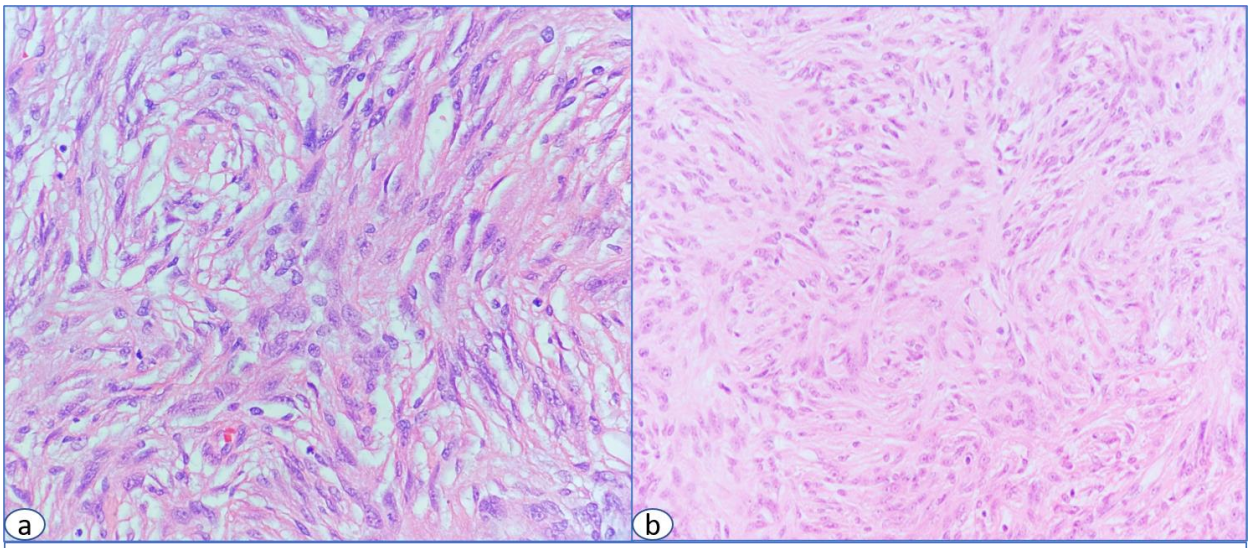

Figure 2: Microscopic examination of the atypical meningioma (a&b), featuring meningothelial whorls. (Haematoxylin & Eosin, 400X, 200X respectively).

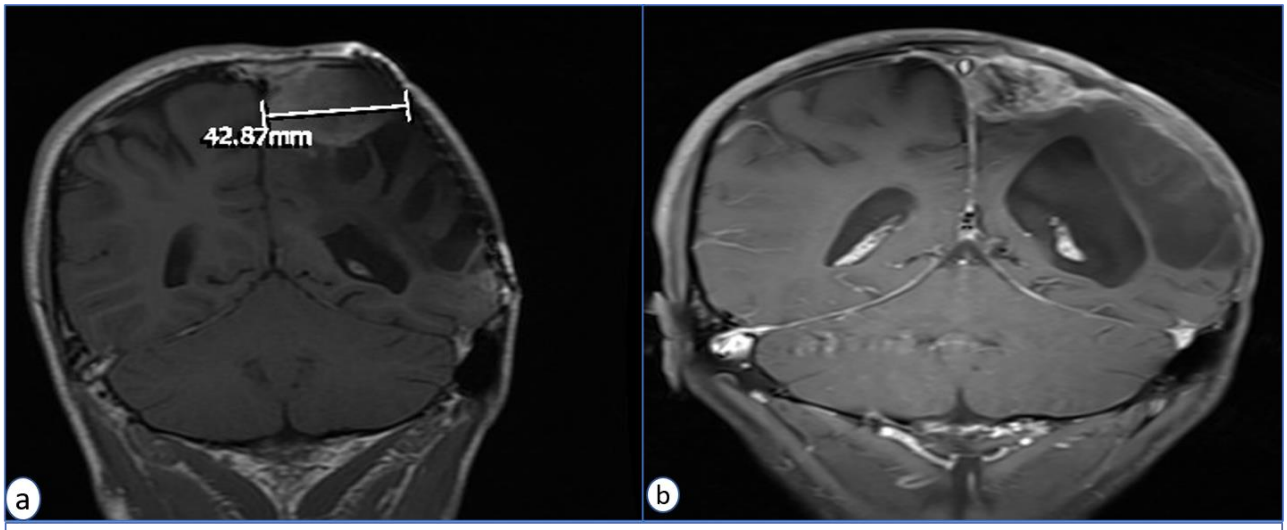

Figure 3: (a) MRI scan, T1 with contrast coronal cut showing significant interval progression of the known residual nodules in the left hemisphere measuring at least 4 cm at maximum diameter. (b) MRI scan, T1 with contrast coronal cuts showing further progression of the tumor with evidence of central necrosis.

