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Primary Intracranial Fibrosarcoma in a Patient with a Remote History of Chest Wall Liposarcoma: Case Report and Discussion of the Literature

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ABSTRACT

We present a case of a primary leptomingeal fibrosarcoma in a patient, who had previously undergone radical resection of a liposarcoma of the chest and abdominal wall 18 years prior. In the year following resection of his intracranial fibrosarcoma and treatment with adjuvant radiotherapy, the patient was diagnosed with an in-situ recurrence of his original chest and abdominal wall liposarcoma. Primary intracranial fibrosarcomas are rare, particularly in the setting of a previous metachronous systemic sarcoma. Moreover this case is of particular interest since the patient was being treated for diabetes with agents that inhibit peroxisome proliferator-activated receptors (PPARs) and recent reports have suggested a potential relationship between these nuclear receptors and the development of fibrosarcomas and liposarcomas. With reference to the current case report, we briefly review the current guidelines for the management of intracranial fibrosarcoma and discuss the postulated relationship between PPAR agonists and sarcomas.

Key words: Primary intracranial fibrosarcoma, liposarcoma, PPAR, thiazolidinedione.

INTRODUCTION

Primary sarcomas of the brain and meninges are uncommon, accounting for 1.5% of intracranial neoplasms[7,34]. They are thought to arise from mesencyhmal cells of the dura mater, leptomeninges, vascular adventitia, or the stalk of the choroid plexus[43,56]. These tumors most often affect young and middle-aged adults, typically involving the supratentorial compartment.

Herein the authors report a patient with a primary fibrosarcoma of the leptomeninges that had neuroimaging properties of a meningioma. The patient had a remote history of a chest and abdominal wall liposarcoma 18 years prior, yet the pathologic review of the intracranial lesion revealed no histologic similarities or evidence of adipocytic differentiation. Given the rarity of primary intracranial fibrosarcoma, its neuroimaging mimicry of meningioma, and the unusual occurrence of a remote history of a sarcoma with differing histology, the present case is a useful contribution to the literature. The case is also of particular interest as the patient was being treated for his diabetes with thiazolidinediones (TZD), agonists of peroxisome proliferator-activated receptors (PPARs). PPARs are a group of nuclear receptor proteins that function as transcription factors to regulate gene expression[41]. Though their specific role is still undefined, some have suggested that PPARs may be related to the development of fibrosarcomas and liposarcomas; hence the present case may further inform this dialogue.

