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Case Report

Malignant ossifying fibromyxoid tumor of the brain treated with post-operative fractionated stereotactic radiation therapy: A case report and literature review

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ABSTRACT

Background: Ossifying fibromyxoid tumor (OFMT) is a rare musculoskeletal soft-tissue neoplasm of uncertain histogenesis most frequently occurring in the lower extremities. Conventionally, considered benign, these tumors are often managed by surgical resection followed by surveillance. However, malignant OFMTs with an increased propensity for local recurrence and distant metastasis have been recently identified, and the role of adjuvant therapy in these more aggressive cases is unclear.

Case Description: We present, to the best of our knowledge, the first reported case of a primary, malignant, and intracranial OFMT. A 29-year-old female presented with recurrent headaches secondary to a large mass in her right frontal lobe. She underwent gross total resection of the brain mass with final pathology consistent with malignant OFMT demonstrating high-risk features including increased cellularity, grade, and mitotic activity. Due to these high-risk features, she received postoperative fractionated stereotactic radiation therapy (FSRT) to the resection cavity, and to the best of our knowledge, she represents the only known patient with OFMT to be treated with adjuvant FSRT. She tolerated the adjuvant treatment well with no acute or late toxicities and remains disease-free over 5 ½ years after resection.

Conclusion: Adjuvant FSRT appears to be a safe and efficacious approach for managing this rare intracranial disease presentation. We review this patient's clinical course in the context of the literature to demonstrate the difficulties associated with accurate diagnosis of this rare tumor and the controversial role of adjuvant therapy in preventing disease recurrence in this patient population.

Keywords: Adjuvant therapy, Malignant intracranial ossifying fibromyxoid tumor, Malignant ossifying fibromyxoid tumor, Radiation therapy, Stereotactic radiotherapy

INTRODUCTION

Ossifying fibromyxoid tumor (OFMT) is a rare musculoskeletal soft-tissue neoplasm of uncertain histogenetic lineage.[4] To date, only a few hundred cases have been reported in the literature.[1] While OFMTs most frequently occur in the subcutaneous soft tissues or skeletal muscles of the

lower extremities, other common sites include the upper extremities, trunk, head and neck (mandible, nasal cavity, and paranasal sinuses), mediastinum, and breast.[2,5,10] These tumors have historically been reported to present as slowly enlarging, well-circumscribed, painless masses attached to subcutaneous tendons, or muscle.

Although OFMTs have traditionally been considered to be benign, variants with a relatively high propensity for local recurrence and distant metastasis have more recently been reported in the literature.[5] Folpe and Weiss[5] defined "typical," "atypical," and "malignant" histologic categories of OFMT based on cellularity, grade, and mitotic activity. Malignant subtypes are associated with increased risks of local recurrence and distant metastases (60% and 60%, respectively).[5] Surgical resection followed by surveillance has traditionally been considered standard management for benign OFMT.[5] However, no guidelines are available to define the role of adjuvant chemotherapy and radiation in the treatment of malignant OFMTs. We describe, to the best of our knowledge, the first reported case of a primary malignant OFMT of the brain as well as the only reported case of OFMT to undergo treatment with postoperative stereotactic radiation therapy (SRT). In this report, we will review the clinical and histologic features of this rare tumor as well as prognostic stratification and emerging paradigms in the management of more aggressive malignant subtypes.

CASE DESCRIPTION

A previously healthy 29-year-old female presented to our institution with recurrent headaches, which progressively worsened over 2–3 months and were refractory to symptom-directed medical management. Through an interpreter, she reported headaches radiating from her occipital to frontal area and worsened in the mornings. She also reported a 2-week history of intermittent dizziness and nocturnal fevers. On presentation to the emergency department, she experienced an episode of vomiting. Physical exam confirmed a history of chronic hearing loss and use of hearing aids; however, no other neurological deficits were noted.

CT imaging of the head showed a peripherally hyperdense, centrally hypodense lesion in the right frontal lobe measuring 1.4 × 1.2 cm. Additional lesions were not readily apparent on the non-contrast CT image. Subsequent brain MRI with and without contrast showed a large, lobulated, enhancing mass in the right inferior frontal lobe with extensive surrounding edema. The mass measured 4.1 × 3.5 × 4.2 cm in size. A T1-weighted MRI sequence showed a hypointense mass [Figure 1a] with diffuse enhancement on the post-contrast sequence [Figure 1b]. The T2 MRI sequence showed heterogeneous cystic and necrotic areas [Figure 1c]. FLAIR signal abnormality demonstrated extensive surrounding edema involving the right frontal, parietal, and temporal lobes [Figure 1d]. Staging CT imaging of the chest/abdomen/pelvis confirmed no evidence of distant systemic disease.