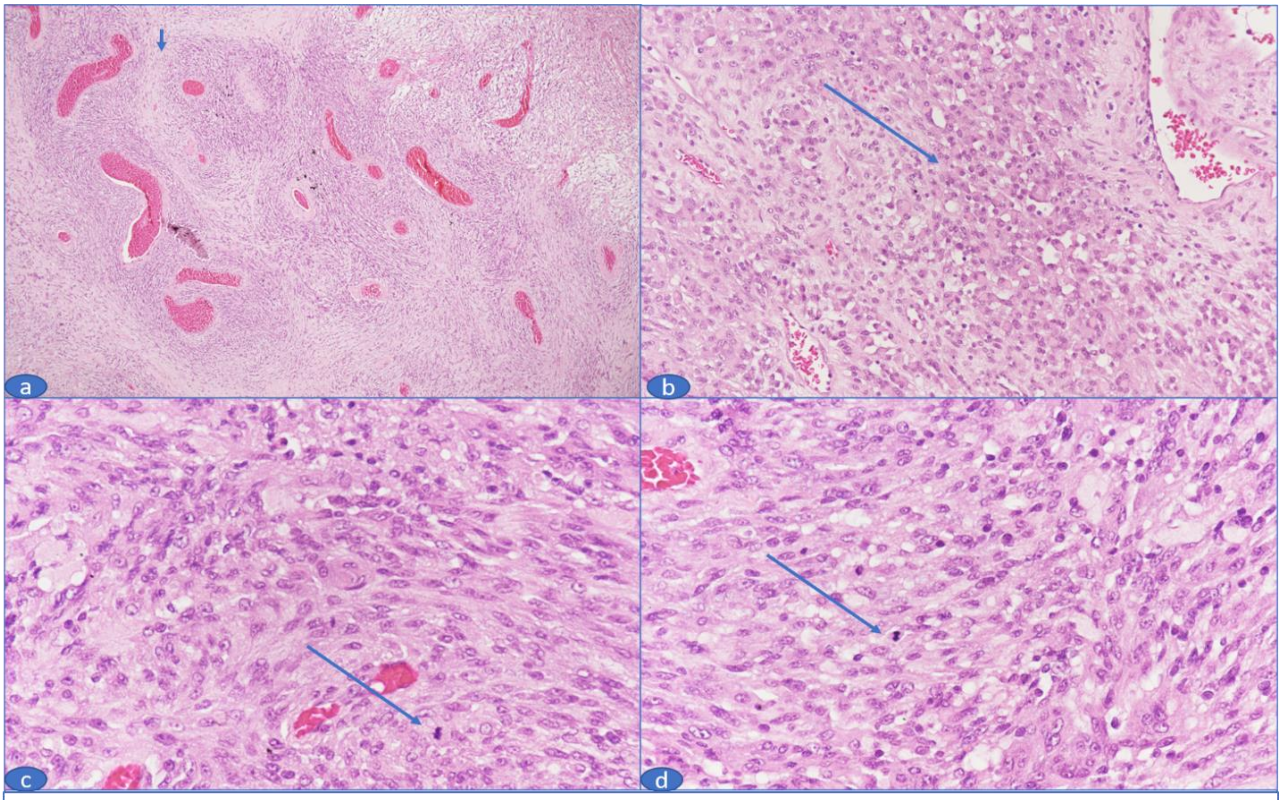

Figure 4 : Microscopic examination of the anaplastic meningioma harbouring foci of necrosis (marked with an arrow) (a), rhabdoid anaplastic features (marked with an arrow) (b), numerous mitoses (marked with an arrow) and moderate atypia (c &d) (Haematoxylin & Eosin, 100X, 200X, 400X, respectively)