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CASE REPORT

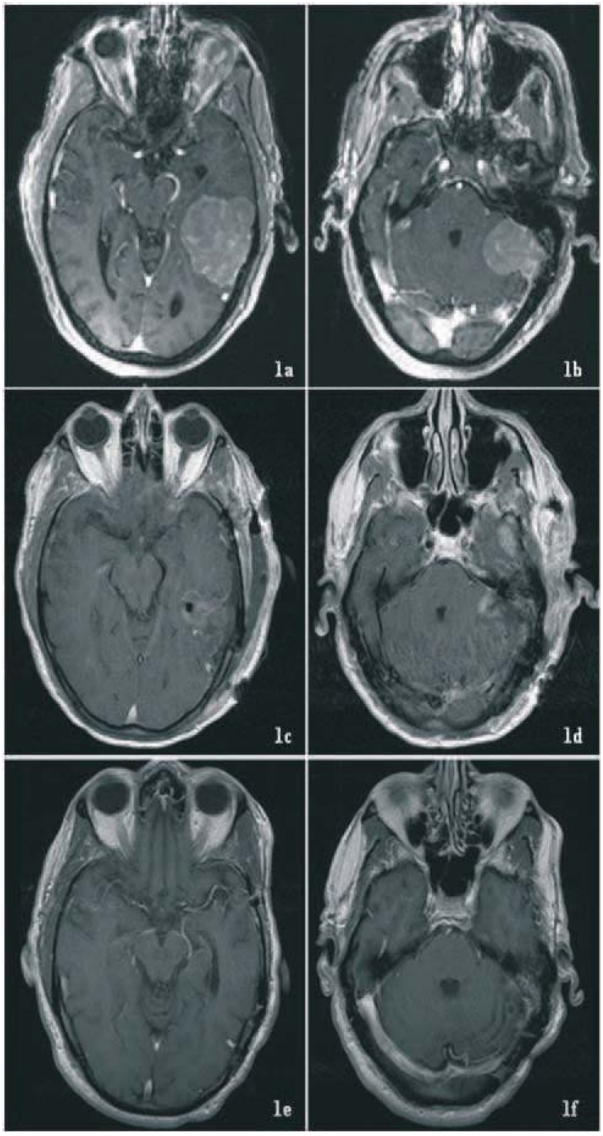
History, Presentation and Examination

A 65 year-old male with diabetes mellitus type II and hypercholesterolemia presented with profound memory loss, dyspnea and unsteady gait which developed over a period of 2 months. He had been treated for diabetes with rosiglitazone (Avandia™, GlaxoSmithKline Pharmaceuticals) and pioglitazone (Actos™, Takeda Pharmaceuticals), both belonging to the peroxisome proliferator receptor agonists group, for 3 years and 15 months respectively, showing moderate diabetic control. The patient was also status post resection of a liposarcoma of the left chest and abdominal wall 18 years prior. Subsequent to the surgical resection of his liposarcoma, the patient did not receive any adjuvant chemotherapy or radiation therapy. The patient's family history was significant for a mother who had died from malignancy, yet additional information on the cancer type and location could not be elicited. Pertinent findings on physical exam included a left-sided ptosis and protrusion of the left chest and abdominal wall in the area of previous surgery.

DIAGNOSTICS

Magnetic resonance imaging (MRI) and MRI angiography of the brain with and without gadolinium demonstrated a bilobed infra and supratentorial enhancing extra-axial mass, centered in the left lateral posterior fossa and extending superiorly over the tentorium into the supratentorial compartment to involve the left posterior temporal region. Based on the imaging appearance of the mass, a diagnosis of tentorial meningioma was favored. The lesion measured 3.8 x 2.9 cm in the posterior fossa and 4.8 x 4.4 cm supratentorially (anterior-posterior by transverse, respectively), resulting in 2 to 3 mm of left-to-right midline shift. The lesion had eroded into the left mastoid. There was trapping of the left temporal horn from the supratentorial component and the infratentorial portion exerted mass effect on the cerebellum, pons and fourth ventricle, though the forth ventricle remained patent and no hydrocephalus was present (Figure 1). The mass also compressed the left transverse and sigmoid sinuses and the jugular vein. Based on imaging characteristics, a diagnosis of tentorial meningioma was favored.

Figure 1: 1a, b) Pre-operative T1 post-contrast axial MRI; 1b, c) Post-operative day one T1 post-contrast axial MRI; 1d, e) T1 post-contrast axial MRI approximately 1 year and 10 months post-operatively.



MANAGEMENT

The patient was placed on corticosteroids and prophylactic anticonvulsants and surgery was recommended. A left temporal and sub-occipital frameless stereotactic craniotomy with resection of the supra- and infratentorial extensions was completed.

PATHOLOGY

Intraoperatively, the frozen section was interpreted as fibroblastic meningioma. Upon review of the permanent sections and immunohistochemical stains, a diagnosis of low grade fibrosarcoma was established. The tumor had a predominantly fascicular growth pattern consisting of elongate spindle cells (Figure 2A). There were no whorls, psammoma bodies or other meningothelial properties observed. Immunohistochemistry for EMA, claudin and S-100 protein was negative, further ruling out a fibroblastic form of meningioma. Immunostains for desmin, smooth muscle actin, CD31 and CD34 were negative. The only immunohistochemical stain that showed immunoreactivity was vimentin, which stained strongly. The fascicular growth pattern, the deposition of collagen and the immunoprofile suggested the diagnosis of fibrosarcoma. The lack of necrosis and highly anaplastic nuclear features, along with a low proliferative activity (less than one mitosis per ten HPF; MIB-1 proliferation index 8%) (Figrure 2B), suggested it was low grade. The patient's previous chest and abdominal wall sarcoma was reviewed, confirming its diagnosis as low grade liposarcoma. The chest and abdominal wall liposarcoma and the leptomeningeal fibrosarcoma were histologically distinct. There was no evidence of adipocytic differentiation in the leptomeningeal tumor, essentially ruling out the possibility of a latent metastatic lesion. Thus, the leptomeningeal tumor was most consistent with a primary low grade fibrosarcoma.

Figure 2A: Histopathology of this patient's dural-based neoplasm. Highly elongate, spindled tumor cells with moderate nuclear anaplasia were disposed in fascicles with only modest deposition of extracellular collagen. There was no evidence of meningothelial of meningothelial or adipocytic differentiation and immunohistochemical testing did not reveal a distinctive expression profile. These findings were consistent with fibrosarcoma (H&E, 200X).