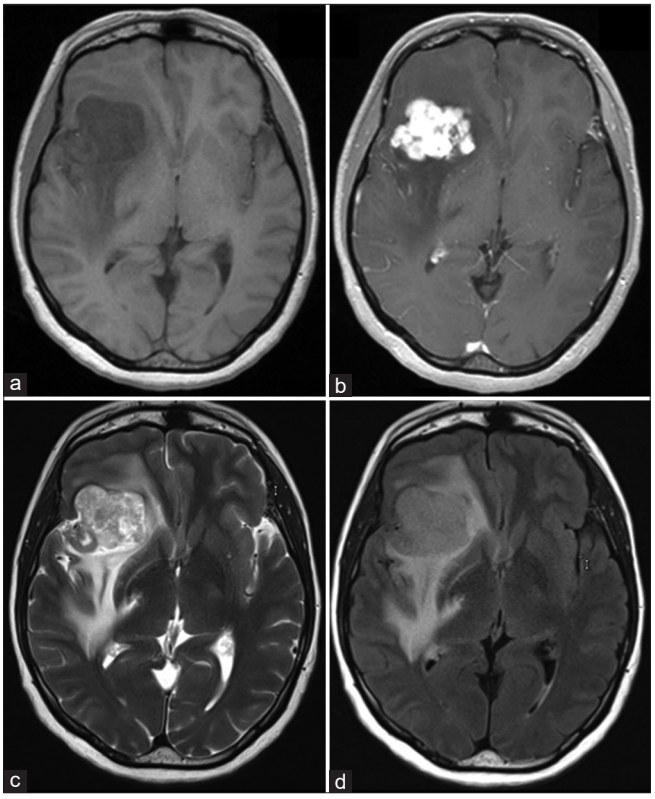

Figure 1: Brain MRI with and without contrast demonstrated a 4.2 cm lobulated, enhancing mass in the right inferior frontal lobe with extensive surrounding edema. The mass appears hypointense on the T1-weighted MRI non-contrast sequence (a) with diffuse enhancement on the post-contrast sequence (b). The extent of edema is noted on T2-weighted (c) and T2/FLAIR (d) images.

She underwent a gross total neurosurgical resection. The well-circumscribed superficial part of the tumor was sent for frozen section and was consistent with a low-grade neoplasm of unknown etiology. The tumor was dissected away from the surrounding brain in multiple specimens (piecemeal). No residual tumor was noted in the resection cavity by the neurosurgeon after completion of the procedure. Postsurgical brain MRI confirmed the absence of residual tumor in the right frontal resection cavity. The patient recovered after surgery with no complications.

Final pathology showed a non-infiltrating neoplasm composed of lobules of round to spindle-shaped cells arranged in cords among a myxoid and collagenous matrix [Figure 2]. Some areas showed densely hyalinized collagen that gradually transitioned to osteoid. An ultrastructural analysis of the tissue confirmed that these cells were undifferentiated and embedded within a rich collagen matrix with multiple cell junctions. The tumor appeared to be well circumscribed from the adjacent brain parenchyma with a

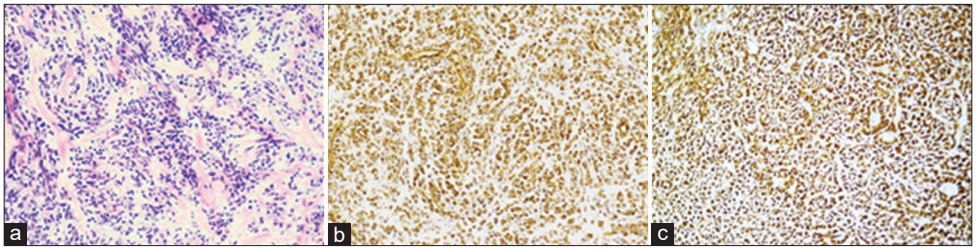

Figure 2: Pathology revealed a well marginated neoplasm composed of lobules of round to spindle-shaped cells arranged in nests and cords among a myxoid and collagenous matrix surrounded by a peripheral rim of bone. Hematoxylin and eosin staining demonstrating lobules of spindle-shaped cells (×20) (a). Strong, diffuse immunohistochemical staining for vimentin (×20) (b). Diffuse immunohistochemical staining for CD56 (×20) (c).