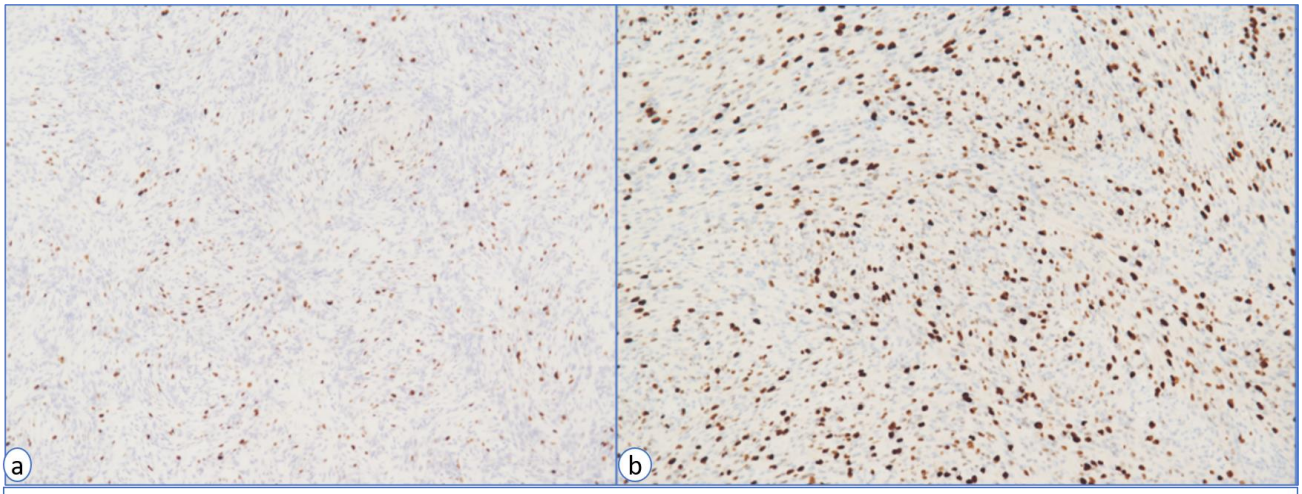

Figure 5: KI67 proliferative index; a) showing a percentage of approximately 20 % in atypical meningioma, reaching almost 40% in anaplastic meningioma (b). (Immunohistochemistry, 200x).

DISCUSSION

Meningiomas originate from clonal proliferation of arachnothelial cells of the meninges [2]. The pathogenesis has been linked to loss of chromosome 22, which also has an essential role in NF2 mutated patients [2]. NF2 encodes the tumor suppresser gene Merlin, in this present case Next Generation Sequencing (NGS) revealed a truncated Merlin protein with loss of a portion of the N-terminal FERM domain and the entire Cterminal domain. The N terminal FERM domain directs the tumor suppressing function of the Merlin protein by interfering in the localization of the proteins to the plasma membrane and interacting with C-terminal FERM domain. The result of these alterations is inactivating the Merlin gene [3]. However, it should be noted that the exact mechanism of Merlin and chromosome 22 in meningioma tumorigenesis is yet abstruse and has been associated with the cytoskeletal remodeling process [3]. In general, the literature described the occurrence of meningiomas in NF2 patients as being more aggressive, they grow 50-75% faster and larger than sporadic meningiomas and they often show a higher histological grade ie; CNS WHO grade 2 or 3. They also have a greater propensity to transform to a malignant neoplasm and have a higher rate of recurrence [2]. The WHO classification of tumors of the central nervous system (2021) categorized meningiomas into CNS WHO grades 1, 2, and 3. This grading scheme is based on specific histopathological parameters: CNS WHO grade 1 (benign) is characterized by low proliferation rates and lack of anaplastic features or brain invasion; CNS WHO grade 2 (atypical) is achieved by specific subtypes such as chordoid or clear cell types or by fulfilling either one of two major criteria or three of five minor criteria. The major criteria include the presence of (4 -19) mitotic figures in 10 high power fields or direct brain invasion, while the minor criteria include (1) increased cellularity, (2) small cells with high N/C ratio, (3) large prominent nucleoli, (4) pattern less or sheet-like growth pattern (5) foci of spontaneous or geographic necrosis. The Ki67 proliferative index or MIB count does not directly affect the WHO grade; however, it is usually estimated around 4% and up to 20% in atypical meningioma [4, 5].