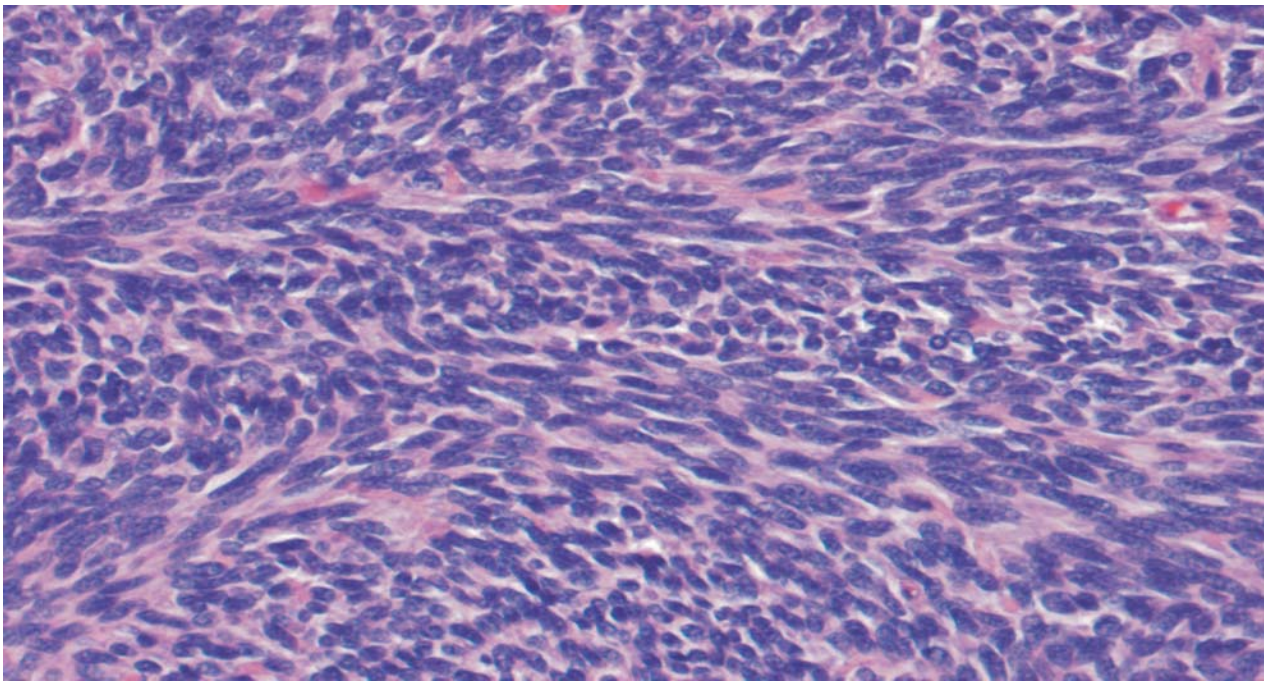
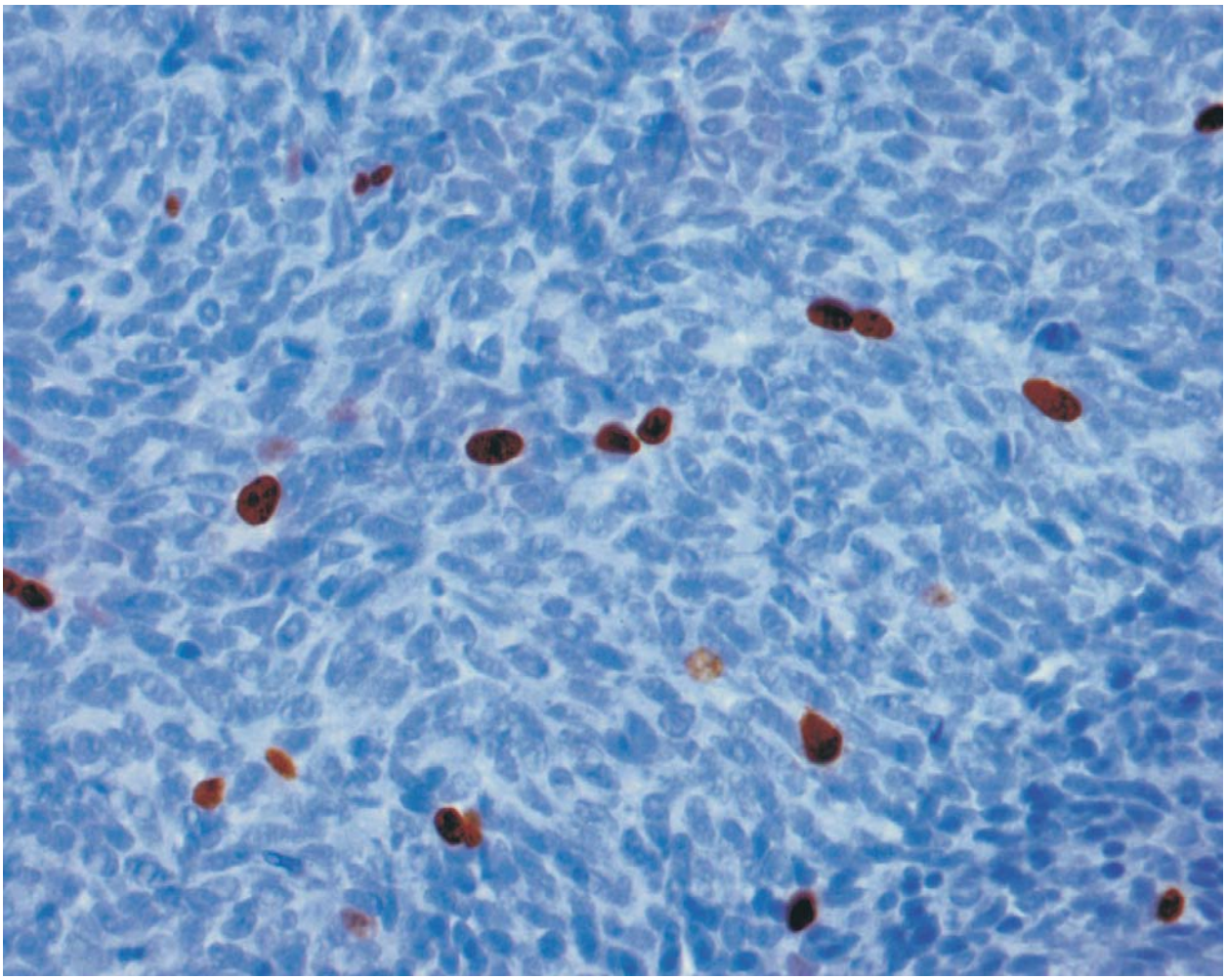