pseudo capsule. Immunohistochemical staining suggested lineages of mixed differentiation, including neuronal, glial, and myogenic lineages. CD56, neurofilament, desmin, and vimentin were among the immunohistochemical markers demonstrating strong positivity [Table 1] and [Figure 2]. High risk features, including a Ki-67 index of 20–30% and 3 mitotic figures per 50 high power fields, revealed a more aggressive malignant tumor. Due to the mixed differentiation, the tumor was difficult to classify. A diagnosis of supratentorial primitive neuroectodermal tumor was considered but not consistent with the dense collagen and myogenic differentiation. A consensus diagnosis of malignant OFMT was made, with pathologists at another tertiary care center in agreement.

Due to the aforementioned high-risk features, a neuro-oncology tumor board consensus decision was made to proceed with adjuvant fractionated SRT (FSRT) to the resection cavity. Head CT imaging from the radiation planning session was fused to an MRI T1 post-contrast volumetric sequence for better depiction of the resection cavity. The planning target volume (PTV, volume to where 100% of the dose was prescribed) consisted of the resection cavity plus a 3-mm margin to account for errors during planning and treatment delivery [Figure 3a]. A 3-arc volumetric modulated arc therapy plan with 6 megavoltage photons was used for dose delivery. Plan review ensured that 95% of the planning target volume was covered by the total dose of 21 Gy (100% isodose line) [Figure 3b]. Furthermore, standard dose constraints to the optics, brainstem, spinal cord, and other organs at risk were met. Daily cone beam CT and 6-degrees of freedom treatment couch corrections (Varian Edge™) were also used to reduce set up errors and improve positioning of the target. A prescription dose of 21 Gy was delivered in 7 Gy treatments over 3 consecutive daily fractions to the PTV approximately 6 weeks after surgery. The postoperative cavity was prescribed 24 Gy through a simultaneous integrated boost. The patient tolerated the treatment well with no unexpected toxicities noted by clinicians or the patient. Over 5 ½ years after resection, she continues to have no clinical or radiographic evidence of recurrent or progressive intracranial or systemic disease.

Table 1: Immunohistochemical marker positivity among ossifying fibromyxoid tumors in the literature and the case discussed in this report.

Protein	Overall % positivity in the literature (%)	Case	References
S100	50–94	-	[2,5,7,10,13-15]
Vimentin	79–100	+	[10,13-15]
NFP	75	+	[7,14]
GFAP	7–50	+	[10,13–15]
SMA	2–50	-	[7,10,13-15]
Desmin	0–70	+	[2,5,7,10,13]
CD34	0	-	[2,10]
Pan Cytokeratins	0–14	-	[5,7,10,13-15]
EMA	0–16	-	[7,10,14,15]
CD56	41–83	+	[7]
HMB45	0	-	[10]
EAAT4	79	ND	[7]

ND: Not done, NFP: Neurofilament protein, GFAP: Glial fibrillary acidic protein, SMA: Smooth muscle actin, EMA: Epithelial membrane antigen, HMB45: Homatropine methylbromide 45, EAAT4: Excitatory amino-acid transporter 4

DISCUSSION

We have highlighted the first account of a primary, malignant, intracranial OFMT, which also represents the first case with extended follow-up to be successfully managed with resection and adjuvant FSRT. Predominately occurring in the lower extremities, OFMTs were historically characterized by their benign pathology and clinical course. Since they were originally believed to have limited potential for local recurrence and distant metastasis, surgical resection followed by surveillance has traditionally been the standard of care. More recently, however, cases of OFMT with malignant pathologic features and a more aggressive clinical course have been increasingly reported.[5] However, diagnostic criteria for identifying more aggressive malignant subtypes are