CNS WHO grade 3 or "anaplastic meningioma" is defined as an overtly malignant neoplasm (resembling that of carcinoma, melanoma or sarcoma), with elevated mitotic activity, marked nuclear pleomorphism and necrosis. They account for approximately 1-3% of all reported meningioma cases and usually arise de-novo, however, occasional cases are recurrent disease or related to prior radiation [5]. Predictably recurrence rates are variable and interrelated to the initial CNS WHO grade and the completeness of the surgical resection, the recurrence rate of sarcomatous meningiomas ranges from 50% to 94%, and the overall survival is around 2 - 5 years [5]. Recurrent grade 2 meningiomas are generally treated by stereotactic radiosurgery (SR) but this treatment modality always carries a risk of malignant transformation. It is recognizable that high-grade meningiomas harbor higher mutation burden, and typically shows stepwise progression, deletion of chromosome 22 as well as deletions in other chromosomes such as (1p, 14q, and 10q) [6, 7]. Few reports indicated that the presence of promoter mutation of TERT is commonly present in the high grade meningiomas [8, 9]. This finding is valuable in assessing prognosis, survival, and for individualized therapeutic options [2]. Meningiomas formerly treated with adjuvant radiation showed a significantly higher incidence of copy number alterations than radiation-naïve meningiomas [10]. Post radiation transformation of meningioma to osteosarcoma and chondroblastic osteosarcoma have been previously reported [11, 12]. The duration described in the literature after radiation therapy and the occurrence of the tumor varies from 5

years to several decades [13, 14]. According to previous researchers this transformation might take 2 to 16 years [15, 16]. In the present case, the time span between initial radiation exposure and the emergence of anaplastic meningioma was approximately 7 years. Anaplastic meningiomas may show several morphologic patterns, thus other primary central nervous system tumors and specifically other CNS sarcomas should be excluded in the presence of such a poorly differentiated malignant neoplasm. There is no consensus for the role of radiotherapy and chemotherapy in therapeutic management. Large number of studies found no definite advantage of adjuvant radiotherapy in treating meningiomas and several studies emphasized the risk of radiation-induced toxicity [4]. However, in CNS WHO grade 3 meningiomas, radiotherapy is still considered necessary in the patient management plan because of the potential for recurrence and worse prognosis. On the other hand, chemotherapy has not shown a conclusive effect on atypical and anaplastic meningiomas and thus should be reserved for recurrent resistant cases and after utilizing all standard therapies [17, 18]. Peyre *et al*., reported that secondary anaplastic meningiomas usually harbors TERT mutations more often than de novo anaplastic meningioma [11, 12]. Given the histological, immunohistochemical and the time management course and most importantly the NGS results, this case likely represents post radiation transformation of an atypical meningioma to an anaplastic/ sarcomatous meningioma despite the lack of TERT mutation in our patient. Development of secondary malignancies is a notorious risk after long-term radiation therapy [19]. Cahan's established a diagnostic criterion to define radiotherapy-related secondary brain malignancies, this criterion includes the following i) tumors positioned in a prior radiation field, ii) an acceptable latency period, usually several years interval between the radiation therapy and the onset of the secondary tumor, iii) a different histology from the primary disease [20]. Absence of any underlying carcinogenic gene related disease such as tuberous sclerosis and neurofibromatosis [20]. In the present case, radiotherapy induced malignant transformation is not established due to the existence of NF2 genetic mutation. Herein we present a case report of post radiation transformation of an atypical meningioma to a sarcomatoid subtype (anaplastic CNS WHO grade 3), in a 17-year-old adolescent with NF2 mutation after multiple recurrences. To the best of our knowledge, only two cases of post- radiation transformation of meningioma, have previously been described in the literature [11, 12].

CONCLUSION

Post-surgical radiation therapy in CNS WHO grade 2 meningioma may not constantly be the optimal treatment for all patients. Genetic sequencing and risk benefit analysis should be considered prior to treatment of meningiomas particularly for young adults and children. We suggest that detection of TERT promoter mutation and NF2 or NF1 alterations through next generation sequencing should be reflected in the patient management plan, attempting to avoid the hazard of developing radiation related dismal malignancies.

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