Figure 2B: An immunohistochemical stain for MIB-1 revealed a proliferation index of 8% (400X).



POSTOPERATIVE COURSE

After the operation, improvement in the patient's memory, performance of activities and gait was noted along with resolution of the left-sided ptosis. After consultation with radiation oncology, the patient was subsequently treated with intensity modulated radiation therapy using 6 mV photons to 50.4 Gy at 1.8 Gy per fraction in 28 total fractions, followed by a boost adding 9 Gy at 1.8 Gy per fraction in 5 fractions, both delivered to the 98% isodose line for a total delivery dose of 59.4 Gy. This was delivered over 47 calendar days. The following year, on a routine chest x-ray, an abnormality was found. Positron emission tomography (PET) along with a CT guided needle biopsy revealed a liposarcoma of the chest and abdominal wall. Radical resection of the recurrent tumor combined with supplemental adjuvant radiotherapy was performed. Pathology evaluation of the tumor revealed it was similar in nature to the primary sarcoma resected years ago and, therefore, this was considered to be a clinical recurrence. At two years follow up from resection of his intracranial fibrosarcoma (his last follow up visit was at 25.5 months postoperatively), the patient is doing well and undergoing regular surveillance.

DISCUSSION

Albeit rare, CNS sarcomas are the most common primary non-meningothelial tumors of the dura. Only occasionally are they based

in the parenchyma. The majority of primary meningeal sarcomas are of unknown etiology; however, a significant percentage occur after therapeutic cranial irradiation.

Diagnosing a fibrosarcoma can be challenging, given that their gross pathology and imaging features can closely mimic classic meningioma, meningioma en plaque or diffuse meningeal involvement (meningio-angiomatosis)[20]. In one study, immunohistochemistry was evaluated as a diagnostic aid[21]. Vimentin positivity and lack of glial fibrillary acid protein (GFAP) reactivity are helpful in distinguishing fibrosarcoma from gliosarcoma. Cytokeratin positivity has been reported in meningiomas, and its positivity in some fibrosarcomas might suggest a relation to meningomas. However, cytokeratin is not consistently positive, even in cases where there was obvious involvement of the meninges[30,68]. In the present case, the tumor showed no evidence of glial differentiation. It showed no immunoreactivity for EMA, S-100, cytokeratin, or claudin, essentially ruling out meningioma.