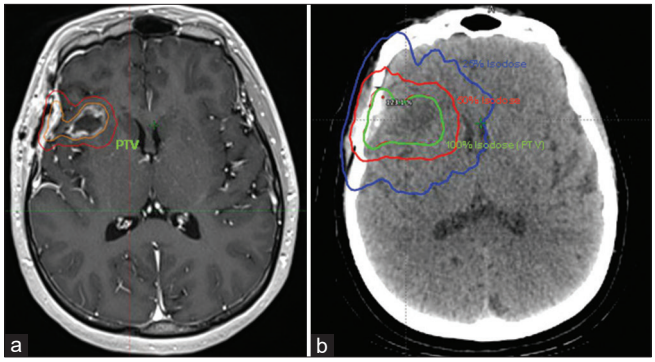

Figure 3: The planning target volume (PTV) (100% of the dose was prescribed to this volume) consisted of the resection cavity (outlined in orange) plus a 3 mm margin (outlined in red) as identified on the T1 post-contrast sequence (a). A 3-arc VMAT plan with 6 megavoltage photons shows the 100% isodose line (21 Gy) covering the PTV target (resection cavity + 3mm margin) on the planning CT head (b).

controversial. The ability to accurately diagnose malignant OFMTs is imperative to ensure appropriate management of these patients.

In 2003, Folpe and Weiss originally defined pathologic criteria for diagnosing OFMT with malignant behavior.[5] OFMT were classified as typical, atypical, or malignant based on high risk features including (1) high nuclear grade, (2) high cellularity, and (3) mitotic activity of >2 mitoses per 50 HPF[5]. While typical tumors fail to meet any of the aforementioned criteria, malignant tumors tend to meet all three criteria. Atypical tumors do not satisfy all criteria for malignancy. It is important to note that although typical and atypical tumors are not considered malignant, they do have potential to recur (12% and 13%, respectively) and metastasize (4% and 6%, respectively).[5] Malignant OFMTs, on the other hand, demonstrate a much higher risk of both local recurrence and distant metastasis (60% and 60%, respectively).[5] The malignant OFMT case discussed in this report satisfied all three criteria by demonstrating high grade, high cellularity, and high mitotic activity of 3 mitoses per 50 HPF.

While Folpe and others reported that grade and proliferation significantly correlated with rates of local recurrence and distant metastasis among OFMT, other groups have questioned the existence of malignant OFMT. Miettinen *et al*.[10] reviewed one of the largest studies of 106 OFMT and found a correlation between mitotic rates and local recurrences among the 41 patients with long-term follow-up (22%, $n = 9$). However, they failed to identify any tumors with distant metastases and concluded that metastasizing OFMTs may represent misdiagnosed malignancies, such as sarcomas.[10] Multiple studies have therefore aimed to identify molecular biomarkers that may facilitate diagnosis of malignant OFMT by differentiating them from other malignancies.

OFMTs closely resemble other mesenchymal tumors under the microscope and therefore immunostaining for molecular markers is crucial for diagnosis. Common immunohistochemical findings of an OFMT are summarized in [Table 1]. The mesenchymal marker, vimentin, is strongly expressed in nearly all OFMT; however, it is also highly expressed in other mesenchymal tumors. To date, the best defining characteristics of OFMTs include the peripheral rim of bone tissue and positive S-100 immunostaining. However, up to 20% of OFMTs lack ossifying tissue and are termed non-ossifying OFMTs.[2]

Moreover, while more than two-thirds of OFMTs are positive for S-100 by immunohistochemistry, not all OFMT, including the case discussed in this report, demonstrate S-100 immunostaining [Table 1]. Typical OFMTs are more likely to express S-100 positivity than atypical and malignant OFMT, which further adds to the controversy of whether malignant OFMTs exist.[5] Folpe and Weiss[5] suggested that loss of S100 may occur during the malignant transformation of OFMT. In the case described in this report, histology demonstrating negative immunostaining for S100 in the presence of a peripheral rim of bone corresponded to our diagnosis of malignant OFMT.

Gebre-Medhin *et al*.[6] identified the PHF1 gene as a defining chromosomal rearrangement of OFMTs. PHF1 interacts with polycomb repressive complex 2 (PRC2), a protein that regulates developmental gene expression, suggesting that deregulation of PRC2-associated genes could be involved in OFMT development. Interestingly, this gene rearrangement is also commonly observed in endometrial stromal tumors. Similar to S100, PHF1 rearrangements are more frequently found in typical and atypical OFMTs than malignant OFMTs.[6] PHF1 rearrangement was not detected in the case discussed in this report, further supporting our diagnosis of a malignant OFMT variant. Therefore, S100 and PHF1 rearrangements may not only serve as a helpful tool for OFMT diagnosis, but also be a tool for distinguishing malignant OFMTs from their benign counterparts.