There is no gold standard for the treatment of primary intracranial fibrosarcoma, as its rarity has precluded definitive recommendations. These tumors have a strong tendency to recur at the primary site despite aggressive surgical resection[9,35] and also have a high incidence of meningeal seeding and systemic metastases[21]. Time to recurrence or progression is variable and can occur years later[21]. In one study, 18 patients were treated for primary sarcoma of the CNS by marginal excision with or without adjuvant radiochemotherapy. There were no significant differences in survival or recurrence based on treatment noted in this small study. However, a worse prognosis (survival) was seen in patients with high-grade sarcomas (28% at 5 years) compared to patients with low-grade sarcomas (83% at 5 years)[46]. There is only one reported 10-year survivor in the literature, a child whose treatment included subtotal resection and a relatively low dose of radiation (45Gy)[61]. When wide en bloc resections cannot be performed, radiation therapy doses must be high enough to control gross residual disease. Doses of 64-66 Gy are required to treat microscopic residual extracranial fibrosarcomas[24,58,59]. Since the whole brain cannot tolerate such high doses of radiation, cone-down external beam techniques may be used. The patient presented here received a total of 59.4 Gy using intensity modulated radiotherapy. At present, there are no for using neuraxis radiotherapy to prevent cerebrospinal fluid seeding in the setting of this disease[21].

The development of leptomeningeal fibrosarcoma in a patient with prior systemic liposarcoma raises two questions: i) can the patient's presentation be categorized into a particular syndrome; and ii) is there some other relationship between the intracranial fibrosarcoma and the systemic liposarcoma?

Given the patient had multiple sarcomas, the Li-Fraumeni Syndrome, a rare autosomal dominant hereditary disorder associated with the development of multiple malignancies should be considered[39]. In the present case, the patient was initially diagnosed with liposarcoma at the age of 47. The patient reported his father died of 'natural causes.' His siblings and children were reportedly healthy. The only first-degree relative who had cancer was the patient's deceased mother; however, the type and age of diagnosis of the cancer are unknown. Hence the diagnostic criteria for the Li-Fraumeni Syndrome are not fulfilled.

Recently an association between peroxisome proliferator-activated receptors (PPARs) and sarcomas has been described. PPARs are ubiquitously expressed and play an essential role in modulating cellular differentiation, development, and metabolism (carbohydrate, lipid, and protein)[4,19]. Their name reflects the fact that they increase peroxisome numbers in rodent liver tissue, apart from improving insulin sensitivity[31]. Three types of PPARs have been identified: alpha (á), gamma (ã), and delta (ä) [synonymous to beta (â)][4]. Interestingly, thiazolidinediones, a class of anti-diabetic medications, act as an agonist ligand for PPARã[38]. Some evidence suggests that their activity may lead to terminal

adipocyte differentiation[13]. In one study of TZDs on adipocyte differentiation in liposarcoma patients, the activation of the PPARã was found to up-regulate adipsin, a gene responsible for adipocyte differentiation, in one patient but no clinical or histological effects in that specific cases were observed[16]. It has also been reported that PPARã stimulation leads to apoptosis of a colon cancer cell line[12]; however, the anticancerous effect of TZDs was proven to be independent of PPARã activation in another report[47].

Other reports suggest that PPAR agonists have the opposite effect, and may be linked to the development of different types of sarcomas including liposarcoma and fibrosarcoma, in rodents[28]. Our patient, as a known diabetic, was being treated with rosiglitazone and pioglitazone, which are both TZDs, for more than 4 years prior to diagnosis of the intracranial fibrosarcoma. Thus, the present case certainly raises the possibility of a relationship between TZD therapy and fibro- and liposarcomatous disease[28]. Given the preliminary findings in rodents[28], further investigation of this relationship may be warranted.

CONCLUSIONS

Primary fibrosarcomas of the brain are uncommon tumors, usually of high histological grade, with a high rate of local recurrence[21]. The prognosis of primary CNS sarcomas seems to be largely determined by histological grade[46]. The standard of management of these cases has yet to be established. However, from the limited information available in the literature, the most successful treatment is subtotal or gross tumor resection. The logic of chemoradiation as an adjuvant therapy is understood, but the extent of its contribution to recurrence prevention is presently unknown. The role of PPAR stimulation on the development of sarcomatous disease, if any, requires further investigation.

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