To better understand gene expression differences between subsets of OFMT, Graham *et al*.[7] performed gene expression profiling between typical and malignant OFMTs. Gene expression profiles of eight typical and five malignant OFMTs were compared and, interestingly, minimal gene expression differences were found between the two subsets of OFMTs. While this study is limited by small sample numbers, the preliminary results may provide further evidence for the existence of malignant OFMTs due to the similarity in their gene profiles.[7]

Another point of contention regarding OFMTs is their lineage of differentiation. While OFMTs were originally

thought to be derived from schwannoma or cartilaginous lineages based on published immunohistochemical and ultrastructural analyses,[4,13] gene expression and proteomics data from Graham *et al*.[7] suggested that OFMTs may undergo a neuronal lineage of differentiation. EAAT4, a member of the neuronal glutamic acid transporter known to be highly expressed in the cerebral cortex, was also expressed at high levels in 80% of OFMTs.[7] Other neuronal genes, such as neurofilament protein and CD56, were also identified in 75% and 41% of OFMTs, respectively.[7] Interestingly, neurofilament protein and CD56 immunostaining [Figure 2c] were positive in our case; however, there was no EAAT4 immunostaining performed on this case [Table 1]. While these results have not yet been confirmed, they suggest a potential neuronal lineage of differentiation.

To the best of our knowledge, the case discussed in this report, while subject to the limitations inherent to case reports, represents the first OFMT to be diagnosed as a primary case in the CNS. While others have reported paraspinal OFMTs, the paraspinal tumors were believed to have originated in the surrounding muscle and soft tissues with invasion into the spinal canal or bone.[3,12] If OFMTs do indeed arise from a neuronal lineage, it is likely that more OFMTs cases, similar to the one described in this report, may be diagnosed in the CNS.

Historically, the standard of care for OFMTs has been surgical resection with wide margins. Guidelines for adjuvant therapy have not been clearly defined for more aggressive OFMT subtypes and the literature regarding adjuvant radiation and chemotherapy for OFMTs is limited.[11] One report from our literature review described a case of orbital OFMT that recurred twice after resection and was treated with adjuvant radiation (dose not specified) after the second recurrence.[11] The patient has reportedly been disease-free for 18 months after adjuvant radiation. Therefore, there may be a role for adjuvant radiation therapy in preventing local recurrence after resection.

The patient discussed in this report was treated with postoperative SRT due to the high-risk features noted on pathology. Due to the lack of data governing the management of this unique presentation of this rare malignancy, management decisions were extrapolated from studies guiding adjuvant therapy for resected brain metastases. The surgical cavity mildly decreased in size in the 6 weeks between resection and CT simulation yet remained roughly 3 cm in greatest dimension. Historically, to control the rate of radionecrosis, doses for single fraction SRT for lesions of this size are strongly de-escalated. On a recent Phase III trial where doses were progressively de-escalated for increasingly large lesions, 1-year local control was 91% with gross total resection and adjuvant, single fraction SRT for cavities under 2.5 cm in diameter but just 40% for those 2.5–3.5 cm in size.[9] Thus, there is increasing interest in fractionation, because smaller fraction sizes offer a radiobiologic advantage that may allow for delivery of a higher biologically effective dose without increasing the risk of radionecrosis. For this reason, we chose to fractionate SRT. A recent meta-analysis of 24 studies compared outcomes with multi-fraction versus single-fraction postoperative SRT for brain metastases and found a trend towards improved 1-year local control (86.8% vs. 68.0%, $P = 0.08$) and a numerically decreased rate of radionecrosis (7 vs. 10%, $P = 0.46$).[8] A large, randomized, multi-institution, and phase III trial prospectively addressing this question is currently underway (NCT04114981). While FSRT is routinely used in the effective management of brain metastases, there have been no reports of OFMTs treated with FSRT. The patient described in this report is now over 5 ½ years out from resection with no evidence of disease recurrence or long-term toxicity.

In summary, we present the first account of a primary, malignant, intracranial OFMT, which also represents the first case to be successfully managed with resection and adjuvant FSRT. Despite high-risk features consistent with malignant potential as reported in the literature, the patient remains disease and complication free over 5 ½ years after gross total resection and adjuvant FSRT, suggesting that this is a safe and efficacious approach. If OFMTs do indeed demonstrate a neuronal lineage of differentiation, more cases of malignant OFMTs localized to the brain in the future may be encountered. Therefore, it is imperative to identify safe and effective approaches for diagnosing and managing this patient population.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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